BLA Clinical Review Memorandum

Application Type	Original BLA
STN	125736/0
CBER Received Date	July 27, 2020
PDUFA Goal Date	March 27, 2021
Division / Office	DCEPT/OTAT DHM II/OCE
Priority Review (Yes/No)	Yes
Reviewer Name(s)	Poornima Sharma, MD
Review Completion Date / Stamped Date	3/26/2021
Supervisory Concurrence	Bindu Kanapuru, MD Bindu George, MD Marc Theoret, MD
Applicant	Celgene Corporation
Established Name	Idecabtagene vicleucel (bb2121)
(Proposed) Trade Name	ABECMA
Pharmacologic Class	BCMA-directed, genetically modified autologous T cell immunotherapy
Formulation(s), including Adjuvants, etc.	50% Plasma-Lyte A and 50% Cryostor CS10 resulting in DSMO concentration of 5%
Dosage Form(s) and Route(s) of Administration	Intravenous
Dosing Regimen	Single dose containing 300 to 460 $x10^6$ CAR- positive T cells by IV infusion and preceded by fludarabine and cyclophosphamide for lymphodepletion
Indication(s) and Intended Population(s)	Proposed: For the treatment of adult patients with multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a

	proteasome inhibitor and an anti CD38 antibody. <u>Recommended:</u> For the treatment of relapsed or refractory multiple myeloma after 4 or more prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 monoclonal antibody.
Orphan Designated (Yes/No)	Yes

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Glossary

AE adverse event
AESI adverse event of special interest
Allo allogeneic
AR adverse reaction
Auto autologous
BLA biologics license application
BOR best overall response
CAR chimeric antigen receptor
CMC chemistry, manufacturing and controls
CI confidence interval
CNS central nervous system
CR complete response
CRS cytokine release syndrome
CSF cerebrospinal fluid
CSR clinical study report
CTCAE common terminology criteria for adverse events
DMC data monitoring committee
DLBCL diffuse large B-cell lymphoma
DLT dose-limiting toxicity
DOR duration of response
eCTD electronic common technical document
ECOG eastern cooperative oncology group
EEG electroencephalogram
EORTC European organization of research and treatment
ETASU elements to assure safe use
FDA food and drug administration
G-CSF granulocyte-colony stimulating factor
HRQoL health related quality of life
HLH/MAS hemophagocytic lymphohistiocytosis/macrophage activation syndrome
HSCT hematopoietic stem cell transplantation
IV intravenous
IMWG international myeloma working group
IMiD Immunomodulatory drug
IND investigational new drug application
ISS integrated summary of safety
IQR interquartile range
IRC independent response committee
IR information request
LTFU long-term follow up
mAb monoclonal antibody
MedDRA medical dictionary for regulatory activities
MR minimal response
MRD minimal residual disease
CTCAE Common Terminology Criteria for Adverse Event
NGS next generation sequencing

MM Multiple myeloma
MMSE mini mental status exam
NE not evaluable, not estimable
NESI neurotoxicity events of special interest
NHL non-Hodgkin lymphoma
NT neurologic toxicity
ORR objective response rate
OS overall survival
PD progressive disease
PFS progression-free survival
PI proteasome inhibitor
PI prescribing information/package insert
PK/PD pharmacokinetics/pharmacodynamics
PREA pediatric research equity act
PR partial response
PRO patient reported outcome
PS performance status
PT preferred term
RCL replication competent lentivirus
RCT randomized controlled trial
REMS risk evaluation and mitigation strategy
SAE serious adverse event
SAP statistical analysis plan
s CR stringent complete response
SCT stem cell transplantation
SD stable disease
SOC system organ class
SCE summary of clinical efficacy
SCS summary of clinical safety
SPD sum of the products of greatest diameter
TEAE treatment-emergent adverse event
VGPR Very good partial response

1. Executive Summary

The clinical review team recommends regular approval of idecabtagene vicleucel (also known as bb2121 or ABECMA) for the treatment of adult patients with relapsed or refractory multiple myeloma after 4 or more prior lines of therapy including an immunomodulatory agent (IMiD), a proteasome inhibitor (PI) and an anti-CD38 monoclonal antibody.

bb2121 is a genetically modified autologous T cell immunotherapy product consisting of autologous T cells transduced with a lentiviral vector (LVV) expressing a chimeric antigen receptor (CAR) targeting the B-cell maturation antigen (BCMA). The recommended regimen is a single dose of bb2121, with a dose range of 300-460 x10^6CAR+ T cells administered by IV infusion and preceded by fludarabine and cyclophosphamide conditioning for lymphodepletion.

bb2121 has orphan designation for the treatment of multiple myeloma. Therefore, this application does not trigger PREA.

The applicant's proposed indication for this product was the treatment of adult patients with multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody. In support of this proposal, the applicant submitted efficacy and safety data from the clinical study MM-001, a single arm, open-label, multicenter study that evaluated bb2121, preceded by conditioning therapy, in adults with relapsed and refractory multiple myeloma as well as supportive safety and efficacy data from Phase 1 study CRB-401. Supplemental safety data was provided from studies MM-001 Japan, MM-002 and MM-003.

Efficacy:

The efficacy of bb2121 is based on overall response rate (ORR), complete response rate (CR) rate and duration of response as determined by an independent response committee (IRC) in Study MM-001, which enrolled adults with relapsed and refractory (R/R) multiple myeloma after at least three prior lines of therapy including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody. Of the 140 subjects who underwent leukapheresis, 127 (91%) received conforming bb2121, 12 subjects did not receive the product (9%) and one subject who received non-conformal product (1%) was a non-responder. One hundred and twenty-seven subjects were evaluated for efficacy. The majority of the subjects (100/127;79%) were treated at the recommended dose schedule of 300-460 $x10^6$ CAR+ T cells. The median number of prior systemic therapies for these efficacy evaluable subjects was 6 (range 3-16). 85% of the subjects were triple class refractory to a proteasome inhibitor, an IMID and anti CD38 antibody, 95% were refractory to anti-CD38 antibody therapy and 26% were penta-refractory (refractory to 2 PIs, 2 IMiDs and anti-CD38 antibody therapy). In these 100 subjects, the overall response rate according to IMWG (International Myeloma Working Group, 2016) Uniform Response Criteria was 72% (95% CI:62%, 80%) with a stringent CR rate of 28% (95% CI:19%, 37%) and median time to first response was one month. Of the 72 subjects who achieved an objective response, the median duration of response was 11 months (95% CI 10.3, 11.4) and an estimated 35% (95% CI: 23, 47)maintained a response for at least 12 months. At a median follow up of 10.7 months, the median duration of response for stringent CRs was 19 months (95% CI 11.4, NE) and an estimated 65% (95% CI: 42, 81) maintained response for at least 12 months. Similar efficacy was observed in the triple class refractory subgroup. Study MM-001 met the study objective that ORR was statistically significantly greater than the prespecified null hypothesis rate of 50%.

Safety:

Study MM-001 was the primary source of the safety data and included a total of 127 subjects with relapsed and refractory myeloma treated with bb2121 across a dose range of 150.5 $x10^6$ to 518.5 $x10^6$CAR + T cells. Grade 3 or higher adverse reactions of special interest included cytokine release syndrome (9%), neurological toxicity (4%), hemophagocytic lymphohistiocytosis (1.6%), infections (23%), and prolonged cytopenia (61%). Main causes of death from bb2121 included CRS and HLH/MAS, bronchopulmonary aspergillosis in the setting of prolonged neutropenia from HLH/MAS, gastrointestinal bleeding from prolonged thrombocytopenia and CMV/pneumocystis carinii pneumonia. Prolonged cytopenia requiring stem cell rescue was observed in 2.3% of the subjects and warrants boxed warning along with CRS, neurotoxicity and HLH/MAS. New safety signals identified from other studies included in the BLA are cerebral edema, Grade 3 myelitis and Grade 3 parkinsonism which are included in the safety information of the label.

During study MM-001, life-threatening adverse reactions attributed to bb2121 were mitigated by mandated site and investigator training, careful site selection and monitoring, and instructions for early detection and management of the most serious complications. The life-threatening and fatal adverse reactions warrant warnings and precautions in the USPI, including a boxed warning for cytokine release syndrome (CRS), neurologic toxicity (NT), hemophagocytic

lymphohistiocytosis (HLH;/MAS) and prolonged cytopenia. FDA determined that a REMS with elements to assure safe use (ETASU) is necessary for bb2121. The focus of the REMS ETASU is site preparation, patient education, and risk mitigation strategies, with emphasis on early recognition and treatment of CRS and neurologic toxicity. HLH/MAS and prolonged cytopenia requiring stem cell rescue have been added to the REMS education materials and knowledge assessment to educate health care provider regarding these safety signals.
Long-term safety after treatment with bb2121, particularly regarding the risk of insertional mutagenesis-related secondary malignancies, remains a concern due to the limited duration of follow-up. Therefore, a post-marketing requirement (PMR) safety study is warranted. The applicant agreed to conduct an observational registry study that will collect safety information on a minimum of 1500 patients treated with the marketed product, including key early adverse reactions and follow-up for 15 years for detection and evaluation of secondary malignancies. No routine collection of samples to test for competent lentiviral replication is planned as part of this study.
In consideration of granting regular approval to bb2121 in relapsed or refractory myeloma patients who have received at least four prior lines of therapy, the clinical team considered the following aspects:

1) The magnitude of benefit observed with bb2121 in Study MM-001, specifically the determination that median DOR of 11 months in all responders (ORR=72%) and response duration of at least 12 months in an estimated 65% of the stringent CR (s CR=28%) subjects after administration of a single infusion constitutes clinical benefit in relapsed and refractory myeloma population.
2) Historical data in a myeloma population refractory to anti-CD38 antibody therapy demonstrating ORR of 29% in triple refractory subgroup and 38% for the “not triple refractory” subgroup with standard of care therapies.(Gandhi et al, 2019).
3) The available therapy for R/R myeloma population who have received at least four prior therapies and whose disease is penta-refractory (2 PIs, 2 IMiD and an anti-CD38 antibody). Selinexor in combination with dexamethasone has traditional approval with an ORR of 25%, CR rate of 1% and median DOR of 3.8 months.
While drugs approved under accelerated approval are not considered available therapies, these are discussed below to provide context to the efficacy data for bb2121. Belantamab approved under accelerated approval demonstrated an ORR of 31%, CR rate of 3% with 73% of the responders had DOR of ≥6 months in a triple class refractory myeloma population. The median duration of response was not reached given that the median follow up for this population was 6.3 months. Recently, accelerated approval was granted to melphalan flufenamide for relapsed or refractory myeloma after at least four prior lines of therapy and triple class refractory disease based on ORR of 24% and median DOR of 4.2 months(95% CI : 3.2, 7.6).
4) 88% of the efficacy evaluable population in Study MM-001 had received 4 or more prior lines of therapy with six median prior lines of therapy indicating that risk and benefit of bb2121 has been established in a later line setting(at least four prior lines).
For additional details, please refer to 11.4 Recommendations on Regulatory Actions.
In summary, Study MM-001 represents an adequate and well controlled study that demonstrated high response rates and durability of CR with an acceptable safety profile. Given the life-threatening nature of the disease in the indicated population, the adverse reactions of cytokine release syndrome (CRS), HLH/MAS neurotoxicity (NT) and prolonged cytopenia if managed appropriately, represent toxicities that are acceptable from a benefit-risk perspective. Thus, the overall benefit-risk profile favors regular approval of bb2121 in patients with relapsed or refractory multiple myeloma.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Table 1: Demographic Information for Study MM-001:

	Enrolled population n=140	bb2121Treated Population n=127	Efficacy population N=100
Age (years)			
Mean (STD)	60 (9)	59.8 (9.4)	60 (9.5)
Median (min, max)	60.5 (33, 78)	61 (33, 78)	62 (33, 78)
Sex n (%)			
Male	82 (58.6)	76 (59.8)	60 (60)
Female	58 (41.4)	51 (40.1)	40 (40)
Race n (%)			
Asian	3 (2.1)	3 (2.3)	2 (2)
Black or African American	8 (5.7)	6 (4.7)	6 (6)
White	113 (80.7)	102 (80.3)	78 (78)
Unknown	10 (7.1)	10 (7.8)	9 (9)
Other	6 (4.3)	6 (4.7)	5 (5)
Ethnicity n (%)			
Hispanic or Latino	13 (9.3)	10(7.8)	8 (8)
Non-Hispanic	112 (80)	103 (81)	80 (80)
Not reported	9 (6.4)	9 (7)	8 (7)
Other	6 (4.3)	5 (3.9)	4 (4)

Source: FDA Analysis

Enrolled population includes all subjects who underwent leukapheresis in Study MM-001.
bb2121 treated population includes all subjects who received conforming bb2121 at any dose level during the study (150.5 to 518.4 $x10^6$ CAR + T cells).
Efficacy population includes subjects who received conforming bb2121 at the dose range recommended for approval: Range 300 to 460 $x10^6$ CAR + T cells. Further details of the population are described in Section 6.1.10.

Reviewer's comment:
The median age of the study population was 60 years which is considerably lower compared to the general population of patients with MM (median age at diagnosis in the U.S. population is 69 years, NCI SEER). Overall, 20% of the population diagnosed with myeloma in the US is African American. However, only 6% of the study population is African American despite approximately 73% of the study population being enrolled from the US, raising concern about racial disparities in accessing clinical trials in multiple myeloma. No significant differences were identified in the demographics of the population treated at the recommended dose range compared to the entire study population and the enrolled population.

1.2 Patient Experience Data

Quality-of-life outcomes were assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC-QLQ-C30), EORTC-QLQ-MY20 (Multiple Myeloma Module) and the Euro Qol instrument EQ-5D-5L.

Reviewer Comment: The Applicant did not seek a labeling claim based on clinical outcomes assessment (COA) data and these data were not incorporated in the PI. The data were not evaluated as part of the application review, given the limitations of COA in uncontrolled, open-label trials. As with time-to-event endpoints, interpretation of patient-reported outcomes is challenging in uncontrolled clinical trials, because it is unclear to what extent the outcomes can be attributed to the treatment effect of the regimen vs. to underlying disease and patient characteristics.

Table 2: Patient Experience Data in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☒	Patient-reported outcome	Clinical Study Report:MM-001: Section 9.5.1.2
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

Source: FDA Analysis

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Multiple myeloma (MM) is a malignant hematological disorder characterized by the clonal proliferation of plasma cells producing a monoclonal immunoglobulin. Clinical manifestations of multiple myeloma include anemia, hypercalcemia, renal failure, osteolytic bone lesions, osteopenia, pathological fractures and infections.

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. Multiple myeloma primarily affects older individuals, with a median age at diagnosis of 69 years, only 10 percent of patients are younger than 50 years and 2 percent are younger than 40 years. Multiple myeloma is more frequently prevalent in men compared to women (approximately 1.4:1). While myeloma affects all races, the incidence in Africans Americans and blacks from Africa is two to three times higher compared to white population ;16.5/100,000 in blacks versus 8.2/100,00 in whites (SEER 21 2013-2017, estimates for males).
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* or penta-refractory** demonstrate low response rates and have poor overall prognosis. In a retrospective analysis of 249 MM patients with anti-CD38 antibody refractory disease who were treated with available therapies, overall response rate was 31% (ORR was 38% for the “not triple class refractory”, 29% for triple class or quad refractory population). While the duration of response was not provided for this population, the median PFS of 3.4 months and median OS of 9.3 months indicates that the responses were not durable. (Gandhi 2019). 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.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Standard of care for newly diagnosed multiple myeloma typically consists of treatment with a triplet or quadruplet regimen including a proteasome inhibitor, an immunomodulatory agent and corticosteroids. In patients deemed eligible for autologous hematopoietic stem cell transplant (ASCT),induction chemotherapy is followed by ASCT and maintenance therapy. There are multiple approved regimens for the treatment of relapsed or refractory myeloma (Table 3 and 4). There is no single standard for relapsed and refractory myeloma patients. A preferred order for regimens has not been established since there has not been a head to head comparison of these regimens. Most patients experience a serial relapse and the choice of therapy is determined by the response to prior therapies, aggressiveness of the relapse and the comorbidities. In general, three drug combinations are preferred given the patient’s tolerability.

At least two non-cross reacting drugs are used in a triplet combination and retreatment with a regimen that includes a particular drug or another drug in the same class may have clinical efficacy depending on duration of response with initial exposure. The main classes of agents are monoclonal antibodies, proteasome inhibitors, immunomodulatory drugs, alkylators, anthracyclines , corticosteroids, and other agents such as panobinostat, selinexor and most recent approval belantamab.

Three therapies are currently approved in the United States for the treatment of relapsed and refractory myeloma patients exposed to a proteasome inhibitor, an immunomodulatory agent and anti-CD38 antibody therapy: Selinexor, a nuclear export inhibitor in combination with dexamethasone has regular approval for treatment of penta-refractory myeloma population with 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. The efficacy data which was the basis for the approvals is summarized in Table 3b.Melphalan flufenamide, an alkylating agent, in combination with dexamethasone recently received accelerated approval in R/R myeloma patients who have received at least four prior lines of therapy with triple class refractory disease. There remains need for additional therapies in myeloma population refractory to major classes of anti-myeloma agents particularly, anti-CD 38 refractory myeloma.

Table 3: Currently Available Therapies for the Treatment of Relapsed or Refractory Multiple Myeloma

Drug	Approval	Indication	Endpoint	Trial design/Result
Velcade (Bortezomib)	Accelerated (2003)	At least 2 prior lines	ORR	Single arm trial: ORR 28%
Velcade (Bortezomib)	Regular (2005)	1-3 prior lines	TTP, OS	RCT: Velcade vs. Dex TTP: 6.2 vs. 3.5 months HR=0.55, OS: HR=0.57
Doxil (Liposomal doxorubicin)	Regular (2007)	1 prior line	TTP	RCT: Doxil +V vs. V TTP: 9.3 vs. 6.5 months HR=0.55
Revlimid (lenalidomide) with dex	Regular (2005)	1 prior line	TTP	RCT: Rd vs. Dex Study 1: TTP: 13.9 vs. 4.7 months (HR-0.28) Study 2: TTP: 12 vs. 4.7 months (HR=0.32)
Kyprolis (carfilzomib)	Accelerated (2012)	1 prior line	ORR	Single arm trial: ORR 23%
Kyprolis with Rd	Regular (2015)	1-3 prior lines	PFS	RCT: KRd vs. Rd PFS 26.3 vs.17.6 months HR=0.69
Kyprolis with Dex	Regular (2016)	1-3 prior lines	PFS	RCT: Kd vs. Vd PFS: 18.7 vs.9.4 months
Pomalyst (Pomalidomide)	Accelerated (2013)	At least 2 prior lines, including len and bortez	ORR	RCT: P vs Pd ORR: 7.4% vs. 29.2%
Pomalidomide and dexamethasone	Regular (2015)	At least 2 prior lines, including len and PI	PFS/OS	RCT: Pd vs. dex

Drug	Approval	Indication	Endpoint	Trial design/Result
				PFS: 3.6 vs. 1.8 months (HR=0.45) OS: 12.4 vs. 8.0 months (HR=0.70)
Farydak (Panobinostat) with Vd	Accelerated (2015)	At least 2 prior lines, including bortez and IMiD	PFS	RCT: FVd vs. Vd PFS: 10.6 vs.5.8 months (HR=0.52)
Ninlaro (ixazomib) with Rd	Regular (2015)	At least 1 prior line	PFS	RCT: Ixaz + Rd vs. placebo + Rd PFS: 20.6 vs. 14.7 months
(Darzalex) Daratumumab	Accelerated (2015)	At least 3 prior lines including PI and IMiD	ORR	Single-arm trial ORR: 29% (median 5 prior lines of therapy)
Darzalex with Rd	Regular (2016)	At least 1 prior line	PFS	RCT: DRd vs. Rd PFS: NE vs. 18.4 months (HR=0.37) ORR=91.3%
Darzalex with Vd	Regular (2016)	At least 1 prior line	PFS	RCT: DVd vs. Vd PFS: NE vs. 7.2 months (HR=0.39) (median 2 prior line of therapy) ORR=79.3%
Darzalex with Pd	Regular (2017)	At least 2 prior lines, including len and PI	ORR	Single-arm trial ORR: 59.2% (median 4 prior lines of therapy)
Empliciti (elotuzumab) with Rd	Regular (2015)	1-3 prior lines	PFS	RCT: ERd vs. Rd PFS: 19.4 vs.14.9 months (HR=0.70)
Empliciti with Pd	Regular (2018)	At least 2 prior lines, including len and PI	PFS	RCT: EPd vs. Pd PFS: 10.3 vs.4.7 months (HR=0.54)
Sarclisa (Isatuximab)with Pd	Regular (2020)	At least two prior therapies including Len and PI	PFS	RCT: Isa-Pd vs. Pd: 11.5 vs. 6.5 months (HR=0.59) (median 3 prior lines of therapy)
(Darzalex Faspro) Daratumumab hyaluronidase	Regular (2020)	At least 3 prior lines of therapies including a PI and IMiD, or double refractory to PI and ImiD.	ORR PFS	RCT: Darzalex Faspro s/c vs. IV daratumumab: ORR:41% vs. 37%. PFS: 5.6 months vs. 6.1 months (median 4 prior lines of therapy)

Drug	Approval	Indication	Endpoint	Trial design/Result
(Darzalex Faspro) Daratumumab hyaluronidase with Vd	Regular (2020)	At least 1 prior therapy		Extrapolated data from RCT of DVd vs. Vd. RCT: DVd vs. Vd PFS: NE vs. 7.2 months (HR=0.39) (median 2 prior line of therapy) ORR=79.3%
(Darzalex Faspro) Daratumumab hyaluronidase with Rd	Regular (2020)	At least 1 prior therapy	ORR	Single arm trial, ORR=91%
Xpovio (selinexor) with Vd	Regular (2020)	At least 1 prior therapy	PFS	RCT: SVd vs. Vd PFS: 13.9 vs. 9.5 months, (HR=0.70)

Source: FDA review

ORR = overall response rate; TTP = time to progression; OS = overall survival; RCT = randomized controlled trial; V = Velcade; dex = dexamethasone; HR = hazard ratio; Rd = Revlimid + dex; PFS = progression-free survival; KRd = Kyprolis + Rd; Kd = Kyprolis + dex; Vd = Velcade + dex; len = lenalidomide; PI = proteasome inhibitor; P = pomalidomide; Pd = pomalidomide + dex; FVd = panobinostat + Vd; Ixaz = ixazomib; IMiD = immunomodulatory agent; DRd = daratumumab + Rd; NE = not estimable; DVd = daratumumab + Vd; ERd = elotuzumab + Rd; EPd = Elotuzumab + pomalidomide+dexamethasone; Anti CD38 mAb=Anti CD38 monoclonal antibody; ISA= Isatuximab; s/c=subcutaneous; SVd= Selinexor, Velcade and dexamethasone; DOR=Duration of response; HR=hazard ratio . CR*= Complete response + stringent Complete response; mths=months; NR=not reached.

Table 4: Approvals for population previously exposed to a PI, an IMiD and anti-CD38 antibody Therapy

Drug	Median prior lines /Refractory status	Approval	Trial Design /N	ORR 95% CI	CR	Duration of Response (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

(Source: FDA review)

2.3 Safety and Efficacy of Pharmacologically Related Products

bb2121 is the first BCMA directed chimeric antigen receptor (CAR) T cell product approved for the treatment of patients with relapsed or refractory multiple myeloma. However, there are four FDA-approved CD19-directed CAR T cell products approved for other indications.
Tisagenlecleucel treats children and young adults with relapsed/refractory (r/r) B cell precursor acute lymphoblastic leukemia. Tisagenlecleucel, axicabtagene ciloleucel and lisocabtagene maraleucel treat adults with relapsed/refractory large B cell lymphoma.
Axicabtagene ciloleucel was recently approved for the treatment of relapsed or refractory follicular lymphoma after two or more lines of systemic therapy.
Brexucabtagene autoleucel is a CD19 directed CAR T product that was granted accelerated approval for the treatment of relapsed/refractory mantle cell lymphoma.
Clinical experience with these agents has revealed a distinct pattern of toxicity, including infections and cytopenia, but most notable for cytokine release syndrome and neurological toxicity.
Cytokine release syndrome (CRS) is a constellation of symptoms precipitated by cytokines and chemokines released from T cells upon their activation by engaging with target antigens. The hallmarks of CRS are fever, hypoxia, and hypotension, but patients may also experience malaise, fatigue, coagulation abnormalities, myalgias, and/or cardiac, renal, hepatic, or gastrointestinal toxicities. Symptom severity ranges from mild to life-threatening or fatal. Supportive care with intravenous (IV) fluids, supplemental oxygen, vasopressors, and endotracheal intubation and mechanical ventilation address the symptoms of CRS, while treatment with the IL-6 receptor monoclonal antibody tocilizumab works to control the underlying cytokine storm.
Hemophagocytic lymphohistiocytosis/ Macrophage activation syndrome (HLH/MAS) has also been reported following CAR T therapy and is characterized by hyperactivation of macrophages and lymphocytes, cytokine production, lymphohistiocytic tissue infiltration and immune mediated multiorgan failure. CRS and HLH/MAS might belong to the same spectrum of systemic inflammatory disorders with overlapping clinical and laboratory features.
The immune effector cell-associated neurotoxicity syndrome (ICANS) is less well-characterized than CRS. Its pathophysiology remains a poorly defined area of active investigation. ICANS may present as headache, encephalopathy, confusion, somnolence, seizures, tremor, delirium, motor weakness, aphasia, or cerebral edema, again running the gamut in severity from trivial to fatal. Most commonly, ICANS occurs in patients who also experience CRS, but it may also occur independently. Corticosteroids are the mainstay of treatment, supplemented by sedatives and anti-epileptics.
In addition to the above risks, CAR-T cell therapy using lentiviral vectors carries risk for insertional mutagenesis and thus secondary malignancies in its recipients. Therefore, all products have a pre- and post-marketing requirement of 15-year follow up for long term adverse events.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Idecabtagene vicleucel (bb2121) is a novel product with no prior human experience and has not been marketed in any country.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Key regulatory activity from the submission are summarized below:

October 30,2015: IND 16664 became active for bb2121 under the sponsorship of Bluebird Bio.

May 11,2016: Orphan drug designation (ODD #(b) (4)) granted to bb2121 for the treatment of multiple myeloma. Per the Pediatric Research Equity Act (PREA) and 21 Code of Federal Regulations (CFR) 314.55(d), ODD products are exempt from pediatric study requirements. As such, the applicant did not include a pediatric assessment in this biologics license application (BLA) for bb2121.

May 30, 2017: End of Phase 2 meeting with sponsor re. clinical development plan for bb2121, specifically MM-001. (Meeting ID # 10784); Agency recommended that sponsor consider a randomized controlled trial comparing bb2121 to another therapy. Agency recommended that sponsor clarify the protocol eligibility criteria related to number of prior therapies and regimens required for study participation and that protocol include definitions for relapsed or refractory myeloma. FDA recommended that subjects without evidence of medullary disease (solitary plasmacytoma) be excluded from the protocol to allow for a prognostically homogenous study population. Sponsor was advised to include information about bridging therapies, specifically the plan to measure disease after completion of bridging in the protocol. To ensure interpretability of results from a single arm trial, Agency recommended that sponsor minimize missing data and study dropouts, accurately capture subject disposition, record bb2121 dose received by each subject and consider central radiology review for efficacy outcomes that require imaging.

July 11, 2017: FDA notified of IND ownership change from Bluebird Bio to Celgene Corporation.

September 19,2017: bb2121 granted "Breakthrough therapy Designation" (BTD) for the treatment of patients with BCMA-expressing multiple myeloma refractory to or relapsed after at least three lines of prior therapies including a proteasome inhibitor, an immunomodulatory agent and daratumumab.

March 1, 2018: Type B BTD (CRMTS #11071) multidisciplinary meeting: Initial agreement was reached with the sponsor that high and durable overall response rate (ORR) may be considered a suitable endpoint for Study MM-001. FDA recommended a minimum follow up of 9-12 months for duration of response (DOR) given the durability of response noted in recent approvals. Agency clarified that the basis of the approval and the approval pathway for bb2121 will be determined during review of the BLA in context of the available therapies. Sponsor notified its plan to conduct an RCT (MM-003) comparing bb2121 to triplet therapy (daratumumab, pomalidomide and dexamethasone) to support future label expansion in third line setting. Agency provided feedback regarding the eligibility criteria, the appropriate control arm and efficacy endpoints for the RCT study. Agency recommended CDRH consultation to develop a validated assay for BCMA and for the MRD assay.

June 4, 2018: E-mail communication: Sponsor communicated its plan to increase the upper end of dose range for bb 2121 to 450x10e6 CAR+ T cells in Study MM-001 given the safety and efficacy data at the higher dose in the Phase 1 study. Agency did not agree with sponsor's proposal to use efficacy data from 80 subjects including 15 subjects treated at upper end of dose range at 400 $x10^6$ CAR+ T cells in MM-001 with supportive data from Study CRB-401 as basis for BLA submission. FDA recommended that sponsor enroll sufficient number of subjects at higher dose (450x10e6 CAR+ T cells) in study MM-001 to support approval at that target dose. In response, sponsor proposed to increase sample size by expanding enrollment to up to

140 subjects with plan to treat 119 subjects in MM-001. This increase in sample size resulted in increased statistical power for primary endpoint (ORR) and key secondary end point (CR rate).

July 20, 2018: Type B meeting (CRMTS# 11288); Written Responses: Agency did not recommend pooling of efficacy data for 150 million dose cohort with the higher doses given the lower ORR and small sample size noted in this dose cohort. FDA notified the sponsor that the proposed dose for labeling purposes will be review issue and will depend on the adequacy of the data. Given that the efficacy data from MM-001 was premature and with the uncertainty in product comparability between studies MM-001 and CRB-401, agreement could not be reached regarding pooling of data for efficacy across dose range or studies. Agency recommended that discussion regarding pooling of efficacy data be scheduled at the time of pre-BLA meeting.

November 2, 2018: Agency accepted the proprietary name ABECMA.

May 3, 2019 (CRMTS # 11744): Meeting with the sponsor to reach agreement on the proposed content and format of the clinical sections of the BLA. FDA recommended that sponsor submit duration of response (DOR) data from approved agents in a comparable population to provide context to the efficacy observed with bb2121 in MM-001. FDA accepted sponsor's proposal to not pool efficacy data for MM-001 and CRB-401 (not submit ISE) but rather submit efficacy data in parallel within Summary of Clinical Efficacy with pooled datasets from both studies included in Section 5.3.5.2

July 24, 2019: Type B meeting request: Written response only: Agency communicated concerns about the real-world evidence (RWE) study (NDS-MM-003) which was being conducted to provide an indirect comparison of effectiveness of bb2121.Issues with the RWE study include selection of a population which may not be comparable to subjects enrolled in Study MM-001 due to missing baseline patient characteristics, missing or absent data on efficacy assessments which may bias the outcomes and heterogeneity of real world data from different databases that will be collated for analysis.

November 29, 2019: E-mail correspondence regarding SAP for Study MM-001: Agency recommended that BLA submission identify subjects who are penta-refractory, and that SAP prespecify the efficacy adjudication for subjects who attain response after bridging or do not have baseline assessment after bridging and prior to receiving bb2121. Agency recommended that primary analysis for MRD negativity be limited to CR subjects in keeping with FDA guidance.

December 12, 2019: Pre-BLA meeting (CRMTS#12106): Agreement was reached to integrate efficacy data for subjects treated at 150x10e6 CAR+ T cells across studies MM-001 and CRB-401 given the limited sample size (four subjects) in study MM-001.To provide adequate durability of response follow up (≥9 months) for subjects treated at 450x10e6 CAR+T cells, sponsor proposed to provide a 30-day efficacy update with a data cut off on January 14, 2020. FDA agreed that the efficacy update could be provided as a late submission component.

March 30, 2020: Original BLA 125724 submitted.

May 11, 2020: FDA issued a refusal to file letter due to CMC related issues.

June 25, 2020: Type A meeting held with Applicant to discuss Refusal to File letter dated May 11,2020. The new BLA will include efficacy update with data cut-off on Jaunary 14, 2020 upon

submission. Agreement reached regarding for thedata cut off dates for the 90-day safety update:
MM-001, CRB-401, MM-001-Japan: Data cut off April 7, 2020
MM-002 and MM-003: Data cutoff date June 5, 2020.

July 27,2020: Original BLA 125736 resubmitted.

2.6 Other Relevant Background Information

Four protocol amendments were filed to study MM-001 prior to the data cutoff date of 14 January 2020.A summary of major changes associated with each amendment is provided below:

Amendment 1(November 2017): This amendment was introduced prior to enrollment of any study subjects. Eligibility criteria were updated to exclude subjects with a history of subarachnoid hemorrhage, other central nervous system (CNS) bleed and therapeutic anticoagulation due to increased risk of bleeding associated with CRS and NT. This change was triggered by an AE of subarachnoid hemorrhage that occurred in the setting of Grade 4 neurotoxicity in Study CRB-401. Eligibility criteria was amended to exclude Waldenstroms syndrome, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin change) or amyloidosis. The inclusion criteria for defining adequate bone marrow function at screening was updated to ANC ≥ 1000 cells/mm3 and platelet count ≥50,000 cells/mm^3 in the absence of growth factor within 7 days or transfusion support within 7 days of screening. The safety monitoring plan was updated to require 14-day hospitalization and twice weekly visits in Weeks 3 and 4. Specific guidance on monitoring and management of Grade 3 and 4 neurotoxicity was updated including management of cerebral edema.

Amendment 2 (June 2018): The upper bound of the dose range for bb2121 was increased from 300 $x10^6$ to 450 $x10^6$ CAR+ T cells based on safety and efficacy data from Study CRB-401. The sample size was increased to enroll up to 140 subjects with up to 119 subjects treated with bb2121 . This resulted in increased statistical power for primary and key secondary endpoints. Interval between bridging therapy and leukapheresis was extended from 7 to 14 days.

Amendment 3 (September 2018): In response to a fatal CRS event in a subject who had clinical deterioration due to disease related complications prior to treatment with bb2121, the protocol was amended to require re-assessment of subject eligibility within 72 hours of lymphodepletion. This was to ensure absence of intercurrent illness that may increase risk of excessive toxicity from the investigational therapy. The protocol was amended to delay bb2121 infusion until any active infection resolved and organ toxicities recovered to ≤ Grade 2.

Amendment 4 (July 2019): MRD assessment by (b) (4) was changed from a secondary endpoint to an exploratory endpoint. MRD response was not planned to be adjudicated by IRC. The timing of the primary analysis was modified from 6 months to 10 months after bb2121 infusion based on health regulatory interactions.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty.

3.2 Compliance with Good Clinical Practices and Submission Integrity

MM-001 is being conducted under IND 16664 in compliance with Good Clinical Practice. The Bioresearch Monitoring (BIMO) team elected to inspect four (4) U.S clinical study sites for high priority inspection. These sites were: Hackensack University Medical Center, UT Southwestern Medical Center, UCSF Parnassus and Icahn School of Medicine at Mount Sinai. BIMO's selections were based on the sites' relatively high numbers of enrolled subjects, financial disclosures, and preliminary data review.

No significant inspectional findings were observed. Please refer to BIMO memo for further details:

Table 5: BIMO Inspection Sites

Site ID	Establishment for Inspection	FDA form 483 issued	Inspection Status
102	Hackensack, New Jersey	No	No action indicated
104	Dallas, Texas	No	No action indicated
108	San Francisco, California	No	No action indicated
109	New York, New York	No	No action indicated

Source: BIMO Review Memo

3.3 Financial Disclosures

Table 6: Financial disclosures

Covered clinical study (name and/or number):MM-001 and CRB 401
Was a list of clinical investigators provided? X Yes ☐ No (Request list from applicant)
Total number of investigators identified: 19 principal investigators and 296 other important personnel for MM-001 9 principal investigators and 222 other important personnel for CRB 401
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 8 investigators in MM-001 4 investigators in CRB-401

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: 0 Significant payments of other sorts: 12 _____ Proprietary interest in the product tested held by investigator:0 _____0 Significant equity interest held by investigator in sponsor of covered study:0 _____ Is an attachment provided with details of the disclosable financial interests/arrangements? X Yes ☐ No (Request details from applicant) Is a description of the steps taken to minimize potential bias provided? X Yes ☐ No (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0 Is an attachment provided with the reason? ☐ Yes ☐ No (Request explanation from applicant) N/A

Source: FDA review

Study MM-001:
One principal investigator and one sub-investigator each disclosed total payments greater than $25,000 from advisory board, consultant fees, speaker fees and honoria. The disclosure from principal investigator exceeded $100,000. Other significant financial disclosures included stock ownership by a sub investigator ($80,000) and spouse of another sub investigator ($47,000). Potential bias in efficacy results introduced by these payments was minimized through the use of an independent response committee (IRC) who reviewed efficacy data and adjudicated response to therapy for each subject based on IMWG uniform response criteria.

Study CRB-401:
Two principal investigators and 1 sub-investigator each disclosed payment greater than $100,000 from consultant fees, speaker fees, honoraria, and research agreement. One principal investigator received over $1million from CRADA agreement. The principal investigator is an inventor on a patent application of (b) (4) . This principal investigator enrolled 10 subjects out of 62(15%) which is unlikely to significantly influence the efficacy results from the study.
The primary objective of CRB-401 was safety and dose finding. A safety review committee reviewed safety data and made dosing and cohort expansion decisions. Main efficacy analysis was based on response assessments determined by investigators according to IMWG uniform response criteria. However, disease response was also analyzed by IRC minimizing investigator bias.

Reviewer comment:
The applicant employed appropriate risk-reduction strategies to minimize bias. The disclosed significant payments are unlikely to have negatively impacted the integrity of MM-001 or CRB-401's conduct or findings.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

Idecabtagene vicleucel (bb2121) is a BCMA directed, genetically modified, autologous T cell immunotherapy. To prepare bb2121, a patient's own T cells are harvested and genetically modified *ex vivo* by lentiviral transduction to express a chimeric antigen receptor (CAR) comprising an anti-BCMA single chain variable fragment linked to 4-1BB and CD3 ζ co-stimulatory domains. The anti-BCMA CAR T cells are expanded and infused back in to the patient, where they can recognize and eliminate BCMA-expressing target cells.

1.In Study CRB-401, subjects were treated with product manufactured using version (b) (4). In Study MM-001, subjects were treated with product manufactured using version (b) (4) All manufacturing versions across the clinical development program were deemed comparable by the CMC review team. Version (b) (4) is the manufacturing process for the commercial product.

2. Filling strategy: In Study MM-001, on-site manipulation resulted in bb2121 dose administered close to the individual target doses. To eliminate on-site manipulation and potential dosing error, the applicant has developed a validated commercial fill procedure in which the drug product is filled into multiple bags using a single bag size filled with the same volume yielding 2-5 bags per patient. With this fill strategy, the average dose administered per subject will be 390 $x10^6$ CAR+ T cells delivered in 2-3 bags Post-late cycle meeting, a modified approach to the validated filling scheme was considered so as to provide an average dose of 420$x10^6$ CAR+ T cells delivered in 3-4 bags per patient. Even with this optimized commercial fill strategy, it is estimated that 36% of the patients treated with bb2121 may receive lots with <400$x10^6$ CAR+ T cells with the recommended dose range of 300-460 $x10^6$ CAR+ T cells.

Reviewer's comment: Given the dose response relationship observed within the recommended dose range (numerically higher ORR, CR and median DOR) with 440-460 $x10^6$ compared to 300-340 $x10^6$ CAR + T cells, we recommend that the applicant further optimize the filling strategy to accommodate higher end of the dose range (up to 460$x10^6$ CAR+ T cells).

3.Recent reports of MDS and AML in sickle cell disease patients treated with Lentiglobin bb305, a gene therapy product sponsored by Bluebird Bio. have resulted in temporary suspension of the clinical trial by the sponsor and additional work up is underway to evaluate the risk of insertional oncogenesis with the lentiviral vector used in this product. Given this ongoing concern, specific questions were raised with the CMC team regarding 1) the similarity between the lentiviral vector (LVV) used in bb2121 and bb305 2) the risk of insertional oncogenesis with bb2121. CMC team explained that while LVV used in bb2121 has the (b) (4) compared with LVV used in bb305, they have (b) (4). Therefore, CMC considers bb2121 to have distinct risk for insertional mutagenesis compared to bb305. In addition, CMC has reviewed insertional analysis data for bb2121 which support lack of insertional mutagenesis.

4. All subjects in MM-001 were treated at sites affiliated with a cell-processing facility, In the commercial setting, no on-site dose manipulation of bb2121 is allowed Therefore, CMC is not restricting dispensation of bb2121 to sites with a cell processing facility. Clinical team recommended that CMC ensure maintenance of cold chain, chain of custody and appropriate

storage facilities for free standing infusion centers not affiliated with a cell processing facility. The method of receipt and storage of bb2121 will be either on-site storage, where product is transferred to on-site vapor phase liquid nitrogen storage or just-in-time-delivery, where bb2121arrives on or near the date of infusion and remains in a liquid nitrogen dry vapor shipper until the product is thawed for patient's administration. The liquid nitrogen shipper has an 8-day expiration. In the event of unforeseen delay in administration of the product beyond the expiration of the shipper, product could be returned to the applicant and turned around within 48 hours of the initial pick up at the infusion site. Alternatively, if available, a replacement product can be delivered to the infusion site within 24 hours.

Reviewer's comment: As a part of the commercial site on-boarding and activation process, all sites are required to complete training including chain of identity, product handling, receipt, storage and product administration. In addition, Section 2.2 of the label includes a section that outlines how the product will be handled upon receipt at the infusion centers. Overall, the plan outlined for product handling at sites without on-site cold storage facilities appears reasonable from clinical perspective.

4.2 Assay Validation

Per Chemistry, Manufacturing and Controls (CMC) reviewer, the assays that were utilized for the bb2121 manufacturing and cell persistence determination, and immunogenicity were validated.

4.3 Nonclinical Pharmacology/Toxicology

Per FDA's pharmacology and toxicology reviewer, no carcinogenicity or genotoxicity studies have been conducted with bb2121.The Applicant has conducted integration site analysis across 20 clinical lots of bb2121.There was no evidence of integration preference for promoter region or region near oncogenes and polyclonality was observed with highest frequency of any one insertion event of (b) (4). An independent growth assay did not exhibit any cytokine independent growth indicative of malignant transformation. Based on this data, the pharmacology/toxicology team is not recommending a post-approval study of insertional mutagenesis.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

ABECMA (bb2121)) is a genetically modified autologous T cell immunotherapy product consisting of autologous T cells transduced with a lentiviral vector (LVV) expressing a chimeric antigen receptor (CAR) targeting the B-cell maturation antigen (BCMA). The 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 anti-BCMA 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 of bb2121 results in CAR+ T cell proliferation, cytokine secretion, and subsequent cytolytic killing of BCMA-expressing cells.

4.4.2 Human Pharmacodynamics (PD)

Markers of T cell activation such as IL-2, IL-6 , IFN-gamma and TNF were induced in a dose dependent manner after bb2121 infusion. In general, peak levels of these factors were observed within 7 days post-infusion and they returned to baseline level within one month.
After bb2121 infusion, soluble BCMA (sBCMA) levels decreased and reached a nadir within 2-3 months. The magnitude and kinetics of sBCMA change from baseline to nadir was comparable for 300 and 450 $x10^6$ CAR+ T cell dose cohort. In general, responders had lower median

soluble BCMA concentrations at baseline and nadir (median concentrations at nadir was below LLQ) compared to non-responders (median sBCMA at nadir was 243ng/ml).

4.4.3 Human Pharmacokinetics (PK)
Following infusion, bb2121 exhibited rapid multi-log expansion followed by a bi-exponential decline. The median time to maximal expansion in peripheral blood (T_{max}) occurred at 11 days post-treatment. Persistence of bb2121 in peripheral blood was observed for up to one-year post-infusion. In general, the exposure of bb2121 increased in a dose-dependent manner across the dose range. However, due to high inter-subject variability, there was overlap in exposure across the dose range.
Please refer to the Clinical Pharmacology Review Memo for additional details.

The CDER pharmacometric team performed a dose response assessment between 460 to 518 $x10^6$ CAR+T cells to consider extending the higher end of the dose range.This was a univariate analysis which was performed using a logistic regression model. The limitations of the analysis include lack of a validated model, absence of a training and a validated dataset to support the model, limited sample size of 5 subjects treated within the dose range in the primary study MM-001 and pooing of data across studies (CRB-401 and MM-001)with different eligibilities , and schedule assessments which preclude pooled clinical efficacy analysis.

4.5 Statistical

Please see the statistical review memo for details.
The statistical reviewer verified the key efficacy endpoint analyses.

4.6 Pharmacovigilance

The safety concerns of CRS and NT require that ABECMA be available in the context of a REMS program with elements to assure safe use (ETASU) in place to ensure that benefits of receiving the drug product outweigh the risks. The following are the elements of the risk mitigation strategy:

<u>For hospitals and associated clinic(s):</u>

To become certified to dispense ABECMA:

- Have a minimum of two doses of tocilizumab available on-site for each patient for immediate administration (within 2 hours).
- Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the hospital and associated clinic(s).
- Have the authorized representative complete the ABECMA REMS Training Program provided by the REMS Program in person or via live webcast.
- Have the authorized representative successfully complete the Knowledge Assessment and submit it to the REMS Program.
- Have the authorized representative enroll in the REMS Program by completing the Site Enrollment Form and submitting it to the REMS Program.
- Train all relevant staff involved in prescribing, dispensing, or administering of ABECMA and/or managing CRS and neurologic toxicity on the REMS Program requirements using the Training Program.
- Have all relevant staff involved in prescribing, dispensing, or administering of ABECMA and/or managing CRS and neurologic toxicity successfully complete the Knowledge Assessment.

- Establish processes and procedures to ensure relevant new staff involved in the prescribing, dispensing, or administration of ABECMA and/or managing CRS and neurologic toxicity are trained and complete the Knowledge Assessment.
- Establish processes and procedures to verify that a minimum of two doses of tocilizumab are available on-site for each patient and are ready for immediate administration (within 2 hours).
- Establish processes and procedures to provide patients with the Patient Wallet Card.

Prior to dispensing:
- Verify that a minimum of two doses of tocilizumab are available on-site for each patient and are ready for immediate administration (within 2 hours) through the processes and procedures established as a requirement of the REMS Program.

Prior to infusion:
- Provide the patient with the Patient Wallet Card

To maintain certification to dispense:
- Have a new Authorized Representative enroll in the REMS Program by completing the Site Enrollment Form.

To maintain certification to dispense, if ABECMA has not been dispensed at least once annually from the date of certification in the REMS Program:
- Train all relevant staff involved in prescribing, dispensing, or administering of ABECMA and/or managing CRS and neurologic toxicity on the REMS Program requirements using the Training Program.
- Have all relevant staff involved in prescribing, dispensing, or administering of ABECMA and/or managing CRS and neurologic toxicity successfully complete the Knowledge Assessment

At all times:
- Report any serious adverse event suggestive of CRS or NT to Celgene or FDA.
- Maintain records of staff REMS program training
- Maintain records that processes and procedures required by REMS are in place and are being followed and provide this documentation upon request to Celgene or a third party acting on behalf of Celgene.
- Comply with audits carried out by Celgene Inc., or a third party acting on behalf of Celgene, to ensure that all training, processes, and procedures are in place and are being followed

<u>For Applicant:</u>
The Applicant must provide training to relevant staff who prescribe, dispense or administer ABECMA. Training includes: i) Live Training Program ii) Knowledge Assessment. The training must be provided in-person or via live webcast.

To support REMS program operations, Applicant (Celgene Inc.) must ensure the following:
- Ensure ABECMA is distributed only to certified hospitals or their associated clinics.
- Establish and maintain the REMS Program website, www.AbecmaREMS.com. The REMS Program website must include the option to print the Prescribing Information (PI), Medication Guide, and REMS materials. All product websites for consumers and healthcare providers must include prominent REMS-specific links to the REMS Program

website. The REMS program website must not link back to the promotional product website(s).
- Make the REMS Program website fully operational and all REMS materials available through website and call center.
- Establish and maintain a REMS Program Call Center for REMS participants at 1-888-423-5436.
- Establish and maintain a validated, secure database of all REMS participants who are enrolled and/or certified in the REMS Program.
- Ensure hospitals and their associated clinics are able to enroll in the REMS Program in person, online, fax and telephone.
- Notify hospitals and their associated clinics within 7 calendar days after they become certified in the REMS Program.

To ensure REMS participants' compliance with the REMS program, Celgene, Inc. must:
- Verify annually that the designated authorized representative for certified hospitals and their associated clinics remains the same. If different, the hospital and their associated clinics must re-certify with a new authorized representative.
- Maintain adequate records to demonstrate that REMS requirements have been met, including, but not limited to records of: ABECMA distribution and dispensing; certification of hospitals and their associated clinics, and audits of REMS participants. These records must be readily available for FDA inspections.
- Monitor hospitals and their associated clinics on an ongoing basis to ensure the requirements of the REMS are being met. Take corrective action if non-compliance is identified, including de-certification.

- Maintain an ongoing annual audit plan of hospitals and their associated clinics. Audit all certified hospitals and their associated clinics no later than 180 calendar days after the hospital places its first order of ABECMA to ensure that all REMS processes and procedures are in place, functioning, and support the REMS Program requirements. Certified hospitals and their associated clinics must also be included in Celgene's ongoing annual audit plan. Celgene must also take reasonable steps to improve implementation of and compliance with the requirements in the ABECMA REMS Program based on monitoring and evaluation of the ABECMA REMS Program.

The pharmacovigilance plan includes a long-term, prospective, non-interventional registry study in 1500 patients treated with bb2121.This PMR study will follow the recipients of bb2121 for 15 years to characterize the incidence and severity of selected AEs, including secondary malignancy. Secondary malignancies must be reported by treating physicians to the Applicant within 72 hours of knowledge of the diagnosis to expedite AE reporting and to initiate a separate, non-protocol-related process for tumor specimen processing, and testing for bb2121 vector sequence for secondary malignancies of T cell origin.

Reviewer's comment:
The REMS with ETASU and the PMR safety study are the recommendation of the clinical review team with concurrence from the pharmacovigilance reviewers from the Center for Biologics Evaluation and Research (CBER) Office of Biostatistics and Epidemiology (OBE), Center for Drug Evaluation and Research (CDER) Division of Risk Management (DRISK), and the CBER Safety Working Group. The goal of the REMS is to ensure that sites are prepared for the safety risks of bb2121 that were identified in the IND phase of product development. The PMR registry study addresses the theoretical concerns of insertional mutagenesis and/or the development of a bb2121 related secondary malignancy. The applicant is proposing to enroll approximately 1500 patients and follow each patient for up to 15 years in the registry study. The clinical review team agrees that the label inform of the requirement to monitor patients at the certified healthcare facility daily for at least seven days following infusion of bb2121 for signs and symptoms of CRS and neurologic events. This recommendation is based on the requirements in the protocol, the clinical data related to the timing of onset of neurologic and CRS events, and the availability of guidance to treat these serious adverse events. The knowledge of and experience with CAR-T cell therapy products has expanded over the intervening years, and with adequate safety procedures in place, outpatient monitoring is considered acceptable after bb2121 infusion.
Given the safety signals of HLH/MAS and prolonged cytopenia requiring rescue stem cell therapy, we recommend that educating health care providers regarding these adverse events be included under REMS with appropriate modification of the REMS training materials and knowledge assessment.
In addition, the primary safety endpoint of the PMR registry trial should be modified to include 1)HLH/MAS 2) prolonged cytopenia that requires rescue stem cell therapy including the timing of the transplantation and outcome of hematopoietic reconstitution and survival. The Applicant will submit annual report for prolonged cytopenia requiring rescue stem cell transplantation and secondary malignancies.
Discussions with the applicant are ongoing regarding the final REMS and ETASU documents. Please refer to the action letter for final wording of the PMR.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

The review of the clinical efficacy was based upon Study MM-001 clinical study report, case report forms, and submitted data, in addition to multiple information requests. Primary efficacy analyses were verified, and exploratory analyses were conducted using (b) (4) software.
The clinical review was primarily based upon Study MM-001 with the efficacy data cutoff date of 14 January 2020 for 127 subjects. The protocol design is described in section 6.1.2, Design overview.
The clinical safety review was primarily based upon analysis of 127 subjects in study MM-001 at the primary data cutoff date of 16 October 2019. Review of safety included review of the following: clinical study report (CSR), summary of clinical safety (SCS), ISS, analysis of datasets relevant to safety for Study MM-001, subject narratives, case report forms (CRFs) if needed, information in numerous information requests (IRs) and data in the public domain. (b) (4) was used to reproduce key safety analyses based on submitted analysis (ADaM) datasets. The 90-day safety update with a data cutoff date of April 7, 2020 had no additional subjects in study MM-001. No additional safety signals were identified.

Applicant provided safety data from 62 subjects in the supportive study CRB-401 in the integrated summary of safety (ISS) datasets. Safety data from three other studies:MM-001 Japan, MM-002 and MM-003 was included in the Summary of Clinical Safety. Study MM-003 is a randomized controlled study and to preserve randomization, only aggregate data in 22 subjects from the two treatment arms was presented. Overall, MM-001-Japan had three subjects who were treated and the safety data from MM-002 (31 subjects) and MM-003 were deemed not to be different from that of Study MM-001. (Please refer to Tables 6 and 8 regarding Studies MM-001, CRB-401, MM-001-Japan, MM-002 and MM-003),
Given the small number of subjects in these studies ,availability of only aggregate safety data from both arms (bb2121 and standard of care) in Study MM-003 and the adequate sample size of 127 subjects in Study MM-001, decision was made to not include these additional studies in detailed safety analyses.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

Please see 5.1 Review Strategy.

5.3 Table of Studies/Clinical Trials

Overview of studies for efficacy and safety:
Safety and efficacy analyses of this BLA application are based on Study MM-001.127 subjects who received conforming bb2121 are included in the safety analysis with a data cutoff date of October 16,2019. The efficacy analysis includes 127 subjects with an updated data cutoff that is 3 months later than the safety data cutoff (January 14, 2020).

Table 7: Table of Primary and Supportive Studies for bb2121

Trial	Design	Population	Primary Endpoint	N Treated	Data Cutoff
MM-001 Primary study for efficacy and safety	Single arm, open-label, multicenter Phase 2 study Dose Cohorts: 150 x 10^6 N= 4 300 x 10^6 N=70 450 x 10^6 N=53	Age ≥ 18 years with R/R* myeloma after ≥3 lines	ORR per IRC	N=127[a] for safety and efficacy	October 16, 2019 for safety January 14,2020 for efficacy
CRB-401 Supportive study for efficacy and safety	Single arm, open-label, multicenter Dose -escalation & Dose -expansion Phase 1 study Dose Cohorts: 50 x 10^6 N= 3 150 x 10^6 N=18 450 x 10^6 N=38 800 x 10^6 N= 3	Age ≥ 18 years Dose escalation: Relapsed or refractory myeloma after ≥3 lines Dose expansion: R/R myeloma after ≥3lines	Safety	N=62 for safety and efficacy	July 22,2019 for safety and efficacy

a=One subject treated with non-conforming product is not included in safety or efficacy analysis.
*Relapsed and refractory myeloma
IRC: Independent Response Committee
Dose is in CAR+ T cells
Source: BLA submission 125736;/0

Table 8: Long term follow up studies

Trial	Design	Population	Primary Endpoint	N Enrolled	Data Cutoff
GC-LTFU-001	Long-term follow-up protocol for subjects treated with gene-modified T Cells	All adult and pediatric subjects who received at least one gene-modified T cell infusion in a Celgene sponsored study after discontinuation from or completing the parent study	Safety: Delayed adverse events including new malignancies, autoimmune or hematological disorder	N=15[d]	July 22, 2019 (CRB-401) October 16, 2019 (MM-001)
LTF-305	Long-term follow up of subjects treated with bb2121	Subjects treated with bb2121 after completing follow up in Study CRB-401	Survival , Adverse events	N=20	July 22,2019

[d] Includes 5 subjects from Study MM-001 and 10 subjects from Study CRB-401; 4 of 10 subjects from Study CRB-401 were initially enrolled in Study LTF-305 and later transitioned to Study GC-LTFU-001.
Source: BLA submission 125736;/0

Reviewer's comments:

- We performed a detailed review of the efficacy and safety data from 127 subjects with relapsed and refractory myeloma who received conforming product in Study MM-001. Given the limited sample size of subjects (n=4) treated at 150 x10^6 CAR+ T cells in Study MM-001, efficacy data for this dose cohort was combined with supportive data from CRB-401 as agreed during the pre-BLA meeting. (See Section 6.1.11 Efficacy Analysis). Otherwise, efficacy and safety data from the pivotal Study MM-001 was adequate to support the review of the BLA submission. Given the adequacy of the data from the pivotal study and the differences in the eligibility criteria, schedule of assessments and collection of safety data, a pooled safety or efficacy analysis with supportive study CRB-401 was not performed.
- However, for purposes of safety assessment Study CRB-401 was evaluated to confirm the consistency of the safety findings from Study MM-001 and Study CRB-401. Thus, the review of CRB-401 was limited to the safety dataset (ADAE dataset) and relevant narratives for Study CRB-401. The notable difference between the safety finding between the two studies related to one event of focal cerebral edema in the setting of grade 4 neurotoxicity in Study CRB-401. This information was included in the safety information of the label. No additional safety signals were identified. Due to the limited nature of the review of Study CRB-401, detailed description of the study design and its results were not included as a separate subsection in Section 6 of the memo
- Safety data from the long term follow up studies were integrated and presented with the safety data for the primary studies.

In addition to MM-001 and CRB-401, the following additional studies are included for safety review:

Table 9: Overview of studies providing additional safety data for bb2121

Trial	Design	Population	Primary Endpoint	N Treated	Data Cutoff
MM-001-Japan	A Phase 2, Multicenter Study open in Japan. Dose : 450 x 10^6 CAR+ T cells	Age ≥ 18 years with R/R myeloma after ≥3 lines of therapy	ORR per IRC	3	October 16, 2019

Trial	Design	Population	Primary Endpoint	N Treated	Data Cutoff
MM-002	Phase 2, Open-label, single arm, multicenter, multicohort study. Dose: CAR+T cells 300 x 10^6: n=18 in Cohort 2 450 x 10^6 :n=13 in Cohort 1	Age ≥ 18 years Cohort 1: R/R myeloma after ≥3 lines of therapy Cohort 2a & 2b: Myeloma relapsed after 1 prior line of therapy Cohort 2c: High risk myeloma: less than VGPR to front line ASCT.	ORR and CR rate per IRC	31	October 16, 2019
MM-003	Phase 3, Multicenter, randomized, open-Label study. Control arm: DPd, DVd, IRd, Kd, EPd. Treatment arm: bb2121 Dose: 150-450 x 10^6 CAR+T cells	Age ≥18 R/R myeloma after 2-4 lines of therapy	PFS	22[C]	October 16, 2019

Source: BLA submission 125736;/0

R/R= Relapsed and refractory myeloma

c= To preserve the randomization of this ongoing study, only aggregated data from the 2 treatment arms are presented. The number of subjects exposed to bb2121 is not reported separately.

DPd= daratumumab, pomalidomide, dexamethasone

DVd= daratumumab, velcade, dexamethasone

IRd= Ixazomib, lenalidomide, dexamethasone

Kd=Carfilzomib, dexamethasone

EPd= Elotuzumab, pomalidomide, dexamethasone

Reviewer's comment:

- The clinical review team did not perform a detailed safety analysis given the limited number of patients treated in these studies, inclusion of R/R myeloma in setting other than 4th line and adequacy of the primary study for safety review. Review of the datasets, clinical summary of safety and narratives from these studies was performed One case of Grade 3 Myelitis was identified in Study MM-002 which was included in the safety information of the prescribing information. (Please see Section 8 for a brief narrative). As with Study CRB-401 the limited nature of the findings was the basis for not including a detailed description of the design of the study and results in a separate subsection under Section 6.
- The 90-day safety update for these studies presented safety data on 89 additional subjects treated in Studies MM-001 Japan and MM-002. A pooled safety analyses for adverse events of special interest was performed across studies MM-001, CRB-401, MM-002 (Cohort 1) and MM-001-Japan to evaluate a dose toxicity relationship for 300 x10^6 and 450 x 10^6 CAR+ T cells using this safety update. The 90-day safety update identified a new signal: one case of Grade 3 parkinsonism in Study MM-002 which was

included in the safety information of the label. Please see Section 8: Integrated overview of Safety for additional details

Additional data included in the BLA submission:

- Results from Study NDS-MM-003, a global non-interventional study comparing the findings from the pivotal Study MM-001 to the outcomes in the real-world subjects who matched the study population and received available alternative therapies.
- Systematic literature review and matching-adjusted indirect treatment comparison (MAIC), which used aggregate summary data from published studies for selinexor/dexamethasone and belantamab and subject-level data from Study MM-001.

Reviewer's comment:
Given the limitations of real-world data and MAIC, a detailed review of these studies was not conducted. Please see Section 9.2 for additional details.

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)

The application was not presented to an Advisory Committee as it did not raise significant efficacy concerns or any new safety concerns.

5.4.2 External Consults/Collaborations

MRD evaluated by NGS is a secondary endpoint and the primary analysis for MRD negative response was based on sensitivity of (b) (4). The clonoSEQ Assay is an in vitro diagnostic that uses (b) (4) next-generation sequencing (NGS) to identify and quantify rearranged (b) (4) receptor gene sequences, as well as translocated (b) (4) sequences in DNA extracted from bone marrow from patients with multiple myeloma. This assay was originally approved for use in multiple myeloma, as a *De Novo* (DEN170080) on 9/28/2018 in patient's bone marrow for monitoring burden of disease before and after treatment. A CDRH consult was obtained to ensure that the Adaptive Clono SEQ next generation sequencing assay (NGS) was analytically validated for use in relapsed/refractory multiple myeloma. CDRH review team confirmed that this assay was being utilized according to the FDA approved label and instructions for use. No further validation was recommended. With the Adaptive Clono SEQ NGS, all subjects must have calibration performed on pre-treatment (at screening or baseline) samples to identify a trackable sequence. Post-treatment monitoring for MRD can only be performed if a trackable sequence is identified at screening or baseline. To confirm that the NGS assay has efficacy at (b) (4) (primary threshold used for MRD analysis), a limit of detection of (b) (4) was utilized which require a DNA input of at least (b) (4) micrograms.

5.5 Literature Reviewed (if applicable)

1. Gandhi UH, Lakshman A, Gahvari Z, McGehee E, Jagosky MH, Gupta R, et al. Natural History of Patients with Multiple Myeloma Refractory to CD38-Targeted Monoclonal Antibody-Based Treatment. Blood. 2019;132:3233.
2. NCI SEER Cancer Stat Facts, 2019. Cancer Stat Facts: Myeloma. https://seer.cancer.gov/statfacts/html/mulmy.html.
3. Kumar S, Paiva B, Anderson K, et al. International Myeloma Working Group Consensus Criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncology 2016;17: e328-46.
4. Lee DW, Gardner R, Porter DL, et. al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014; 124 (2): 188-195.

5. Shah N, Chari A, Scott E, Mezzi K, Usmani SZ. B-cell maturation antigen (BCMA) in multiple myeloma: rationale for targeting and current therapeutic approaches. Leukemia. 2020;34(4):985-1005.
6. Salem DA, Maric I, Yuan CM, Liewehr DJ, Venzon DJ, Kochenderfer J, et al. Quantification of B-cell maturation antigen, a target for novel chimeric antigen receptor T-cell therapy in Myeloma. Leuk Res. 2018;71:106-111.
7. Seckinger A, Delgado JA, Moser S, Moreno L, Neuber B, Grab A, et al. Target expression, generation, preclinical activity, and pharmacokinetics of the BCMA-T cell bispecific antibody. EM801 for multiple myeloma treatment. Cancer Cell. 2017;31(3):396-410.

6.1 Study MM-001(KarMMa)

Study MM-001 was the pivotal study that constitutes the primary evidence of safety and efficacy of bb2121 in the treatment of adult patients with relapsed and refractory myeloma who have received at least three prior regimens including a proteasome inhibitor (PI), an immunomodulatory agent (IMiD) and an anti-CD38 antibody.

6.1.1 Objectives (Primary, Secondary, etc.)

Primary Objective: Evaluate the efficacy as defined as overall response rate (ORR) of bb2121 in subjects with relapsed and refractory multiple myeloma (RRMM) .

Secondary Objective:
Assess:

- Safety of bb2121 in subjects with relapsed and refractory multiple myeloma.
- Complete response (CR) rate, time to response (TTR), duration of response (DOR), progression free survival (PFS), time to progression (TTP) and overall survival (OS).
- The proportion of subjects who attain minimal residual disease (MRD) negative status by next generation sequencing (NGS).
- The expansion of chimeric antigen receptor (CAR)+ T cells in the peripheral blood.
- The development of an anti-CAR antibody response.
- The changes in health-related quality of life (HRQoL) using the European Organization for Research and Treatment of Cancer – Quality of Life C30 questionnaire (EORTC-QLQ-C30), the European Quality of Life-5 Dimensions health state classifier to 5 Levels (EQ-5D-5L) and the European Quality of Life Multiple Myeloma Module (EORTC-QLQ-MY20).

6.1.2 Design Overview

MM-001 was an open label, single-arm, multicenter, international, Phase 2 study of bb2121's safety and efficacy in the treatment of adults with relapsed and refractory multiple myeloma. The study consisted of 3 periods: pre-treatment (screening and leukapheresis), treatment (lymphodepletion and bb2121 infusion) and post-treatment (for a minimum of 24 months post-bb2121 infusion or until documented disease progression whichever is longer). Upon discontinuation from this study, subjects were asked to participate in the separate LTFU study (Study GC-LTFU-001) to be monitored for delayed toxicities from bb2121 for 15 years. The first subject was infused on 5 February 2018 with data cut off for this BLA on October 16,2019 for safety and January 14,2020 for efficacy. The enrollment is complete, and the study is ongoing for follow up.

Reviewer's comment: At the time of study inception, the relapsed and refractory myeloma population eligible for this study did not have an accepted standard of care therapy rendering a

randomized controlled trial design infeasible. This is reflected in the significant heterogeneity in the treatments received by a comparable cohort of relapsed and refractory myeloma patients included in the real-world evidence study (NDS-MM003) included in the submission. Approximately 90 different regimens were administered to these 190 R/R myeloma patients treated in the real-world setting and included in the study. This indicates the lack of an accepted standard of care for this population. (For details on NDS-MM-003,see Section 9.2) Therefore, a single arm trial design is reasonable for this late line population .

6.1.3 Population

Key Inclusion criteria:

Adults with relapsed and refractory multiple myeloma were eligible to enroll with the following criteria:

- Must have received at least 3 prior myeloma treatment regimens (induction with or without hematopoietic stem cell transplant and with or without maintenance therapy was considered a single regimen).
- Must have undergone at least 2 consecutive cycles of treatment for each regimen unless progressive disease was the best response to the regimen.
- Must have received a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody.
- Must be refractory to the last treatment regimen.

Additional inclusion criteria included:

- ECOG performance status of 0 or 1
- Measurable disease including at least one of the criteria below:
    - Serum M protein ≥1gm/dl.
    - Urine M protein ≥200mg/24 hours.
    - Involved serum free light chain ≥100mg/L provided serum free light chain (FLC) ratio is abnormal.

Key Exclusion criteria:

- Known CNS involvement with myeloma.
- History of or active plasma cell leukemia or amyloidosis.
- Absence of biochemical measurable disease such as solitary plasmacytoma or non-secretory myeloma.
- AST and/or ALT>2.5x ULN and total bilirubin >1.5xULN except with Gilbert's syndrome.
- Creatinine clearance ≤45ml/minute using Cockcroft-Gault equation.
- Inadequate bone marrow function defined by ANC<1000cells/mm3 in the absence of growth factor support and platelet count<50,000/mm3 in the absence of transfusion support.
- Left ventricular ejection fraction <45% measured by ECHO or MUGA.
- Previous history of an allogeneic stem cell transplantation.
- HIV infection.
- Seropositivity for and with active hepatitis B or hepatitis C viral infection.
- History of class III or IV congestive heart failure or severe non-ischemic cardiomyopathy, unstable angina, myocardial infarction or ventricular arrhythmia within 6 months of study treatment.
- Inadequate pulmonary function defined as oxygen saturation <92% on room air .

6.1.4 Study Treatments or Agents Mandated by the Protocol

Leukapheresis was performed approximately 4-5 weeks prior to planned bb2121 infusion. Up to two leukapheresis procedures were allowed to obtain ≥200 x10^6target mononuclear cells.

Anti-myeloma bridging therapy was allowed after leukapheresis for disease control while bb2121 was being manufactured, prior to administration of lymphodepletion chemotherapy. There was no protocol specified criteria that triggered bridging therapy and it was left at the investigators' discretion. Bridging therapy had to be completed at least 14 days before the initiation of the first dose of lymphodepletion chemotherapy. Bridging therapies could include corticosteroids, alkylating agents, immunomodulatory drugs, proteasome inhibitors and anti-CD38 antibodies as single agents or in combination. Anti-myeloma therapies to which subjects were not previously exposed could not be used as bridging.

Lymphodepletion chemotherapy was administered on days -5, -4 and -3 prior to bb2121 infusion.
On each of the three days, following was administered:

- Pre-hydration with 1000ml 0.9% normal saline IV over 1-3 hours
- Anti-emetics were administered per local institutional guidelines, but dexamethasone or other steroids were not to be administered.
- Cyclophosphamide was administered at a dose of 300mg/m2 over 30 minutes followed by fludarabine at a dose of 30mg/m2 over 30 minutes.
- Fludarabine was dose reduced in subjects with reduced creatinine clearance (30-70ml/minute) and was not administered to subjects with creatinine clearance of <30ml/minute. Subjects with creatinine clearance of 50-70 ml/min should have 20% dose reduction of each daily fludarabine dose, subjects with creatinine clearance of 30-49ml/min should have 40% dose reduction of each daily fludarabine dose.
- Chemotherapy-associated cytopenias were managed with myeloid growth factors and blood factor support according to local institutional guidelines.
- Antiseizure prophylaxis was recommended for any grade CAR-T related neurotoxicity.

Reviewer's comment:

Overall, 29 subjects (23%) had at least one dose adjustment for fludarabine for reduced creatinine clearance. The label will include recommendation to dose reduce fludarabine for renal dysfunction.

bb2121:
bb2121 was administered on day 0, within a 7-day window, after lymphodepletion. Premedication with acetaminophen and diphenhydramine was administered approximately 30 minutes prior to the infusion. Subjects could not receive corticosteroids as premedication. Subjects received a target dose ranging from 150 to 450 x10e6 CAR+ T cells by enrolling into three dose cohorts: 150 x10^6, 300 x$10^6$and 450 x10^6 CAR+ T cells.

Dose range included within each dose cohort:
Dose cohort :150 x10^6 CAR+ T cells included 150.5 to 192.4 x 10^6 CAR+ T cells
Dose cohort: 300 x10^6 CAR+ T cells included 277.2 to 339.2 x 10^6 CAR+ T cells
Dose cohort: 450 x10^6 CAR+ T cells included 447 to 518.4 x 10^6 CAR+ T cells
bb2121 was infused intravenously through a non-filtered tubing Dose within 20% of the target dose was allowed in the study protocol (up to 540 x10^6 CAR+ T cells).

This section summarizes subjects that received a dose outside of the protocol specified dose range for the assigned dose cohort and the limited distribution of subjects exposed to the higher end of the dose range. Of note, all subjects were treated within the protocol specified dose range for the entire protocol. A total of 4 subjects were treated in the $150x10^6$ dose cohort, 70 subjects were treated in the $300 x 10^6$ dose cohort and 53 subjects were treated in the $450 x10^6$ CAR+ T cell dose cohort.
Two subjects were treated with a dose that was out of the 20% range of the planned treatment dose. Subject (b) (6) was assigned to 150 million dose cohort and was treated with 192 million CAR T cells which was >20% of the planned treatment dose. This subject was evaluated in the 150 million dose cohort. Subject (b) (6) was assigned to 450 million dose cohort, however, was treated with dose of 339 million CAR+ T cells as the full dose could not be manufactured (<20% of the planned dose treatment). We re-assigned this subject to 300 million CAR +T cell dose cohort for safety and efficacy analysis.

Within the $450x10^6$ CAR+ T cell dose cohort, only five subjects (4%) received a dose >$460 x10^6$ CAR+ T cells (up to $518.4x10^6$ CAR+T cells) indicating that there is limited clinical experience at that upper end of the dose range.

Reviewer's comment:
Manufacturing of autologous CAR T cells can result in variability in the CAR T cell dose due to differences in the starting leukapheresis material, therefore, a 20% of dose range from target is considered acceptable for clinical trials evaluating CAR T products. While the protocol specified dose, cohorts were 150 to 450 x10e6 CAR+ T cells, the actual administered dose in the study ranged from 150.5-518.4 $x10^6$ CAR+ T cells.

6.1.5 Directions for Use

bb2121 was supplied cryopreserved in a cryostorage bag and labelled with a unique subject identification number. The product was thawed at the infusion site in a water bath and infused within one hour of thaw. Instructions regarding storage and administration of bb2121 were detailed in the Investigational Product Manual

6.1.6 Sites and Centers

A total of 20 study sites from seven countries participated in the study.

6.1.7 Surveillance/Monitoring:

Figure 1:

5. TABLE OF EVENTS

Table 3: Table of Events

	Pre-treatment Period			Treatment Period		Post-treatment Period																				
						Safety Monitoring[ff]						Follow-up														
	Screening[a]	Leukapheresis[b]	Baseline Evaluations[c]	LD Chemotherapy[d]	bb2121 infusion[e]																					
Study Days				D -5, -4 and -3	D0	D 1-6	D7	D9	D 11	D 14	D 17, 21, 24	M1	M2	M3	M4	M5	M6	M9	M 12	M 15	M 18	M 21	M 24/ EOS	PD[y]	CR[y]
Visit Window (Days)					+7					±1	±1	±3	±3	±3	±3	±3	±3	±14	±14	±14	±14	±14	±14	+28	+28
Informed Consent	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Inclusion/Exclusion criteria	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Demographics	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Medical History	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Disease History	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Serum/urine pregnancy test	X	-	X[y]	-	-	-	-	-	-	-	X[ee]	-	-	X[ee]	-	-	-	-	X[ee]	-	-	-	-	-	-
Physical examination including routine neurologic examination and vital signs[dd]	X	X	X	-	Daily (Days 0 through 14)[cc]						X[bb]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X	X	-	X	-	X	-	-	X	X[bb]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 3: Table of Events (Continued)

	Pre-Treatment Period			Treatment Period		Post-Treatment Period																			
						Safety Monitoring[ff]						Follow-up													
	Screening[a]	Leukapheresis[b]	Baseline Evaluations[c]	LD Chemotherapy[d]	bb2121 infusion[e]																				
Study Days				D -5, -4 and -3	D0	D 1-6	D7	D9	D 11	D 14	D 17, 21, 24	M1	M2	M3	M4	M5	M6	M9	M 12	M 15	M 18	M 21	M 24/ EOS	PD[y]	CR[y]
Visit Window (Days)					+7					±1	±1	±3	±3	±3	±3	±3	±3	±14	±14	±14	±14	±14	±14	+28	+28
Height	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Weight	X	-	X	-	Daily						X	X	-	-	-	-	-	-	-	-	-	-	-	-	-
MMSE	-	-	X	-	-	Every other day[ff]					X	X	-	X	-	-	-	-	-	-	-	-	-	-	-
Hematology Panel	X	X	X	-	Daily (Days 0 through 14)						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry Panel	X	X	X	-	Daily (Days 0 through 14)						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TLS/CRS panel[h]	-	-	X	-	Daily (Days 0 through 14)						X	X	-	-	-	-	-	-	-	-	-	-	-	-	-
Lymphocyte subset panel[i]	X[i]	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Coagulation Panel	X	-	X	-	Daily (Days 0 through 14)						X	X	-	-	-	-	-	-	-	-	-	-	-	-	-
Viral Serology Testing[j]	X[k]	X[l]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HBV DNA/HCV RNA Testing[m]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-	X	-	X	-	X	-	-
ECHO/MUGA/ECG[p]	X	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
BNP	-	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Urinalysis	X	-	-	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 3: Table of Events (Continued)

	Pre-Treatment Period			Treatment Period		Post-Treatment Period																			
						Safety Monitoring[ff]						Follow-up													
	Screening[a]	Leukapheresis[b]	Baseline Evaluations[c]	LD Chemotherapy[d]	bb2121 infusion[e]																				
Study Days				D -5, -4 and -3	D0	D 1-6	D7	D9	D 11	D 14	D 17, 21, 24	M1	M2	M3	M4	M5	M6	M9	M 12	M 15	M 18	M 21	M 24/ EOS	PD[y]	CR[y]
Visit Window (Days)					+7					±1	±1	±3	±3	±3	±3	±3	±3	±14	±14	±14	±14	±14	±14	+28	+28
Leukapheresis	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lymphodepletion	-	-	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
bb2121 infusion	-	-	-	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Temperature monitoring	-	-	-	-	Every 6 – 8 hours °							-	-	-	-	-	-	-	-	-	-	-	-	-	-
Efficacy Assessments[hh]																									
Serum PEP/IFE and urine PEP (24-hour urine collection) and urine IFE	X	-	X	-	-	-	-	-	-	-	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum free light chains	X	-	X	-	-	-	-	-	-	-	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quantitative serum immunoglobulins	X	-	X	-	-	-	-	-	-	-	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum β-2 microglobulin	X	-	X[x]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 3: Table of Events (Continued)

	Pre-Treatment Period			Treatment Period		Post-Treatment Period																			
						Safety Monitoring[ff]						Follow-up													
	Screening[a]	Leukapheresis[b]	Baseline Evaluations[c]	LD Chemotherapy[d]	bb2121 infusion[e]																				
Study Days				D -5, -4 and -3	D0	D 1-6	D7	D9	D 11	D 14	D 17, 21, 24	M1	M2	M3	M4	M5	M6	M9	M 12	M 15	M 18	M 21	M 24/ EOS	PD[y]	CR[y]
Visit Window (Days)					+7					±1	±1	±3	±3	±3	±3	±3	±3	±14	±14	±14	±14	±14	±14	+28	+28
Skeletal survey[p]	X	-	-	-	-	-	-	-	-	-	-	As clinically indicated for response assessment												-	-
Clinical Examination for extramedullary disease	X	-	X	-	-	-	-	-	-	-	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PET/CT, CT or MRI for extramedullary disease[q]	X	-	X[x]	-	-	-	-	-	-	-	-	X	-	X	-	-	X	-	X	-	X	-	X	X	X
Bone marrow biopsy	X	-	X[x]	-	-	-	-	-	-	-	-	X	-	X	-	-	X	-	X	-	-	-	X	X	X
Bone marrow aspirate	X	-	X[x]	-	-	-	-	-	-	-	-	X	-	X	-	-	X	-	X	-	X[y]	-	X	X	X
Morphology	X	-	X[x]	-	-	-	-	-	-	-	-	X	-	X	-	-	X	-	X	-	X[y]	-	X	X	X
Cytogenetics/FISH	X	-	X[x]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X[y]	-	-	X[z]	X[z]
BMA Immunophenotyping	X	-	X[x]	-	-	-	-	-	-	-	-	X	-	X	-	-	X	-	X	-	X[y]	-	X	X	X

Table 3: Table of Events (Continued)

	Pre-Treatment Period			Treatment Period		Post-Treatment Period																			
						Safety Monitoring[ff]						Follow-up													
	Screening[a]	Leukapheresis[b]	Baseline Evaluations[c]	LD Chemotherapy[d]	bb2121 infusion[e]																				
Study Days				D -5, -4 and -3	D0	D 1-6	D7	D9	D 11	D 14	D 17, 21, 24	M1	M2	M3	M4	M5	M6	M9	M 12	M 15	M 18	M 21	M 24/ EOS	PD[y]	CR[y]
Visit Window (Days)					+7					±1	±1	±3	±3	±3	±3	±3	±3	±14	±14	±14	±14	±14	±14	+28	+28
Bone marrow CAR+ T cells	X	-	-	-	-	-	-	-	-	-	-	X	-	X	-	-	X	-	X	-	X[y]	-	X	X	X
MRD	X	-	X[x]	-	-	-	-	-	-	-	-	X	-	X	-	-	X	-	X	-	X[y]	-	X	X	X
Gene expression profiling	X	-	X[x]	-	-	-	-	-	-	-	-	X	-	X	-		X	-	X	-	X[y]	-	X	X	X
Biomarker Assessments (research samples)																									
Peripheral blood sample for cytokine (plasma)	X	-	-	-	X	X[u]	X	X	X	X	X[bb]	X	-	-	-	-	-	-	-	-	-	-	-	-	-
Peripheral blood for Immunophenotyping by flow cytometry	X	-	-	-	X	X[v]	X	-	X	X	-	X	-	X	-	-	X	-	-	-	-	-	-	X	X
Peripheral blood sample for biomarkers (PBMC)	X	-	-	-	X	X[v]	X	-	-	X	-	X	-	X	-	-	X	-	X	-	X	-	X	X	X

Table 3: Table of Events (Continued)

	Pre-Treatment Period			Treatment Period		Post-Treatment Period																		
						Safety Monitoring[ff]						Follow-up												
	Screening[a]	Leukapheresis[b]	Baseline Evaluations[c]	LD Chemotherapy[d]	bb2121 infusion[e]																			
Study Days				D -5, -4 and -3	D0	D 1-6	D7	D9	D 11	D 14	D 17, 21, 24	M1	M2	M3	M4	M5	M6	M9	M 12	M 15	M 18	M 21	M 24/ EOS	PD[y]	CR[y]
Visit Window (Days)					+7					±1	±1	±3	±3	±3	±3	±3	±3	±14	±14	±14	±14	±14	±14	+28	+28
Peripheral blood sample for soluble BCMA (serum)	X	-	-	-	X	X[h]	X	-	X	X	X[hh]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Peripheral blood for immunogenicity (serum)	X	-	X[gg]	-	X	-	X	-	-	X	-	X	-	X	-	-	X	X	X	X	X	X	X	X	X
Peripheral blood for PK (CD3+ cells)[ii]	X	-	-	-	-	X[h]	X	X	X	X	X[hh]	X	X	X	X	X	X	X	X[w]	X	X	X	X	X	X
Peripheral blood for RCL testing[ii]	X	-	-	-	-	-	-	-	-	-	-	-	-	X	-	-	X	-	X	-	-	-	X	X	-
Peripheral blood for cellular immunogenicity (PBMC)	X	-	X[gg]	-	-	-	-	-	-	-	-	X	X	X	X	-	-	-	-	-	-	-	-	X	X
Extramedullary plasmacytoma biopsy[ii]	(X)	-	-	-	-	At time of disease progression (optional)																			-
Tumor Biopsy[jj]	-	-	-	-	-	Will be requested if a subject develops a new neoplasm while enrolled in this study; the Sponsor may request a sample of the neoplastic tissue for safety analysis of the bb2121 cells.																			

Table 3: Table of Events (Continued)

	Pre-Treatment Period			Treatment Period		Post-Treatment Period																		
						Safety Monitoring[ff]						Follow-up												
	Screening[a]	Leukapheresis[b]	Baseline Evaluations[c]	LD Chemotherapy[d]	bb2121 infusion[e]																			
Study Days				D -5, -4 and -3	D0	D 1-6	D7	D9	D 11	D 14	D 17, 21, 24	M1	M2	M3	M4	M5	M6	M9	M 12	M 15	M 18	M 21	M 24/ EOS	PD[y]	CR[y]
Visit Window (Days)					+7					±1	±1	±3	±3	±3	±3	±3	±3	±14	±14	±14	±14	±14	±14	+28	+28
Other Assessments																									
Adverse Events and concomitant medications	AEs related to protocol-mandated procedures and associated concomitant medications; ALL SAEs			All AEs and associated concomitant medications								All Grade ≥ 3 AEs, all SAEs, all AESIs and associated concomitant medications (starting at M7)												
HRQoL	X	-	X	-	X	-	-	-	-	-	-	X	X	X	X	X	X	X	X	X	X	X	X	X[kk]	X[ll]
Hospital resource utilization	-	-	X	-	-	Collected continuously																			
Survival Status	-	-	-	-	-	-	-	-	-	-	-	Every 3 months after PD[y]													

Abbreviations: AE = adverse event; AESI = adverse events of special interest; BCMA = B-cell maturation antigen; β = beta; BMA = bone marrow aspirate; BNP = brain natriuretic peptide; CAR = chimeric antigen receptor; CD3 = cluster of differentiation 3; CR = complete response; CRP = C-reactive protein; CRS = cytokine release syndrome; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EM = extramedullary; EMP = extramedullary plasmacytoma; EOS = end of study; FISH = fluorescence in-situ hybridization; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HTLV-1 = human lymphocytic T-cell virus type 1; HRQoL = health related quality of life; ICF = informed consent form; IFE = immunofixation; LD = lymphodepleting; MMSE = Mini Mental State Examination; MRD = minimal residual disease; MRI = magnetic resonance imaging; MUGA = multigated acquisition; PBLs = peripheral blood lymphocytes; PBMC = peripheral blood mononuclear cells; PD = progressive disease; PEP = protein electrophoresis; PET = positron emission tomography; PK = pharmacokinetic; RCL = replication competent lentivirus; TLS = tumor lysis syndrome.

[a] Screening procedures must be completed within 28 days of leukapheresis.
[b] Leukapheresis will be approximately 4 -5 weeks before planned bb2121 infusion on Day 0. All safety evaluations will be performed locally ≤ 3 days prior to leukapheresis.
[c] Baseline evaluations performed within 72 hours prior (or on the same day) to LD chemotherapy.
[d] LD chemotherapy to start 5 days before Day 0.
[e] bb2121 infusion is targeted for Day 0 and must be infused no more than 7 days from the planned infusion day (Day 0). If bb2121 infusion cannot take place by day 7, subjects must wait 4 weeks to receive a second LD chemotherapy prior to bb2121 infusion. Refer to Section 6.2.2 and Section 7.2.1.1 on minimum assessments required to receive LD chemotherapy and bb2121 infusion; Subjects that are enrolled and unable to receive bb2121 infusion will be followed for 30 days for safety from the last study procedure (eg, leukapheresis, LD chemotherapy and bridging therapy). Tocilizumab must be available at the site prior to infusion of the subject.
[f] Serum or urine pregnancy test within 72 hours of LD chemotherapy; in the event of a positive urine pregnancy test, a serum pregnancy test should be performed to confirm result.
[g] MMSE will be performed every other day for the first 14 days (on Days 2, 4, 6, 8, 10, 12 and 14) and then twice weekly through M1 (on Days 17, 21, 24 and M1).
[h] TLS/CRS panel will include total bilirubin, magnesium, uric acid, phosphorus, ferritin, CRP, and creatine phosphokinase. Evaluations will continue until abnormal laboratory values returned to baseline (refer to Appendix F).
[i] Lymphocyte subset panel includes CD3, CD4, CD8 and CD19/CD20; Screening assessment should be performed within 7 days prior to leukapheresis.
[j] Viral serology testing to include HIV, Hepatitis B, Hepatitis C, syphilis and HTLV-1 antibody.
[k] Viral serology testing at screening for US and Canadian sites (include HIV, Hepatitis B, Hepatitis C, syphilis and HTLV-1 antibody); HIV, Hepatitis B and Hepatitis C in EU sites.
[l] Viral serology testing prior to leukapheresis for EU sites only.
[m] HBV DNA and HCV RNA testing to monitor for Hepatitis B or C viral reactivation, only in subjects with a history of HBV or HCV infection, respectively.
[n] Repeat ECHO/MUGA within 2 weeks prior to the start of LD chemotherapy if intervening/bridging therapy includes potentially cardiotoxic drugs (eg, carfilzomib, anthracyclines or high dose cyclophosphamide). ECG to be performed for all subjects within 2 weeks of screening and LD chemotherapy.
[o] After hospital discharge, subjects must monitor their temperature, every 6-8 hours (while awake), post-bb2121 infusion through Month 1 in a diary. Subjects must contact their treating investigator for any fever ≥38° C/100.4°. After hospital discharge, subjects must remain within a 30-minute transportation ride to the treating hospital and must have a dedicated caregiver(s) from day 15 through Month 1.
[p] Skeletal survey is done locally at screening and post-bb2121 infusion as clinically indicated. A PET/CT, CT or MRI scan may be done in place of a skeletal survey provided the same modality will be used for all assessments.
[q] PET/CT, CT or MRI of extramedullary disease required for subjects with a history of or clinical indication of EMPs only assessable radiographically. If a PET/CT, CT or MRI was performed within 30 days of screening as standard of care, it will not need to be repeated and can be used as the screening assessment.
[r] Prior to M18, all bone marrow aspirate assessments will be evaluated for MRD regardless of IMWG response. For M18 and beyond, bone marrow aspirate for MRD assessments will only be performed in subjects with responses of VGPR or better and in subjects with MRD negative status at the last prior assessment.
[s] Blood samples will be collected on Day 2 and Day 4 only; collection of peripheral blood sample for PBMC is not required on Day 4.
[t] Blood RCL collection will be stopped in the event of 2 consecutive undetectable results. Subjects with any +RCL will be monitored closely.
[u] Cytokines to be performed daily on Days 1 through 6. Additional assessments can be performed at time of suspicion of CRS (ie, at time of high fever onset, 24 hours after fever onset and 48 hours after fever onset).
[v] All subjects will be followed for survival every 3 months from the time of documented PD, until last subject last visit on the MM-001 study.
[w] If CAR transgene is detected in ≥ 1% of cells at any time point ≥12 months after last bb2121 infusion, the pattern for vector integration sites will be analyzed. If integration pattern suggests a predominant clone, the specific locations on the host chromosome will be determined, if a predominant integration site is identified a repeat analysis will be conducted within 3 months (refer to Section 6.4.4.1).
[x] Additional baseline assessments must be repeated if a subject received bridging therapy after leukapheresis. Assessments must be performed following bridging therapy and prior to LD chemotherapy. Bone marrow morphology and all other bone marrow assessments will be required. In subjects that did not receive bridging therapy and had inadequate screening bone marrow samples, an additional baseline bone marrow evaluation may also be requested
[y] Per IMWG Uniform Response Criteria all response categories require two consecutive assessments (except radiographic and bone marrow assessments) made at any time prior to start of new therapy.
[z] Subjects with genetic abnormalities at screening (or baseline for subjects that received bridging therapy), repeat cytogenetics/FISH at CR and at the time of PD. Subjects without defined genetic abnormalities at screening (or baseline for subjects that received bridging therapy), repeat cytogenetics/FISH at the time of PD.

[aa] HRQoL should be performed at the time of the PD or CR visit assessment, regardless if it was performed at the last scheduled visit.
[bb] Assessments are performed on D21 only.
[cc] On the day of bb2121 infusion, vital signs are collected prior to infusion, once midway through infusion, once at the end of infusion, and then every 15 minutes thereafter for the first hour then hourly for a total of 4 hours.
[dd] Oxygen saturation via pulse oximetry will be performed at screening, within 3 days of leukapheresis, at baseline, Day 0, M1, M2 and M3.
[ee] Serum or urine pregnancy test performed on Day 24, M3 and M12.
[ff] Safety monitoring period is 30 days. Each subsequent month is defined as 30 days post-bb2121 infusion.
[gg] Only required at baseline prior to start of LD chemotherapy for subjects that are retreated.
[hh] An additional Unscheduled visit may be required proximate to the primary analysis.
[ii] Subject has radiologically measurable EMP (soft tissue or bone related) at the time of PD that is amenable to biopsy. Optional at time of Screening.
[jj] If a subject develops a new neoplasm any time post bb2121 infusion, the Sponsor will request a sample of the tumor biopsy to evaluate the presence of a transgene. In addition to tumor biopsy, a peripheral blood sample for RCL testing and a peripheral blood sample for PK at the time of a new neoplasm will be requested. Refer to the lab manual for tissue collection instructions for liquid and solid hematological malignancies and solid tumors.

1. The protocol required that all subjects be admitted for inpatient monitoring for 14 days after receiving bb2121 to monitor for the risk of CRS (cytokine release syndrome) and neurotoxicity.
2. The IMWG requires concurrent assessment of serum protein electrophoresis, serum immunofixation, serum free light chain, urine protein electrophoresis, urine immunofixation, bone marrow assessment and imaging (if applicable for extramedullary plasmacytoma) to document complete response.

3. For other response categories (PR and VGPR), serum and urine assessments had to be concurrent per IMWG. Assessment of extramedullary plasmacytoma were to be assessed serially as recommended by IMWG according to the protocol specified schedule.
4. Consistent with the IMWG 2016 criteria, all response categories required two consecutive assessments (except radiographic and bone marrow assessments) made at any time prior to start of new therapy.

5. The protocol required that all study subjects undergo bone marrow evaluation and imaging (PET/CT, CT or MRI) for extramedullary disease assessment at the time of CR (complete response) or PD (progressive disease) documentation. For CR and PD assessment, there was 28 days visit window allowed in the protocol to complete all assessments.

6. Consistent with the IMWG 2016 criteria, all response categories required two consecutive assessments (except radiographic and bone marrow assessments) made at any time prior to start of new therapy.

7. MRD assessment was performed at all bone marrow assessment timepoints; at screening, baseline, and Months 1,3,6 and 12, regardless of the IMWG response. Thereafter, bone marrow aspirate for MRD assessment were performed at Months 18 and 24 only in subjects with response of VGPR or better and in subjects with MRD-negative status at the last prior assessment. After Month 24, MRD assessments were performed every 12 months for up to 5 years or until documented PD.MRD was assessed by Clonoseq (NGS) with a LOD of (b) (4) for a sensitivity of (b) (4).

8. All subjects were to be followed until 24 months post-bb2121. If a subject developed PD within 24 months, then subject was evaluated for retreatment with bb2121. The subject was followed in the study from the time of PD through remainder of 24 months during which data was collected regarding anti-cancer treatment post-bb2121, AE collection, survival status, collection of hospitalization details, HRQoL questionnaire, peripheral blood testing for RCL, and cellular kinetics.

9. An independent Data Safety Monitoring Board (DSMB) was established to monitor the safety data approximately every 6 months.

10. An independent response committee (IRC) reviewed efficacy data in order to assess response and progression based on the International Myeloma Working Group (IMWG) Uniform Response Criteria for multiple myeloma(2016).

Reviewer's comment: The protocol schedule of assessment is acceptable.

6.1.8 Endpoints and Criteria for Study Success

Primary endpoint: Overall response rate (ORR) defined as percentage of subjects who achieved partial response (PR) or better according to IMWG (International Myeloma Working Group) Uniform Response Criteria for multiple myeloma 2016, as assessed by an independent response committee (IRC).

Key secondary endpoint: Complete response rate (CR) rate defined as percentage of subjects who achieve CR or stringent CR according to IMWG uniform response criteria as assessed by IRC.

Other Secondary endpoints:

- Time to response
- Duration of response
- Progression free survival
- Time to progression

- Overall survival
- Safety
- Minimal residual disease
- Immunogenicity
- PK (pharmacokinetics)
- Health related quality of life

6.1.9 Statistical Considerations & Statistical Analysis Plan

MM-001 tested the hypothesis that overall response rate (ORR) is >50% with target ORR of 70% against a null hypothesis of ≤50%. With these hypotheses, a sample size of 119 bb2121 treated subjects would provide >99% power at a one sided .025 alpha level. The lower limit of 95% confidence interval for ORR should be greater than 50% for study success. Assuming a 15% dropout rate between enrollment and treatment, a total of 140 subjects were planned for enrollment.
If ORR is tested positive, then CR rate (complete response) would be tested against null hypothesis of ≤10%, with a target CR rate of 20%. The hierarchical testing was used to control for family-wise Type 1 error rate. A sample size of 119 bb2121 treated subjects would provide 89% power at a one-sided .025 alpha level.

Reviewer's comment:

1. Null hypothesis of 50% for ORR was based on the observed clinical efficacy of daratumumab (ORR= 29-36%) in relapsed refractory myeloma patients who had received at least 3 prior lines of therapy including a PI and an IMiD or who were double refractory.[1,2]. Null hypothesis of 50% ORR represented an improvement of efficacy over daratumumab. Target ORR of 70% was based on preliminary efficacy of bb2121 noted in CRB-401 with ORR=81% in 36 evaluable patients receiving bb2121 at doses of 150-800 x10e6 CAR + T cells.
   Belantamab is a recently approved BCMA directed antibody and microtubule inhibitor conjugate. The overall response rate with belantamab was 31% in triple class refractory population. Given the efficacy of this recent approval in a similar population, the proposed null hypothesis of 50% is still relevant in context of available therapies for R/R myeloma.

Key definitions:
Safety:
Treatment emergent adverse events: This trial did not define treatment emergent adverse event. Instead, adverse event reporting was done by following periods:

- Lymphodepleting (LD) chemotherapy to immediately prior to bb2121 infusion
- On or after bb2121 infusion
  - From bb2121 infusion to ≤ 8 weeks
  - >8 weeks after bb2121 to ≤ 6 months
  - >6 months after bb2121 to ≤ 24 months

Adverse events of special interest (AESI):
Diagnosis of new malignancy, new diagnosis of auto-immune like rheumatological disease, new diagnosis of hematological disorder, Grade ≥3 CRS , hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS), neurological toxicity and infection are considered AESI.

Efficacy:
Objective response rate (ORR): The percentage of subjects who achieved partial response (PR) or better according to IMWG Uniform Response Criteria for Multiple Myeloma 2016 as assessed by an independent response committee (IRC).

Complete response rate (CRR): The percentage of subjects who achieve CR (complete response) or sCR (stringent CR) according to IMWG Uniform Response Criteria for Multiple Myeloma 2016 as assessed by an independent response committee (IRC). Complete response requires negative serum and urine immunofixation, complete resolution of any plasmacytoma and <5% plasma cells in the bone marrow. In patients in whom the only measurable disease is by serum FLC (free light chain), a normal FLC ratio of 0.26 to 1.65 is also required. Stringent complete response requires a normal serum free light chain ratio even if FLC is not the only measurable component and absence of clonal plasma cells by immunohistochemistry in addition to all criteria outlined for CR.

Reviewer's comment: Attaining a stringent CR indicates a deeper response and portends a better prognosis than CR in the front line setting particularly after autologous stem cell transplantation. However, its prognostic significance compared to a complete response in relapsed and refractory setting remains poorly understood.
Duration of response (DOR): Time from the date of the first documented response (PR or better) to the first documentation of progressive disease (PD) or death whichever is earlier in responders.

Progression free survival (PFS): Time from bb2121 infusion to the first date of documented progressive disease (PD) or death from any cause during the study, whichever occurs earlier. PFS was also analyzed for the enrolled population and in this population was defined as the time from enrollment (i.e. leukapheresis) to disease progression or death from any cause.

Overall survival (OS): The time from bb2121 infusion to death due to any cause. OS was also analyzed for the enrolled population and in this population, it was defined as time from enrollment (i.e. leukapheresis) to death due to any cause.

MRD status: MRD in the bone marrow were measured using both next generation sequencing (NGS) and (b) (4) . MRD evaluated by NGS was considered a secondary endpoint, and MRD evaluated using (b) (4) was considered an exploratory endpoint. MRD was reported with a sensitivity of (b) (4) . The primary analysis for MRD negative rate was defined as proportion of subjects who achieved a CR or better and MRD negative status at a sensitivity of (b) (4) at any time point within 3 months prior to achieving at least CR until the time of PD or death in bb2121 treated population. The null hypothesis is that MRD negative rate is ≤10%, and the target is ≥20%. With these assumptions, sample size of 119 bb2121 treated subjects would provide 89% power at a one-sided 0.025 nominal alpha level.

Baseline: For the purpose of safety and efficacy, the latest assessment taken on or before LD start date was considered baseline.

Reviewer's comment: SAP specified that primary MRD analysis would be performed in subjects who attained VGPR or better. However, based on Agency's input, Applicant changed primary analysis of MRD negativity in CR or better response category. This change was made

after the SAP was finalized. Time to event endpoints such as OS and PFS are uninterpretable in a single arm trial without a comparator arm.

Key censoring rules:
• ORR, DOR, and PFS will only include data from disease assessments performed prior to retreatment with bb2121, or initiation of any other anti-cancer therapy.
•DOR and PFS:

- Subjects with no post baseline disease assessment and alive were censored at the bb2121 infusion date.
- Subjects who had died or experienced disease progression after start of new anti-myeloma therapy were censored at the last adequate disease assessment date that did not show progression.
- Subjects with PD or death immediately after missing 2 or more consecutive scheduled assessments were censored at the last adequate efficacy assessment date without PD.

OS: Subjects who had not died by the analysis cut-off date were censored at their last date known alive or the analysis cutoff date, whichever was earlier. Subjects who died on or before cut-off date were considered as having events on the date of death.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed
Subject populations in MM-001 were defined and analyzed as follows:
Screened Population:
All subjects who signed informed consent.
Enrolled Population:
All subjects in the screened population who underwent leukapheresis.
bb2121 Treated Population:
All subjects in the enrolled population who have received bb2121 infusion. The bb2121-treated population was used for the primary analysis of efficacy and safety.
Efficacy Evaluable Population:
All subjects in the bb2121-treated population who have had a baseline and at least one post baseline (i.e., post-bb2121 infusion) efficacy assessment.
Pharmacokinetic Analysis Population:
Subjects who received at least one bb2121 infusion and have at least one evaluable CAR T data post-treatment.
Patient reported outcome (PRO) analysis population:
Subjects who complete their baseline PRO questionnaires and have at least one post-baseline measurement in the bb2121-treated population.

Subjects were treated at the following three dose cohorts:
150 x 10^6CAR+ T cells, 300 x10^6CAR+ T cells, 450x10^6CAR+ T cells.

Reviewer comment: All subjects who were treated with conforming bb2121 product were evaluated for safety and efficacy (referred to as bb2121 treated population).

6.1.10.1.1 Demographics

Table 10: Demographic Characteristics of the bb2121 treated population

	bb2121 Treated Population bb2121 (CAR+T cells) Dose Cohort				
Characteristics	150X10e6 (N=4)	300x10e6 (N=70)	450 x10e6 (N=53)	Total 150-450x10e6 (N=127)	Enrolled Population (N=140)
Age (years)					
Mean (STD)	56.5 (8.7)	58.7 (9.4)	61.6 (9.3)	59.8 (9.4)	60 (9)
Median (range)	54 (49, 69)	60.5 (33, 76)	62 (43, 78)	61 (33, 78)	60.5 (33, 78)
Age groups (years) n(%)					
18 to <65	3 (75)	47 (67)	32 (60.3)	82 (64.5)	92 (65.7)
65 to < 75	1 (25)	22 (31)	18 (33.9)	41 (32.2)	43 (31)
≥75	0	1(1)	3(6)	4 (3.1)	5 (3.6)
Sex, n(%)					
Male	4(100)	38 (54)	34 (63)	76 (59.8)	82 (58.6)
Female	0	32 (46)	19 (37)	51 (40.1)	58 (41.4)
Race, n(%)					
Asian	0	3(4)	0	3 (2.3)	3 (2.1)
Black or African American	0	3 (4)	3 (6)	6 (4.7)	8 (5.7)
White	4(100)	58 (83)	40 (76)	102 (80.3)	113 (80.7)
Unknown	0	2 (3)	8 (15)	10 (7.8)	10 (7.1)
Other	0	4 (6)	2 (4)	6 (4.7)	6 (4.3)
Ethnicity, n(%)					
Hispanic or Latino	0	6 (10)	4 (7)	10(7.8)	13 (9.3)
Non-Hispanic or Latino	4(100)	59 (83)	40 (76)	103 (81)	112 (80)
Not Reported	0	1(1)	8 (15)	9 (7)	9 (6.4)
Unknown	0	4 (6)	1 (2)	5 (3.9)	6 (4.3)
Country of Origin					
USA	4 (100)	61 (87)	28 (53)	93 (73)	103 (74)

Source: FDA analysis: ADSL dataset

Table 11: Demographic characteristics of the population treated by the recommended dose range of 300-460 x 10^6 CAR+ T cells

Characteristics	**Total 300-460 x10e6 (N=100)**
Age (years)	
Mean	60
Median (range)	62 (33, 78)
Age groups (years) n(%)	
18 to <65	64 (64)
65 to < 75	32 (32)

Characteristics	Total 300-460 x10e6 (N=100)
≥75	4 (4)
Sex, n(%)	
Male	60 (60)
Female	40 (40)
Race, n(%)	
Asian	2 (2)
Black or African American	6 (6)
White	78 (78)
Unknown	9 (9)
Other	5 (5)
Ethnicity, n(%)	
Hispanic or Latino	8 (8)
Non-Hispanic or Latino	80 (80)
Not Reported	8 (7)
Unknown	4 (4)
Country of Origin	
USA	72 (72)

Source: FDA analysis: ADSL dataset

Reviewer's comment:
The median age of the study population was 60 years which is considerably lower compared to the general population of patients with MM (median age at diagnosis in the U.S. population is 69 years, NCI SEER). 73% of the bb2121 treated population was enrolled from the US. 20% of the population diagnosed with myeloma in the US is African American, however, only 5% of the study population is African American raising concern about racial disparities in accessing clinical trials in multiple myeloma. No significant differences were identified in the demographics of the population treated at the recommended dose range compared to the entire study population and the enrolled population.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Table 12: Baseline Disease Characteristics

Characteristic	bb2121 treated population CAR + T cell Dose Cohort				Enrolled Population
	150 x 10e6 N = 4	300 x 10e6 N = 70	450 x 10e6 N = 53	150-450x10e6 N=127	N=140
Time since initial diagnosis (years)					
Median	9.5	6.7	5.8	6	6
Min, max	6, 12.3	1.7, 17.9	1, 16.8	1, 17.9	1, 17.9
ISS stage at baseline n(%)					
Stage I	0	30 (44)	17 (31)	47 (37)	49 (35)
Stage II	3 (75)	25 (34)	22 (43)	50 (39)	55 (39)

Characteristic	bb2121 treated population CAR + T cell Dose Cohort				Enrolled Population
	150 x 10e6 N = 4	300 x 10e6 N = 70	450 x 10e6 N = 53	150-450x10e6 N=127	N=140
Stage III	1 (25)	15 (21)	14 (26)	30 (23)	36 (26)
Light Chain type, n(%) at baseline(Any)					
Kappa Light Chain	1 (25)	52 (76)	35 (65)	88 (70)	93 (66)
Lambda Light Chain	3 (75)	17 (23)	18 (35)	38 (27)	46 (33)
Not detected	0	1 (0.8)	0	1 (0.8)	1 (0.7)
Immunoglobulin, n (%) At Baseline (Any)					
Ig A	1 (25)	9 (14)	13 (24)	23 19)	25 (18)
Ig G	1 (25)	48 (67)	30 (57)	79 (62)	88 (63)
Ig M	0	1 (1)	0	1 (0.8)	1 (0.7)
Ig D	0	0	0	0	0
Ig E	0	0	0	0	0
Not detected	2 (50)	12 (17)	10 (19)	24 (19)	26 (18)
Baseline cytogenetics risk n(%)					
High Risk	1 (25)	19 (29)	24 (44)	44 (35)	46 (33)
Non-high risk	3 (75)	39 (54)	24 (46)	66 (52)	73 (52)
Missing	0	12 (17)	5 (9)	17 (13)	21 (15)
Presence of extramedullary plasmacytoma n(%)					
Yes	0	34 (49)	16 (30)	50 (39)	52 (37)
No	4 (100)	36 (51)	37 (70)	77 (61)	85 (61)
Lytic Bone Disease n(%)					
Yes	4 (100)	62 (88)	43 (81)	109 (86)	121 (86)
No	0	6 (9)	9 (17)	15 (12)	16 (11)
Unknown		2 (3)	1 (2)	3 (2)	3 (2)
Tumor BCMA expression n(%)					
<50%	0	1 (1)	2 (4)	3 (2)	3 (2)
≥50%	4 (100)	60 (86)	44 (83)	108 (85)	109 (78)
Unknown	0	9 (13)	7 (13)	16 (12)	28 (20)

Source: FDA analysis: ADSL dataset

Table 13: Baseline disease characteristics of the population treated at the recommended dose range of 300-460 x 10^6 CAR+ T cells

Characteristics	300-460 x10e6 N=100
Time since initial diagnosis (years)	
Median	5.9
Min, max	1, 17.9
ISS stage at Study entry n(%)	
Stage I	41 41)
Stage II	37 (37)
Stage III	22 (22)
Light Chain type, n(%) at baseline(Any)	
Kappa Light Chain	68 (68)
Lambda Light Chain	28 (28)
Not detected	4 (4)
Immunoglobulin, n (%) At Baseline (Any)	
Ig A	20 (20)
Ig G	61 (61)
Ig M	1 (1)
Ig D	0
Ig E	0
Not detected	18 (18)
Baseline cytogenetics risk n(%)	
High Risk	37 (37)
Non-high risk	49 (49)
Missing	14 (14)
Presence of extramedullary plasmacytoma n(%)	
Yes	36 (36)
No	64 (64)
Lytic Bone Disease n (%)	
Yes	84 (84)
No	14 (14)
Unknown	2 (2)
Tumor BCMA expression n (%)	
<50%	3 (3)
≥50%	85 (85)
Unknown	12 (12)

Source: FDA analysis: ADSL dataset

Table 14: Previous Antimyeloma Therapies

Characteristic	bb2121 treated population CAR + T cells Dose Cohort				Enrolled Population N=140
	150 x 10e6 N = 4	300 x 10e6 N = 70	450 x 10e6 N = 53	150-450x10e6 N=127	
Number of prior antimyeloma regimens					
Median (min, max)	8.5 (4, 12)	6 (3, 16)	5 (3, 13)	6 (3, 16)	8.5 (4, 12)
Distribution of prior antimyeloma regimens n (%)					
3	0	7 (10)	7 (13)	14 (11)	16 (11)
4	1 (25)	8 (11)	10 (19)	19 (15)	20 (14)
5	0	11 (16)	11 (21)	22 (17)	23 (16)
6	1 (25)	12 (17)	10 (19)	23 (18)	25 (18)
≥ 7	2 (50)	32 (46)	15 (28)	49 (38)	56 (40)
Prior stem cell transplant n (%)					
Yes	4 (100)	67 (96)	48 (90.5)	119 (94)	131 (94)
1 prior transplant	1 (25)	43 (61)	31 (58)	75 (59)	82 (59)
>1 prior transplant	3 (75)	24 (34)	17 (32)	44 (35)	49 (35)
No	0	3 (4)	5 (9)	8 (6)	9 (6)
Prior refractory status n(%)					
Immunomodulatory Agent (ImiD)	4 (100)	70 (100)	51 (96)	125(98)	138 (99)
Proteasome inhibitor (PI)	4 (100)	63 (90)	48 (90.5)	115 (90.5)	126 (90)
Anti-CD38 antibodies	4 (100)	66 (94)	49 (92)	119(94)	131 (94)
Daratumumab	3 (75)	62 (89)	44 (83)	109 (86)	120 (86)
Double refractory (ImiD and PI)	4 (100)	63 (90)	46 (87)	113 (89)	124 (89)
Triple refractory (ImiD, PI and anti-CD38)	4 (100)	60 (86)	43 (81)	107 (84)	117 (84)
Penta-refractory*	1 (25)	24 (34)	8 (15)	33 (26)	37 (26)
Prior refractory to last regimen, n(%)	4 (100)	70 (100)	53 (100)	127 (100)	140 (100)

Source: FDA analysis: ADSL dataset

*Penta-refractory defined as refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab

Previous Antimyeloma Therapies for subjects treated at the recommended dose range of 300-460 x 10^6 CAR+ T cells:

Table 15

Characteristics	300-460 x10e6 N=100
Number of prior antimyeloma regimens	
Median (min, max)	6 (3, 16)
Distribution of prior antimyeloma regimens n (%)	
3	12 (12)
4	14 (14)
5	19 (19)
6	18 (18)
≥ 7	37 (37)
Prior stem cell transplant n (%)	
Yes	92 (92)
1 prior transplant	58 (58)
>1 prior transplant	34 (34)
No	8 (8)
Prior refractory status n(%)	
Immunomodulatory Agent (ImiD)	98 (98)
Proteasome inhibitor (PI)	90 (90)
Anti-CD38 antibodies	95 (95)
Daratumumab	89 (89)
Double refractory (ImiD and PI)	88 (88)
Triple refractory (ImiD, PI and anti-CD38)	85 (85)
Penta-refractory*	26 (26)
Prior refractory to last regimen, n(%)	100 (100)

Source: FDA analysis: ADSL dataset

Reviewer's comment: In general, the baseline disease characteristics of the study population for MM-001 was representative of the general population of patients with relapsed and refractory myeloma. Majority of the subjects treated in the study had Stage I or II myeloma at baseline. Approximately 35% of the treated population had high risk cytogenetics. 39% of the treated population had extramedullary plasmacytomas at baseline.

In an exploratory analyses, baseline bone marrow samples were retrospectively reviewed for BCMA expression using immunohistochemistry (IHC). Out of the 111 subjects evaluable for bone marrow BCMA expression, one hundred and eight (97%) had ≥50% BCMA expression. Out of the three subjects with <50% BCMA expression, two subjects were responders and one subject had stable disease. Study MM-001 did not restrict enrollment based on BCMA expression. Despite this unrestricted eligibility, the vast majority of subjects (97%) that were enrolled in the study had ≥50% BCMA expression indicating that BCMA expression is widely prevalent in relapsed and refractory myeloma.

Given the near-universal expression of BCMA on malignant plasma cells in relapsed refractory myeloma population in study MM-001, a companion diagnostic is not considered to select subjects for treatment with bb2121[5-7].This approach is consistent with the approval of belantamab mafodotin; a first in class BCMA-directed antibody and microtubule inhibitor conjugate which is indicated for the treatment of relapsed/refractory MM irrespective of BCMA expression in malignant plasma cells.
All subjects treated in the study had previously been treated with a proteasome inhibitor, an IMiD and anti CD38 monoclonal antibody and were refractory to the last line of therapy as specified by protocol eligibility criteria. This includes the 14 subjects (11%) who had received 3 prior lines of therapy. 84% of the subjects were triple class refractory and 26% were Penta-refractory. The median prior lines of therapy were six. Overall, the study population was heavily pre-treated. There is no significant difference noted for the baseline disease characteristics and prior anti-myeloma therapy between the population treated at the recommended dose range, the entire study population and the enrolled population.

Bridging Therapies:
The majority of the bb2121 treated population (111 out of 127; 87%) received bridging therapy for myeloma control during bb2121 manufacturing period. The mean duration of bridging therapy was 12.9 days (median =15 days) with a range of 1-33 days.

Table 16 : Antimyeloma Bridging Therapy Agents by Class Received by at least 10%of the bb2121 treated population

Drug Class Drug preferred name	bb2121 treated population N=127 n (%)
Subjects with at least 1 bridging therapy	111 (87%)
Corticosteroid Dexamethasone	94 (74%) 90 (71%)
Proteasome Inhibitor Carfilzomib Bortezomib	53 (42%) 30 (24%) 24 (19%)
Alkylating agent Cyclophosphamide	51 (40%) 47 (37%)
Monoclonal antibodies Daratumumab	38 (30%) 36 (28%)
Immunomodulatory agents Pomalidomide	29 (23%) 24 (19%)

Source: FDA analysis: ADCM dataset

Baseline disease assessment post-bridging:
The protocol mandated that baseline disease staging assessments be repeated following completion of bridging and prior to start of lymphodepletion. However, 13 out of the 111 subjects that received bridging had one element of disease assessment that was missing at baseline. Nine out of these 13 subjects were responders and were further analyzed. For each responder who had received bridging therapy with a missing assessment at baseline, other disease parameters were assessed at baseline which were measurable. Since only one of the three parameters: serum M protein, urine M protein or serum free light chain are required to be

measurable for evaluation of efficacy per IMWG, all 9 subjects are considered evaluable for efficacy. One responder subject (Subject ID:(b) (6)) had missing serum free light chain assessment at baseline which was measurable at screening. This subject had other measurable parameters :serum and urine M protein available at baseline for efficacy assessment. Plasma cell burden in bone marrow biopsy and plasmacytoma are not considered measurable disease parameters for secretory myeloma per IMWG 2016, therefore absence of marrow and imaging at baseline did not render subjects' efficacy inevaluable. Please refer to Table A, Appendix 1 for list of missing assessments in responder population at baseline after receiving bridging therapy.

Response to bridging:

Table 17: Response to bridging therapy was assessed by investigators at the baseline visit.

Response category	Number of subjects N=111 (%)
Partial response	4 (3.6%)
Stable disease	33 (30%)
Progressive disease	66 (59%)
Not available	8 (7%)

Source: FDA analysis: ADSL dataset

Only four subjects (3.6%) treated with bridging therapy had an unconfirmed response of PR based on investigator's assessment. The majority of subjects had either stable disease or disease progression after bridging.

A total of 5 subjects that were enrolled with measurable disease received either bridging therapy or palliative radiation therapy (5/127=4%) and converted to unmeasurable status at baseline assessment (after bridging/palliative radiation and prior to receiving lymphodepletion). The response assessment of these 5 subjects is outlined in Table 17:

Table 18 Response Assessment of study population that received bridging:

Subject ID	Response to bridging therapy/Day	IRC adjudicated best response to bb2121	Study day of progression	FDA re-adjudication of best response
(b) (6)	Partial response /Day -7	VGPR	Day 121	Not evaluable
	Not applicable	S CR	Ongoing response	Not evaluable
	Partial response/Day -7	CR	Day 150	Not evaluable
	Partial response/ Day -9	SD	Day 148	Not evaluable
	Stable disease/ Day -6	S CR	Day 437	Not evaluable

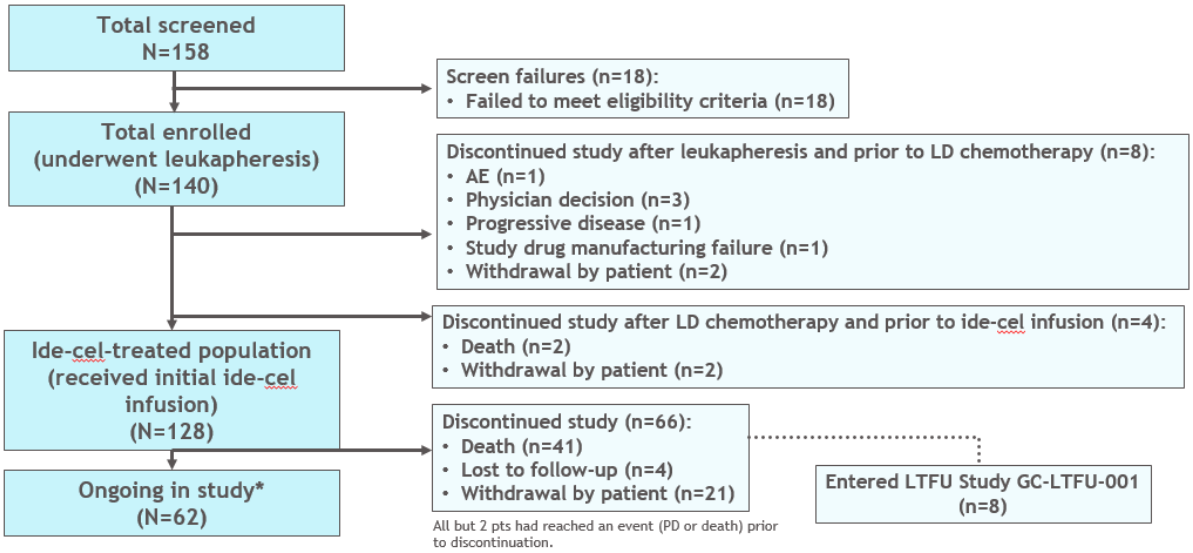
Source: FDA analysis ADRS and ADTTEEFF dataset

* Received only palliative radiation therapy. No systemic therapy was administered.

Reviewer's comment:
Eighty seven percent of the treated population required bridging therapy; reflecting the refractory nature of the treated population. Subjects were not allowed to receive antimyeloma agents during bridging if they were not previously exposed to that agent. This may explain the low overall response rate to bridging therapy at 4%. Post bridging, subjects without measurable disease at baseline could be assessed by the IRC only for CR (complete response) or better, disease progression or stable disease in accordance with the IMWG 2016 guidelines and the protocol. In the absence of measurable disease at baseline, the primary treatment effect of bb2121 cannot be determined with confidence in a single arm trial with ORR as the primary endpoint. Therefore, the review team considered these subjects inevaluable for efficacy.

6.1.10.1.3 Subject Disposition

Figure 2



Source: BLA 125763; AOM September,2020 (Data Cut off January 14,2020).

Out of the 140 subjects that underwent leukapheresis, five subjects were enrolled in the 150 $x10^6$ CAR+T cell dose cohort and four subjects received bb2121 infusion. The fifth subject withdrew consent prior to bb2121 infusion.

A total of 135 subjects underwent leukapheresis (enrolled population) for the 300 and 450 $x10^6$ CAR+ T cell dose cohort. Out of these 135 -subject leukapheresis set:

- 11 subjects were not treated due to withdrawal of consent (3 subjects), physician decision (3 subjects), death (2 subjects), adverse event (1 subject), progressive disease (1 subjects), and study drug manufacturing failure (1 subject).

One subject (ID:(b) (6)) received non-conformal study product which was out of specification with CAR T cell potency of (b) (4). The potency for the CAR T cell activation was 6.8%. This subject was treated in the 300 x10e6 CAR+ T cell dose cohort and was a non-responder. This subject was excluded from safety and efficacy analysis

Reviewer's comment:

1. The disposition table states that 41 subjects have discontinued the study after receiving bb2121 due to death. However, the ADSL datasets identified 44 deaths after receiving bb2121. This discrepancy was clarified with the applicant through an IR. Three subjects who withdrew consent during the follow up period prior to their death were summarized under "withdrawal by patient" category under disposition table.

2. The possibility of manufacturing failure must be considered during risk-benefit analysis of any autologous CAR T cell product. Out of the 140 subjects that underwent leukapheresis, there was one study drug manufacturing failure and non-conformal product was manufactured. The overall manufacturing failure rate of 1.4% is at par with those of commercially available CAR T cell products.

3. The median time from leukapheresis to bb2121 product release was 32 days, from product release to bb2121 administration was 7 days and from leukapheresis to bb2121 administration was 40 days. Given the manufacturing time of approximately 32 days, subjects with a high tumor burden and rapidly progressive disease will require bridging therapy.

4. Subjects that developed PD within 24-months post-treatment were continued in the study for the remainder of 24 months for collection of survival data, HRQoL, safety and PK data. This may explain the high withdrawal rate after treatment with bb2121 (16%) noted in the study.

6.1.11 Efficacy Analyses

Enrolled population includes 140 subjects as depicted in Figure 2.
The efficacy analyses include all subjects who were treated with conforming bb2121 (referred to as bb2121 treated population) and excluded one subject who received the nonconforming product (n=127).
Per the data cut-off date of January 14, 2020, all bb2121 treated subjects had actual median follow up for duration of response (DOR) of 10.5 months (range:.03-20 months). 29 subjects were ongoing responders at the time of data cut off for efficacy analysis. The median follow up for these ongoing responders was 12.9 months (Range: 10.5, 20 months). The follow up for DOR for ongoing responders was at least 12 months in 150 and 300 million dose cohorts. In the 450 million dose cohort, 63% of the ongoing responders had > 9 months but < 12 months follow up for DOR, with remainder 37% having ≥12 months follow up for DOR.
c Four subjects who received bridging therapy and one subject who received palliative radiation therapy had non-measurable disease at baseline and were considered efficacy in evaluable.
Two additional subjects were considered in-evaluable for efficacy as they died from adverse reaction prior to any formal post-baseline efficacy assessment. Overall, seven subjects were considered in-evaluable for efficacy analysis.

Reviewer comment:

- Since the protocol specified primary efficacy analysis was based on bb2121 treated population, the seven efficacy in-evaluable subjects are included in the denominator for calculation of response rates.
- The responder population had at least 9 months follow up for DOR per pre-BLA agreement. The DOR follow up was less extensive in the later introduced 450 million dose cohort compared to the earlier dose cohorts of 150 million and 300 million.

6.1.11.1 Analyses of Primary Endpoint(s)
The primary efficacy analysis was based on ORR as assessed by an independent response committee (IRC) using the IMWG 2016 criteria.
The IRC verified the presence of measurable disease at baseline and evaluability for disease response at each post baseline visit. Disease response was assessed at each time point by the site investigator and by the IRC.IRC assessed response in accordance with IMWG 2016 criteria, supplemental IRC rules and clinical expertise. Two IRC members reviewed the data listing for each response visit. If their response assessment differed regarding the presence of measurable disease at baseline, subject's evaluability for response, response assessment or if the recorded reason for disease progression did not include at least one logical match, then the third IRC member acted as an adjudicator. The adjudicator was blinded to the assessment of the IRC members and reviewed the clinical data prior to adjudication.
If two out of the three IRC members did not agree regarding the presence of measurable disease, evaluability for response, if all three IRC members recorded a different response for a visit or if the reason for PD did not include at least one logical match, then the case was referred for panel adjudication. In panel meetings, all IRC members provided input and final decision was made by the IRC chair.
Reviewer comments:
1. Review team identified 8 cases where the best response (PR or better) was adjudicated by the Panel in the absence of discordant assessments in between the IRC members. Applicant clarified the basis for the deviation in the IRC procedures. For 2 subjects, Panel was convened to review cases and determine final decisions without individual voting to meet timelines. For 3 subjects, cases were referred to the Panel to expedite response adjudication as there were data glitches resulting in misclassification of baseline data requiring re-review of all visits. For remaining 3 subjects, Panel reviewed updated clinical data resulting in re adjudication of response assessment.

2. For four responders, significant discrepancy was identified in between best response adjudicated by different IRC members. Since the IRC charter did not require that IRC members capture reason for response assessment, the rationale for discrepant response assessment could not be ascertained. While this discrepancy may be attributed to the complexity of the IMWG 2016 response criteria, it did not impact the efficacy assessment as the review team concurred with the final response assessment of the adjudication committee in all these cases.

Reviewer identified the following key issues during efficacy review. These issues were discussed with the Applicant via teleconference on November 9, 2020.

1. According to the protocol and IMWG 2016, stringent CR is defined by the concurrent demonstration of negative immunofixation in the serum and urine, normal free light chain ratio and less than 5% plasma cells in bone marrow in the absence of clonal plasma cells by immunohistochemistry. Reviewer identified subjects that were adjudicated as stringent CR without contemporaneous bone marrow assessments performed at the time of response assessment or within the protocol specified visit window (+/- 3 days for the first 12 months and then +/- 14 days). Since the protocol allowed 28 days window to complete missing assessments from CR visit, the review team re adjudicated these stringent CRs to VGPR, if bone marrow assessment supporting sCR was performed outside the 1 month visit window.

The Applicant contended that post- CAR T therapy, initial and rapid clearance of disease in the bone marrow is followed by deepening of biochemical response. Therefore, in the setting of prior bone marrow meeting sCR criteria, or if negative bone marrow results bookend a visit with no biopsy performed, then IRC may consider that visit a sCR without a repeat bone marrow assessment. Given that the protocol and IRC charter prespecified that sCR requires contemporaneous assessment of bone marrow and biochemical parameters, the agency disagreed with post-hoc modification of response criteria and re-adjudicated these cases to VGPR. Such post-hoc modifications in response assessment can result in biased assessment of treatment effect in a single arm trial with ORR as a primary endpoint.

2. Response assessment was based on central laboratory data (bone marrow and efficacy laboratory data) to ensure consistency across investigative sites. The clinical review team applied regulatory flexibility in response assessment by including local efficacy laboratory results where applicable or by changing the timing of best response assessment to meet all the response criteria. This is summarized below:

Subject (b) (6) : Subject was adjudicated by the Applicant as stringent CR at Month 12, however, central assessment of bone marrow performed during the sCR visit was uninterpretable. No additional marrow assessments supporting sCR were available within 1-month allowable time window. Given that the IRC rules allowed that local laboratory data may be used if no overlapping central data was available, the review team accepted local bone marrow assessment performed at Month 12 which supported stringent CR. Subject retained sCR designation at month 12.

Subject (b) (6) : This subject was adjudicated as s CR at Month 9 in the absence of supporting marrow assessment. Subject met bone marrow criteria for stringent CR at Month 12 visit. However, central urine protein electrophoresis and immunofixation was not performed during that visit rendering the assessment incomplete. The review team accepted local urine protein electrophoresis and immunofixation results for the purpose of adjudicating a sCR at Month 12 visit. Urine protein electrophoresis and immunofixation assessments are widely used and standardized tests in myeloma for response assessment. In addition, subject had negative central urine assessments at several time points including Month 9, 15 and 18 , providing confidence in the local test results. Therefore, this subject was considered as sCR at Month 12 for best response.

3. The review team identified a study subject with extramedullary plasmacytoma at baseline who was adjudicated as stringent CR without imaging at the time of response assessment. Subject (b) (6) had a single non-measurable extramedullary gluteal plasmacytoma on CT scan at baseline. This subject was adjudicated as sCR at Month 3 in the absence of any supporting imaging assessment performed post-treatment. A PET/CT scan was performed for this subject at the time of disease progression which served as screening for retreatment with bb2121. Applicant acknowledged that complete resolution of a non-measurable EMP is required on post-treatment imaging for designation of sCR, however, considered this subject as VGPR based solely on biochemical markers. The Applicant contended that serial monitoring of non-measurable EMPs is not required to satisfy response requirement of VGPR per IMWG 2016.

Reviewer's comment: According to practical applications of IMWG 2016, any plasmacytoma at baseline should be serially monitored: otherwise, the patient is considered in-evaluable. Non-measurable EMPs (extramedullary plasmacytomas) at baseline may not be suitable for assessment of VGPR or PR, however, they should be serially monitored as specified in the protocol to assess for disease progression or development of new lesions. Therefore, review team considered this visit as efficacy in evaluable and best response as disease progression.

4. The best response and/or the time of first response was re-adjudicated for subjects who did not have imaging performed as specified in the protocol or within 1 month of stringent CR or CR assessment.
Subject (b) (6) : This subject had plasmacytoma evaluable by imaging (MRI) at screening. Repeat imaging post-treatment was performed at Day 53. However, this subject was adjudicated as s CR at Month 3 in the absence of imaging assessment performed at the visit or an allowable window of 1 month after the visit to asses response. The protocol specified schedule for monitoring plasmacytoma was Month 1, 3, and 6 for the first 1-year post bb2121.Given that subject met biochemical and bone marrow criteria for stringent CR at Month 2 visit with imaging supporting sCR at Day 53, the sCR adjudication was moved at the earlier Month 2 assessment to ensure that all criteria for response were met in the protocol specified window. This re-adjudication did not impact the best response or duration of response.

5. Documentation of response requires two consecutive assessments of the applicable disease parameter (serum M protein, urine M protein or serum FLC) that should be performed any time before institution of any new therapy according to the IMWG 2016, clinical protocol and IRC. Subject (b) (6) was assessed as having sCR at Month 12 in the absence of confirmation of negative urine IFE. Review team downgraded the response to VGPR in the absence of biochemical confirmation as required by the protocol and IMWG 2016.
Reviewer's comment:
The Applicant justified the sCR designation by carrying forward preceding negative urine immunofixation results and substituting them for missing confirmatory test to support sCR assessment at a subsequent visit. Review team interpretation of IMWG 2016 criteria requires biochemical confirmation *after* response assessment has been made and not prior to response assessment. Applicant also proposed use of negative urine IFE results to support s CR for this subject after efficacy data cut off January 14,2020 which the agency did not accept.

Table 19: FDA Re-adjudication of Best Response:

Subject ID	Applicant adjudicated Best response	FDA's Re-adjudicated Best Response	Basis of re-adjudication
(b) (6)	Stringent CR	VGPR	Missing bone marrow assessment, imaging and confirmatory negative serum immunofixation
(b) (6)	Stringent CR	VGPR	Missing confirmatory negative urine immunofixation

Subject ID	Applicant adjudicated Best response	FDA's Re-adjudicated Best Response	Basis of re-adjudication
(b) (6)	Stringent CR	VGPR	Missing confirmatory negative urine immunofixation
	Stringent CR	VGPR	Missing bone marrow assessment
	Stringent CR	VGPR	Missing bone marrow assessment
	Stringent CR	Progressive disease	Missing imaging assessment
	Stringent CR	Not evaluable	No measurable disease at baseline
	VGPR	Not evaluable	No measurable disease at baseline
	Stringent CR	Not evaluable	No measurable disease at baseline
	Complete Response	Not evaluable	No measurable disease at baseline
	Stable disease	Not evaluable	No measurable disease at baseline

^Subject (b) (6) had multiple missing assessments including bone marrow, imaging and biochemical confirmation in support of sCR assessment.
Source: FDA analysis of ADLBEFF, ADRS and ADPL dataset.

Table 20: FDA Re adjudication of time or quality of first response

Subject ID	Applicant adjudicated First Response/ Month	Applicant adjudicated Best Response/ Month	FDA adjudication with underlying basis.	Basis for re-adjudication
(b) (6)	PR/ Month1	PR/ Month1	First response and best response of PR at Month 2	No imaging performed at Month1. Urine criteria for PR not met at Month 1.
(b) (6)	PR/Month1	VGPR/Month 2	First response and best response of VGPR at Month 3.	No Imaging performed at Month 1 or 2.
(b) (6)	CR/Month 1	s CR at Month 2	First response was downgraded to VGPR at Month 1. No change to best response.	Serum IFE at Month 1 was positive for IgG Kappa.

*First response and best response occurred at the same visit based on FDA adjudication.
Source: FDA analysis of ADLBEFF, ADRS and ADPL dataset.

Overall, the best response was re-adjudicated in 11 subjects and timing of first response was modified in two subjects.

Three study subjects did not have assessment for lytic bony lesions at screening or baseline. Since bone lesions are not a part of measurable disease assessment per IMWG 2016, these subjects were considered efficacy evaluable Unknown status of bone lesions at baseline or screening does not influence the final response assessment for these subjects.
Results of the primary endpoint analysis are shown below:
The primary efficacy endpoint was ORR (null hypothesis for ORR ≤50%).
Key secondary endpoint was CR rate (null hypothesis for CR ≤10%).

Table 21: Efficacy Analysis

Response	Enrolled population (for entire study) n=140	Enrolled population (For 300 and 450 million dose cohorts) n= 135	bb2121 treated (150-450 million) n=127	bb2121 treated at recommended Dose range 300-460 million n=100
ORR, n (%) (CR+s CR+PR+VGPR)	89 (63.5%)	87 (64%)	89 (70%)	72 (72%)
95% CI	55%, 71.5%	56%, 72%	62%, 78%	62%, 80%
Stringent CR* n (%)	33 (23.5%)	32 (24%)	33 (26%)	28 (28%)
95% CI	17%, 31%	17%, 32%	18%, 35%	19%, 37%
VGPR n (%)	29 (21%)	28 (21%)	29 (23%)	25 (25%)
95% CI	14%, 28%	14%, 28%	16%, 31%	17%, 35%
Partial response, n (%)	27 (19%)	27 (20%)	27 (21%)	19 (19%)
95% CI	13%, 27%	13%, 27%	14.5%, 29%	12%, 28%
Minimal response, n (%)	2 (1.4%)	2 (1.5%)	2 (1.5%)	0
Stable disease n(%)	20 (14%)	20 (15%)	20 (16%)	15 (15%)
Progressive disease, n (%)	9 (6%)	8 (6%)	9 (7%)	7 (7%)
Not evaluable, n (%)	20 (14%)	18 (13%)	7 (5.5%)	6 (6%)

- *All CRs in the study were stringent CRs.

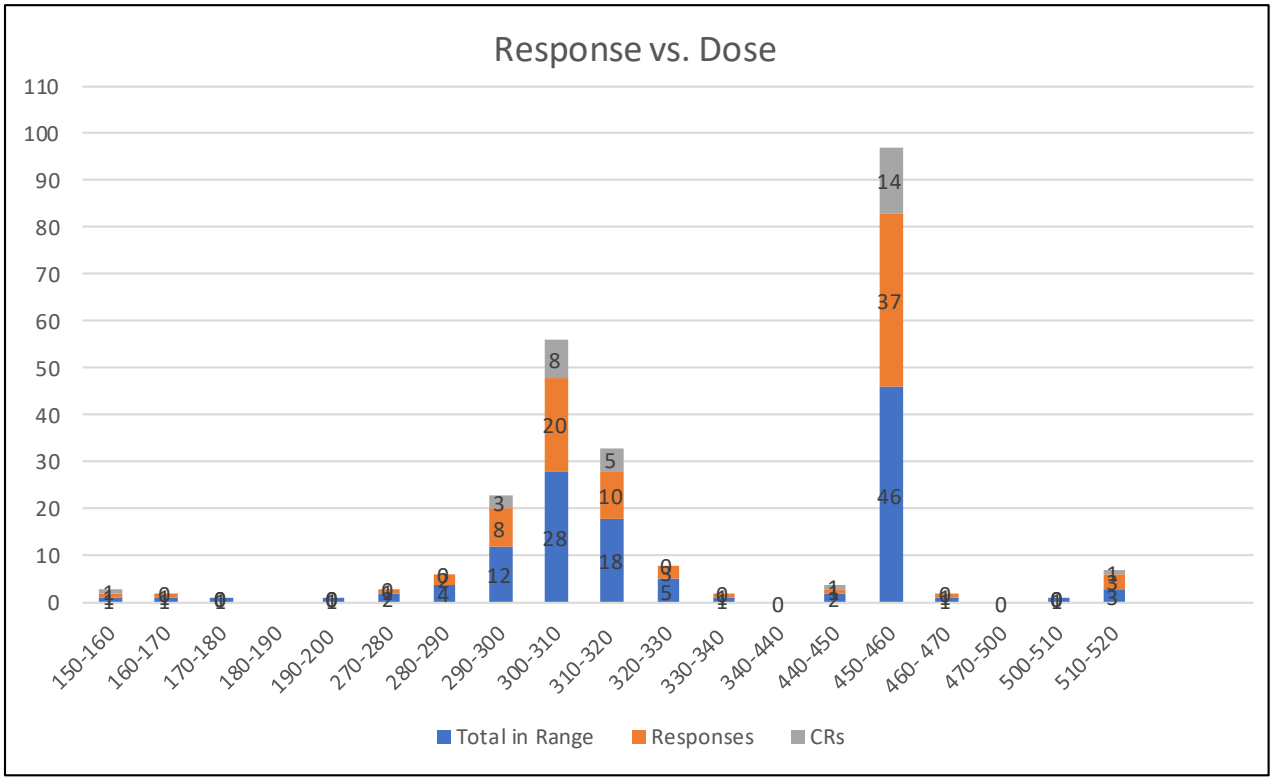
Source: FDA analysis of ADRS dataset.

Out of the 135-subject leukapheresis set for dose cohort 300 x10^6 and 450 x10^6 CAR+ T cells:

- 11 subjects were assigned to a dose but not treated due to consent withdrawal, physician decision, death, adverse event, progressive disease and manufacturing failure (See Section 6.1.10.1.3: Subject Disposition).

- 23 subjects received bb2121 outside the recommended dose range of 300-460 x10^6 CAR+ T cells. 15 out of 23 subjects were responders.
- One subject received bb2121 that did not meet release criteria. This subject was non-responder.

Reviewer's comment: As demonstrated in Table 20 above, for stringent CR, the lower bound of 95% CI exceeded 10% boundary for null across all subgroups included in the efficacy analysis confirming the robustness of the CR data.
The response versus dose assessment is below:
The number in blue indicates how many subjects were in the dose range. The number in the orange bar represents all responses (sCR+PR+VGPR) and the grey bar represents only the sCRs.
Figure 3: Response versus Dose assessment



Source: FDA analysis of ADEX and ADRS dataset

Reviewer's comment:
In the label, the applicant recommends a target dose of 450 x 10^6 CAR + T cells within a range of (b) (4) x 10^6 CAR + T cells. However, the actual administered dose ranged from 150.5-518.4 x 10^6 CAR + T cells. Statistical analyses were used to identify a more appropriate dose range that was efficacious.

Efficacy analysis of the 150 x10^6 CAR+ T cell dose cohort:
The small sample size in the 150 million dose cohort (n=4) in MM-001 is explained on the basis of a shift to enrollment into higher dose cohorts based on emerging dose response relationship from Phase 1 study CRB-401.

Given the limited sample size of 4 subjects in 150 x10^6 CAR + T cell dose cohort, the Agency accepted sponsor's proposal for combining efficacy data for this dose cohort across studies MM-001 and CRB-401 (supportive study) which confirmed the efficacy results from MM-001. . This was done to examine if the combined efficacy results support a dose of 150 x10^6CAR+T cell dose.
As demonstrated in Table 21, the lower bound of 95% CI for ORR does not meet the success criteria of > 50% despite pooling subjects treated at this dose cohort across the two studies indicating lack of efficacy at this dose cohort. Since there is a dose response relationship observed across the dose range, it increases the uncertainty that the lack of efficacy of the 150 million dose cohort to related exclusively to the small sample size.

Table 22: Pooled Efficacy Data for Dose cohort 150 x 10^6 CAR + T cells (Range 140.8-192.4 X 10^6 CAR + T cells)

Study	Subjects treated	ORR n(%)	Lower bound 95% CI ORR rate	CR n (%)	Lower bound 95% CI CR rate
MM-001	4	2 (50%)	6.8%	1(25%)	0.6%
CRB-401	18	10 (55.5%)	30.8%	6 (33%)	13%
Total	22	12 (54.5%)	32%	7 (32%)	14%

Source: FDA analysis of ADRS and Summary of Clinical Efficacy: BLA 125736

For the remainder of the dose range, we analyzed the efficacy at smaller dose range subset in increments of 10 million as shown below. Lower bound of 95% CI did not meet the success criteria of >50% for dose below 300 and above 460 x10^6 CAR + T cells. This is likely due to the small sample size in those dose ranges where the efficacy data is limited.
Based on this dose response subgroup analysis, the reviewer determined that the dose range should not include the lower (dose below 300 x10^6CAR+ T cells) and higher range of the dose (above 460 x10^6 CAR + T cells). Although the dose range of 310-450 x10^6 CAR + T cells had limited sample size such that the lower bounds of the 95% CI were below the proposed null, this dose range was considered efficacious based on extrapolation of the efficacy observed in the dose ranges below and above this dose range. The dose on the label should encompass the dose range between 300-460 x10^6 CAR + T cells supported by the efficacy data and not wide range of (b) (4) x10^6 CAR+ T cells as proposed by the applicant.

Table 23: Dose Range and Response from 270-520 x10^6 CAR + T cells :

Dose Range (x10^6 CAR+ T cells)	Subjects in Range	All Responses (PR or better) n (%)	ORR: Lower Bound 95% CI	CR n (%)	CR rate: Lower Bound 95% CI
270-280	2	1 (50%)	1%	0	
280-290	4	2 (50%)	7%	0	
290-300	12	8 (67%)	35%	3 (25%)	5%
300-310	28	20 (71%)	51%	8 (28.5%)	13%
310-320	18	10 (56%)	31%	5 (28%)	9.7%
320-330	5	3 (60%)	15%	0	

Dose Range (x10^6 CAR+ T cells)	Subjects in Range	All Responses (PR or better) n (%)	ORR: Lower Bound 95% CI	CR n (%)	CR rate: Lower Bound 95% CI
330-340	1	1 (100%)	2%	0	
340-440	None				
440-450	2	1 (50%)	1%	1 (50%)	2%
450-460	46	37 (80%)	66%	14 (30%)	18%
460- 470	1	1 (100%)	2%	0	
470-500	None				
500-510	1	0		0	
510-520	3	3 (100%)	29%	1(33%)	0.8%

Source: FDA analysis of ADRS and ADEX dataset

Table 24: Dose Response Relationship within the approved dose range:

Response	300-340 million cohort n=52	440-460 million cohort n= 48
ORR, n (%)	34 (65%)	38 (79%)
95% CI	51%, 78%	65%, 89.5%
Estimated median duration of response	10.4 months	11.3 months
95% CI	7.2, 11	10.4, 11.4
Median follow up time Range	10 months .03+, 19.7+	10.8 months 1.2, 14.5 +
Stringent CR or CR n (%)	13 (25%)	15 (31%)
95% CI	14%, 39%	19%, 46%
VGPR n (%)	9 (17%)	16 (33%)
95% CI	8%, 30%	20%, 48%
Partial response, n (%)	12 (23%)	7 (14.5%)
95% CI	12.5%, 37%	6%, 28%
Minimal response, n (%)	0	0
Stable disease n(%)	8 (15%)	7 (14.5%)
Progressive disease, n (%)	7 (13%)	0
Not evaluable, n (%)	3 (6%)	3 (6%)

Source: FDA analysis of ADRS and ADEX dataset

Reviewer's comment: Within the recommended dose range of 300-460 x10^6 CAR+T cells, a dose response relationship was identified. A numerically higher ORR, CR rate and median duration of response was noted with the higher dose range of 440-460 x10^6 CAR+ T cells compared to the lower dose range of 300-340 x10^6CAR+ T cells. This information will be included in the label to inform prescribers. 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. (See Section 4.1, CMC for details). 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 cells. 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 (See Table 22 above for distribution of subjects in this dose range). 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 the dose ranges from 460-518 x10^6 CAR+ T cells raises uncertainties about the reliability of the sample size and the efficacy outcome to support extending dose range above 460 x10^6 CAR+ T cells. Finally, the 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. (See Section 4.4, Clinical Pharmacology for details).

6.1.11.2 Analyses of Secondary Endpoints

Table 25: Duration of response:

Parameter	**Dose range 300-460 x 10^6 CAR + T cells, n=100**
Number of subjects with response;(PR or better): n(%)	72 (72%)
Number of events, n (%)	44 (61%)
Progression	42 (58%)
Death	2 (2.7%)
Censored, n (%)	28 (39%)
Ongoing	25 (35%)
Progression after two or more missed assessments	1 (1.4%)
Received a new anticancer therapy	1 (1.4%)
Discontinued study without progression or death	1 (1.4%)
Estimated median DOR	11 months

Parameter	Dose range 300-460 x 10^6 CAR + T cells, n=100
95% CI	10.3, 11.4 months
Median follow up for the dose range	10.7 months
Range	.03+, to 19.7+

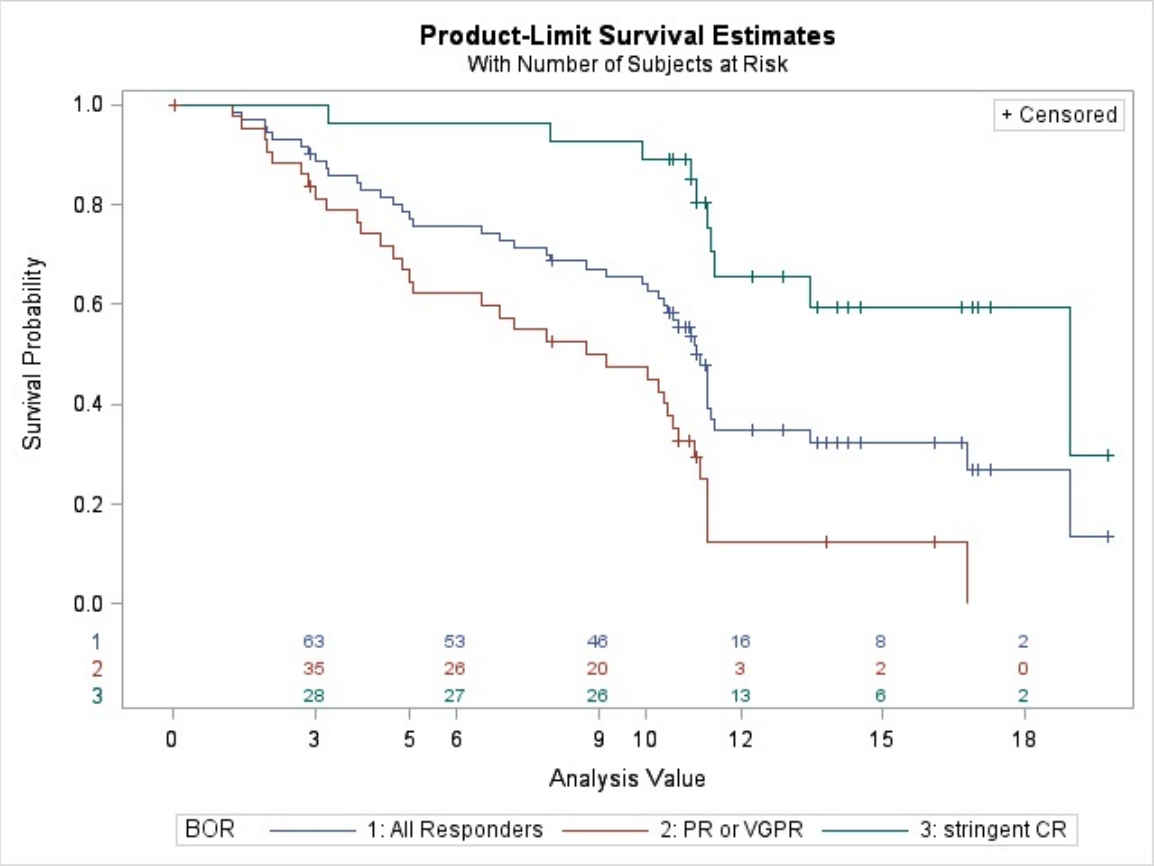
Source: FDA analysis of ADTTEEFF dataset

The median PFS for subjects treated at the 300-460 million dose range is 11.1 months (95% CI: 6.1, 12.1) with median OS of 19 months (95% CI: 18, NE).

The estimated median DOR for responders in 300-460 x 10^6 CAR + T cell dose range based on the depth of response:

Stringent CR= 19 months (95% CI: 11.4, NE) , PR+ VGPR= 9.2 months (95% CI: 5.0, 10.6)
VGPR= 11 months (95% CI: 8.7, 11.3), PR= 4 months (95% CI: 2.7, 7.2).

Figure 4: KM Curve for Duration of Response (DOR) based on the depth of response: Dose range 300-460X10^6 CAR+ T cells:



Source: FDA statistical reviewer

Table 26: DOR Landmark Analysis: KM estimates Dose range 300-460 million CAR+ T cells

DOR Landmarks	all responders (N=72) % (95% CI)	CRs (N=28) % (95% CI)	PR+ VGPR (N=44) % (95% CI)	VGPR (N=25) % (95% CI)
At least 6 months	76% (64, 84)	96% (77, 99)	62% (46, 75)	76% (54, 88)
At least 9 months	67% (55, 77)	93% (74, 98)	50% (34, 64)	68% (46, 82)
At least 12 months	35% (23, 47)	65% (42, 81)	13% (4, 28)	22% (6, 44)
At least 18 months	27% (14, 42)	60% (36, 77)	N/A	N/A

Source: FDA statistical reviewer

Reviewer comment:

Stringent CRs (s CR) tended to have substantially longer DOR (duration of response) compared to PR+ VGPR. However, the estimated median DOR of 19 months for sCRs is skewed given the small sample size of 28 subjects with wide confidence intervals. In addition, 18 out of 28 (64%) stringent CR subjects were censored with 7 subjects (25% of the sCRs) censored prior to 12 months (censored between 10.4-11.2 months). This indicates that the follow up for durability of response may be limited in the sCR subset. To get an accurate

estimate of the durability of response, we also examined the DOR landmark analysis demonstrated in Table 25 above. This shows that an estimated 65% of the sCR subjects remain in response at 12 months, an estimated 22% of the VGPR subjects and 35% of the overall responders are in response at 12 months indicating that the overall durability is driven by the sCR cohort. Stringent CR and observed durability is considered a measure of clinical benefit with this product. This association of stringent CR status and durability is a unique attribute of this product, making it an important regulatory consideration for this application. Other approved therapies for R/R myeloma in a similar later line setting typically have much lower CR rates (See Section 2.2) and CR status has not been typically associated with duration of response (DOR).

Triple Refractory Subgroup Analysis:

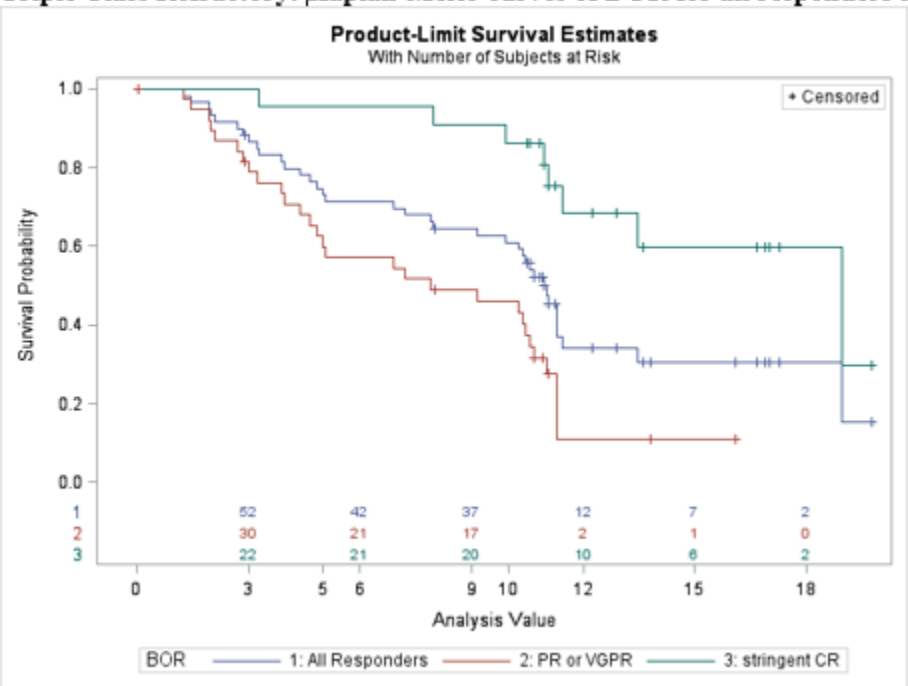
To evaluate the efficacy of bb2121 in the refractory cohort, we performed a subgroup analysis for the triple class refractory multiple myeloma population treated at the dose range of 300- 460 x 10^6 CAR+ T cells.

85/100 (85%) subjects treated within the recommended dose range were triple class refractory. In this subgroup, the ORR was 72%; 95% CI (61%, 81%), s CR rate was 26% ;95% CI (17%, 36%) and VGPR rate was 25%;(16%, 35%). The median follow up (for OS) was 12.9 months (Range: 0.2, 20.8).

The median DOR in this subgroup was 10.9 months 95% CI (9.2, 11.4).

Figure 5:

Triple Class Refractory: Kaplan-Meier curves of DOR for all responders and by BOR



Source: FDA statistical reviewer

Table 27: Triple Class Refractory: DOR Landmark Analysis: KM estimates for Dose range 300-460 million CAR+ T cells.

	All Responders (N=61)	s CR (N=22)	PR+VGPR (N=39)	VGPR (N=21)
Estimated median DOR (95% CI)	10.9 (9.2, 11.4)	19.0 (11.0, NE)	7.9 (4.7, 10.6)	11.27 (5.1, 11.30)
Percentage censored	39%	64%	26%	38%
Median Follow-up (range)	10.5 (0.03+, 19.7+)	11.3 (3.3, 19.7+)	7.2 (0.03+, 16.1+)	10.6 (1.2, 16.1+)
DOR landmarks % (95% CI)				
6-month	71% (58, 81)	95% (72, 99)	57% (40, 71)	71% (47, 86)
9-month	65% (51, 75)	91% (68, 98)	49% (32, 64)	67% (43, 83)
12-month	34% (21, 48)	68% (42, 85)	11% (2, 28)	21% (4, 47)
18-month	31% (18, 45)	60% (32, 79)	N/A .	N/A

Source: FDA statistical reviewer

Reviewer's comment: Triple class refractory is a distinct subpopulation of R/R myeloma with overall poor prognosis and limited therapeutic options. Comparable efficacy of bb2121 including response rate and duration of response for stringent CR in this subgroup compared to the overall treated population indicates that clinical efficacy data are robust.

Minimal Residual Disease (MRD) status:

Minimal residual disease was assessed in the bone marrow samples using a validated and FDA approved Clonoseq assay which is based on next generation sequencing (NGS) methodology. An MRD threshold of (b) (4) was used as prespecified in the study. This sensitivity was based on a LOD of (b) (4) with a DNA input of at least (b) (4) micrograms.

Out of the 28 subjects adjudicated as having CR or better within the approved dose range of 300-460 million CAR+ T cells, MRD was evaluated for 23 subjects. The remaining 5 subjects were MRD in-evaluable for the following reasons:

- 4 subjects ((b) (6)) failed calibration as both screening and baseline bone marrow biopsies did not identify a dominant trackable clone.
- 1 subject ((b) (6)) did not have a screening biopsy and the baseline biopsy failed to identify a dominant trackable clone.

Bone marrow biopsy performed at screening was prioritized for detection of dominant trackable clone (calibration). For five out of the 23 MRD evaluable subjects, screening biopsy was either missing (n=1) or a dominant trackable clone could not be identified at screening (n=4). Therefore, bone marrow biopsy from the baseline visit was used for MRD calibration for these subjects. Successful calibration either at screening or baseline was performed in all 23 MRD evaluable subjects.

One subject (Subject ID:(b) (6)) was reportedly MRD negative at baseline despite having 80% plasma cells in the marrow on morphological assessment. This was considered a false

negative baseline result and therefore, any post-treatment MRD negative result was considered uninterpretable.
On subject (Subject ID :(b) (6)), did not have a baseline MRD assessment as no baseline bone marrow was performed. Therefore, this subject was considered in- evaluable for MRD negativity post-treatment.
Overall MRD negativity defined as the proportion of ≥CR subjects and who are MRD negative at any timepoint within 3 months prior to achieving ≥CR until the time of progression or death was observed in 21/28 subjects (75%; 95% CI: 55%, 89%). Overall, 21/100 (21% 95% CI 13%, 30%) subjects treated within the recommended dose range of 300-460 $x10^6$ CAR+ T cells attained MRD negativity.

Reviewer's comment:
1. As outlined above, calibration was performed on the baseline bone marrow for five subjects. Therefore, no baseline MRD assessment was available for these subjects. Since successful calibration indicated presence of a malignant clone, this was accepted as baseline for post-treatment MRD negative assessment.

2 The attainment of an MRD negative rate of 21% in a heavily pre-treated relapsed refractory multiple myeloma population has not been reported previously. However, ,~~is unprecedented~~, the clinical significance of MRD negativity post- CAR T therapy remains unknown at this time.

6.1.11.3 Subpopulation Analyses: Efficacy
Subpopulation: 65 years and older:
Thirty six out of the 100 subjects treated at the recommended dose of 300-460 million CAR+ T cells were ≥65 years of age (Range 65-78 years). Four subjects (4%) of the subjects were ≥75 years of age. Within the subgroup of subjects ≥65 years of age, the ORR was 83% with stringent CR rate of 30%. Therefore, efficacy of bb2121 in this subpopulation was comparable to the efficacy noted in population <65 years of age.
Subpopulation: Creatinine clearance <45 ml/minute:
Nine subjects (9/127) treated in the study had creatinine clearance of <45 ml/minute (Range: 30 ml/minute to 45 ml/minute) which was lower than protocol specified threshold of 45 ml/minute. Three subjects had creatinine clearance <35 ml/minute. The fludarabine was dose reduced for all of these subjects. Eight out of the nine subjects were treated in the recommended dose range of 300-460 $x10^6$ million CAR+ T cells. ORR in this subgroup was 62.5% (5/8). No s CR were reported in this group. Given the limitation of a small sample size no conclusions can be made about the efficacy of bb2121 in this subgroup. However, considering the mechanism of action of CAR T therapy, it is not expected that its efficacy will be impacted by renal dysfunction.

No subpopulation efficacy analyses were performed for high risk cytogenetics (n=37/100) and extramedullary disease (n=36/100) subgroups given the limited sample size of these subgroups.

6.1.11.4 Dropouts and/or Discontinuations
Summary of Discontinuations

Leukaphereses set, n (%)	**140 (100%)**
Discontinued before bb2121 treatment	12 (8.5%)
Death	2 (1.4%)
Disease progression	1 (0.7%)
Adverse event	1 (0.7%)
Manufacturing failure	1 (0.7%)

Withdrawal by patient	4 (3%)
Physician decision	3 (2%)
Received bb2121 *	**128 (91.4%)**
Discontinued after receiving bb2121	66 (47%)
Death[1]	41 (29%)
Withdrew consent	21 (15%)
Lost to follow-up	4 (3%)
Follow-up ongoing	62 (44%)

Source: FDA analysis of ADSL
*One subject received non-conforming product and was not included in efficacy or safety analysis of bb2121 treated population
[1] Does not include three subjects that died after withdrawal of consent and are included in analyses of deaths in Section 6.1.12.3 Deaths.

6.1.11.5 Exploratory and Post Hoc Analyses
None

6.1.12 Safety Analyses

6.1.12.1 Methods
The key materials used for the safety review included:

- The BLA application electronic submission
- Applicant submissions in response to the review team's information requests
- Proposed labeling for bb2121
- Published literature
- Prior regulatory history

The clinical review of safety was primarily based upon analysis of 127 subjects treated with conforming product at dose of 150.5 to 518.4 x 10^6 CAR+ T cells in the MM-001 study at the primary data cutoff of October 16, 2019 with median duration of follow up of 11.4 months for safety. Though the data cut off for safety was three months earlier than efficacy, median follow up duration of 11.4 months for safety is considered adequate given that most of the treatment emergent safety events have early onset and additional follow up is unlikely to add to new adverse events. The bb2121 analysis datasets (ADAM datasets) were used for the safety analysis. Analyses by the clinical reviewer for safety were performed largely using (b) (4). All narratives and relevant case report forms (CRFs) were reviewed for serious adverse events (SAEs) and deaths that occurred in the primary safety population. Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0, and AE severity was graded using the National Cancer Institute's (NCI's) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Cytokine release syndrome (CRS) severity was graded as a syndrome according to a modification of the 2014 Lee criteria grading system.[11] The modification of the Lee criteria is that neurological AEs are not considered in CRS grading of organ toxicity since neurological toxicity is now considered a distinct entity. Adverse events that were not defined in the CTCAE were evaluated for severity/intensity as mild i.e., Grade 1, moderate (Grade 2), severe (Grade 3), life-threatening (Grade 4), or death (Grade 5).
For the safety review, "Day 1" refers to the day of bb2121 infusion (corresponds to Day 0 in the protocol). The safety analysis was performed for all subjects treated with any dose of conforming bb2121 product and only includes the initial infusion of bb2121. Safety analysis of

the retreatment period is outside the scope of this BLA review and the dosing recommendations are based on anticipated administration of a single dose.
Serious adverse events (SAEs) were defined as any AEs that met at least one of the following criteria: fatal, life threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability, resulted in congenital anomaly or birth defect, or resulted in any other medically important serious event. SAEs were collected from the time of screening. AEs were collected from enrollment until the end of study participation. The adverse event reporting periods and the adverse events that were collected are outlined in Table 28 below:

Table 28: Adverse Event Reporting Periods in Study MM-001

Time Period	Events to Record
Informed consent to start of LDC	Procedure-related AEs and all SAEs.
Start of LDC to 6 months post-bb2121 infusion	All AEs/SAEs regardless of grade or relationship to the study treatment.
From Month 7 post-bb2121 until Month 24/EOS.	All Grade ≥ 3 AEs, all SAEs and AESI regardless of grade or relationship to study treatment.
From Month 25 post-bb2121 to end of study participation	Possibly related Grade ≥3 AEs, possibly related SAEs and possibly related AESI.

Source: Adapted from MM-001 Clinical Protocol
Abbreviations used: LDC: lymphodepleting chemotherapy, AEs: adverse events, SAE: serious adverse events, AESI: adverse event of special interest, EOS: end of study

Reviewer's comments:
1. Adverse drug reactions were defined as AEs occurring after the start of bb2121 infusion, regardless of the perceived relationship with the investigational product. The applicant primarily used preferred terms to report AEs and grouped certain terms, but the grouping used was limited and occasionally missed cases. For a more comprehensive evaluation of safety, the clinical reviewer's analysis included grouped AEs that represented the same or similar clinical conditions. This grouping strategy for safety analyses is aligned with grouping practices for review of similar agents and allows for consistency in the Agency's review. The complete list of FDA's grouped terms is presented in APPENDIX A. Unless otherwise specified, all analyses and tables were generated by the FDA clinical reviewer.

2. The 90-day safety update with data cut-off of April 7,2020 did not include any additional subjects from study MM-001. No new safety signals were identified in this update.

3.Subjects with disease progression within 24 months of bb2121 infusion continued in the study until month 24. Therefore, the safety analysis includes subjects that received new antimyeloma therapy after disease progression. As of the data cutoff date of October 16, 2019, 40 subjects (31%) received at least one subsequent antimyeloma therapy. The safety analysis does not include subjects re-treated with bb2121 as safety review encompassed the initial treatment period for bb2121.

The demographic information and subject disposition for the subjects evaluated for safety are summarized below in Tables 30 and 31:

Table 28: Demographics of Safety Population in Study MM-001

Demographics	bb2121 treated population bb2121 (CAR+T cells) Dose Cohort			
Characteristics	150X10e6 (N=4)	300x10e6 (N=70)	450 x10e6 (N=53)	Total 150-450x10e6 (N=127)
Age (years)				
Mean (SD)	56.5 (8.7)	58.7 (9.4)	61.6 (9.3)	59.8 (9.4)
Median(range)	54(49, 69)	60.5 (33, 76)	62 (43, 78)	61 (33, 78)
Age groups (years) n(%)				
18 to <65	3 (75)	47 (67)	32 (60.3)	82 (64.5)
65 to < 75	1 (25)	22 (31)	18 (33.9)	41 (32.2)
≥75	0	1(1)	3(6)	4(3.1)
Sex, n (%)				
Male	4(100)	38 (54)	34 (63)	76 (59.8)
Female	0	32 (46)	19 (37)	51 (40.1)
Race, n (%)				
Asian	0	3(4)	0	3 (2.3)
Black or African American	0	3 (4)	3 (6)	6 (4.7)
White	4(100)	58 (83)	40 (76)	102 (80.3)
Unknown	0	2 (3)	8 (15)	10 (7.8)
Other	0	4 (6)	2 (4)	6 (4.7)
Ethnicity, n (%)				
Hispanic or Latino	0	6 (10)	4 (7)	10(7.8)
Non-Hispanic or Latino	4(100)	59 (83)	40 (76)	103 (81)
Not Reported	0	1(1)	8 (15)	9 (7)
Unknown	0	4 (6)	1 (2)	5 (3.9)
ECOG performance status				
0	3 (75)	32 (46)	22 (42)	57 (45)
1	1 (25)	37 (53)	29 (55)	67 (53)
2	0	1 (1.4)	2 (3.8)	3 (2.4)
Creatinine clearance ml/mt				
<30	0	0	1 (1.8)	1(0.8)
30-<45	0	4 (5.7)	4 (7.5)	8 (6)
45-<60	0	6 (8.6)	6 (11.3)	12 (9.4)
60-<80	1 (25)	20 (28.5)	14 (26.4)	35 (27.5)
≥80	3 (75)	40 (57)	28 (52.8)	71 (56)
Country				
USA	4 (100)	61 (87)	28 (53)	93 (73)
Netherlands	0	1 (1.4)	5 (9)	6 (4.7)
Belgium	0	1 (1.4)	2 (3.8)	3 (2.4)
Spain	0	7 (10)	6 (11)	13 (10)
Canada	0	0	1 (1.9)	1 (0.8)
France	0	0	8 (15)	8 (6)
Italy	0	0	3 (6)	3 (2.4)

Source: FDA analysis of ADSL.xpt

Table 30: Study MM-001: Subject disposition in safety population

Disposition	150 million N = 4 n (%)	300 million N = 70 n (%)	450 million N = 53 n (%)	Overall N = 127 n (%)
End of Study Status				
Discontinued [a]	3 (75%)	40 (57%)	22 (41.5%)	65 (51%)
Completed [b]	0	0	0	0
Ongoing	1 (25%)	30 (43%)	31 (58.5%)	62 (49%)
Reason for Discontinuation from Study				
Death	2 (50%)	25 (36%)	13 (24.5%)	40 (31.5%)
Withdrew Consent	0	13 (19%)	8 (15%)	21 (16.5%)
Lost to follow up	1 (25%)	2 (3%)	1 (2%)	4 (3%)

Source: Applicant IR Dated January 6, 2021.
a= Discontinued study if subject discontinued long-term follow-up by January 14, 2020 due to death, consent withdrawal or lost to follow up.
b= Completed study is defined as 5 years from last subject receiving initial bb2121 infusion
Based on January 14, 2020 data cut off
Majority of deaths were due to progressive disease. Please see section 6.1.12.3 Deaths for details.

Table 31: Prior lines of therapy in study MM-001:

Characteristic	bb2121 treated population CAR + T cells Dose Cohort			
	150 million N = 4	300 million N = 70	450 million N = 53	Total N=127
Number of prior antimyeloma regimens				
Median (min, max)	8.5 (4, 12)	6 (3, 16)	5 (3, 13)	6 (3, 16)
Distribution of prior antimyeloma regimens n (%)				
3	0	7 (10)	7 (13)	14 (11)
4	1 (25)	8 (11)	10 (19)	19 (15)
5	0	11 (16)	11 (21)	22 (17)
6	1 (25)	12 (17)	10 (19)	23 (18)
≥ 7	2 (50)	32 (46)	15 (28)	49 (39)

Source: FDA analysis of ADSL.xpt

Reviewer's comments: Subjects enrolled in MM-001 were heavily pretreated patients who had received all generally accepted standard therapies for relapsed refractory multiple myeloma. 98% of the patients had ECOG functional status of 0 or 1 and 93% had creatinine clearance at baseline of ≥45 ml/minute. 97% of the population was <75 years of age. The safety population reflects population that is less than 75 years of age with preserved renal function and performance status. Therefore, the safety findings from this study may not be reflective of myeloma population that is older or with poor functional status and renal insufficiency.

6.1.12.2 Overview of Adverse Events

Adverse events (AEs) and serious adverse events (SAEs) were evaluated during clinic visits, hospitalizations, and follow-up visits per protocol-defined guidelines. Safety data are available for a total of 127 subjects who received conforming bb2121 product before the data cutoff of October 6, 2019. Adverse events and deaths were also assessed for the period from enrollment to the planned time of infusion to assess risks for subjects who did not receive bb2121 due to manufacturing issues or adverse events. One hundred and forty subjects underwent leukaphereses; however, twelve subjects (8.5%) did not receive treatment with bb2121 and one subject received the non-conformal product. Two subjects (1%) were reported dead before infusing, four subjects (3%) withdrew, one subject (0.7%) each had an adverse event and progressive disease respectively. Three subjects (2%) were withdrawn based on physician decision and one subject had manufacturing failure (0.7%).

All 127 subjects (100%) had at least one AE. AEs and SAEs are events that occurred after the administration of bb2121. Table 32 presents an overview of all AEs.

Table 32: Summary of Adverse Events Study MM-001

AE/SAE	150 million N = 4 n (%)	300 million N = 70 n (%)	450 million N = 53 n (%)	Overall N = 127 n (%)
All-Grade AEs	4 (100%)	70 (100%)	53 (100%)	127 (100%)
Max Grade 3-5 AEs	4 (100%)	69 (98.5%)	53 (100%)	126 (99%)
Max Grade 3	0	8 (11%)	3 (6%)	11 (9%)
Max Grade 4	3 (75%)	48 (68.5%)	42 (79%)	93 (73%)
Max Grade 3 or 4	3 (75%)	56 (69%)	45 (85%)	104 (82%)
AEs leading to death*	0	2 (2.8%)	5 (9.4%)	7 (5.5%)
SAEs	4(100%)	44(63%)	37(70%)	85(67%)

Source: FDA Analysis using ADAE3 .xpt, Study MM-001
**Excludes death from progressive disease*
AE: Adverse event/s; SAE: serious adverse event/s

Table 33: All grade nonlaboratory adverse events occurring in ≥ 10% of subjects

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

Body System Organ Class AE	All Grades (%)	Grades 3 - 5 (Max Grade) (%)
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
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

Body System Organ Class AE	All Grades (%)	Grades 3 - 5 (Max Grade) (%)
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;*
 # 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.

Reviewer's comments:
1. All grade AEs occurring in 10% or more subjects in study MM-001 are consistent with those seen with the approved anti-CD19 CAR-T products. These AEs reflect the toxicities of the investigational protocol including lymphodepletion with fludarabine and cyclophosphamide. Overall general physical health deterioration may reflect occurrence of disease progression in a heavily pre-treated myeloma population.

2. Although the AEs are presented by system organ class (SOC), some grouped terms include more than one SOC and are indicated with a # sign in Table 33;
e.g. encephalopathy includes nervous system disorders and psychiatric disorders SOCs. We placed these group term AEs under the SOC with most representation in the data for that AE and/or clinically most appropriate e.g. pain in general disorders SOC, rash under skin and subcutaneous disorders SOC, encephalopathy under nervous system disorders SOC etc.

4. Pain as a group term was not included in the label, since we thought it was too broad a category to provide meaningful information to clinicians. This is consistent with labeling of other recent CAR T approvals.

5.The incidence of encephalopathy in Table 33 differs from that in the section on neurologic toxicity given that table 33 includes all reported events of treatment emergent encephalopathy, whether it was adjudicated to be due to the investigational therapy. For example, encephalopathy from concomitant medications or from ICU hospitalization was included in Table 33 but not under neurotoxicity from bb2121. In the section on neurologic toxicity, only those events attributed to CAR-T cell toxicity were included.

6. Infections: The reviewer re-adjudicated AEs that were indicative of infection but were misclassified under other SOCs such as Respiratory, thoracic and mediastinal disorders, Investigations and General disorders and Administration site conditions. The infections were then classified by the pathogen type based on the high-level group terms (AEHLGT). Infections based on location: upper respiratory tract infection, lower respiratory tract infection, pneumonia, and urinary tract infection were analyzed using FDA's grouped terms as these are frequent sites of infections and would be informative to the prescriber. The label includes both infections by pathogen type and location, with some infections included in both grouping. This approach was felt to be most useful to the prescribers.

7. The incidence of hypogammaglobulinemia is a composite of events reported in ADAE dataset and laboratory values of IgG < 500 mg/dl following bb2121 administration.

This period included AEs from leukapheresis until the start of lymphodepletion. Overview of AEs during this time period is shown in Table 34.

Table 34:Adverse Events from Leukapheresis to Lymphodepletion (LDC)

Parameter	Leukapheresis to Lymphodepletion n(%)
Total Number of Subjects	140
Any AE	73 (52)
Any Grade 3-4 AE (Max Grade)	47 (34)
Any Grade 5 AE	2 (1.4)
Any SAE	30 (21)
Related to bridging therapy	27 (19%)

Source: ADAE 3 dataset, includes 1 subject who received non-conforming product
Abbreviations used: AE: adverse event; SAE: serious adverse event

From leukapheresis to LDC; the most frequently reported AEs in 5% or more of subjects were anemia (17%; 24/140), thrombocytopenia (16%; 23/140), neutropenia (11%; 15/140), lymphopenia (6%; 8/140), leukopenia (5%; 7/140) and nausea (5%; 7/140).
This toxicity profile is not unusual for a heavily pre-treated population, the majority of who (119/140=85%) received bridging antimyeloma therapy prior to receiving LD and bb2121.
One subject died from acute respiratory failure and another subject died from plasma cell leukemia during this time period.
Out of the 119 subjects who received bridging therapy, the most commonly reported toxicity of bridging therapy included thrombocytopenia (9%), neutropenia (8%), anemia (7.5%), leukopenia (4%), lymphopenia (4%) and nausea (4%).

Adverse Events from Lymphodepleting Chemotherapy (LDC) to bb2121 infusion:
The lymphodepleting AE period was calculated from the first day of the LDC to prior to bb2121 infusion. 115 of 132 subjects had an AE and ninety-seven (73%) of those were deemed related to LDC. Table 35 gives a summary of AEs unrelated or related to LDC during this time period.

Table 35: Adverse Events in Lymphodepletion period in Study MM-001*

Parameter	Lymphodepletion Period N=132*(%)
Any AE	115 (87)
Any grade 3-4 AE (Max. Grade)	74 (56)
Any grade 5 AE	2 (1.5)
Any SAE	11 (8)
Any AE related to LDC	97 (73)
Any grade 3-4 AE related to LDC	66 (50)
Any grade 5 AE related to LDC	0
Any SAE related to LDC	3(2)

Source: FDA analysis of ADAE 3 dataset
**Includes one subject who received non-conforming product*
Abbreviations: AE: adverse event; SAE: serious adverse event; LDC: lymphodepleting chemotherapy

Two subjects died after receiving LD and prior to receiving bb2121. One subject died from general physical health deterioration and another subject died from septic shock.

Table 36 : Adverse Events in ≥ 10% of subjects in Lymphodepletion Period in Study MM-001 *

Adverse Event	Lymphodepletion Period N=132 (%)
Nausea	45 (34)
Anemia	42 (32)
Neutropenia	41 (31)
Leukopenia	35 (26)
Thrombocytopenia	33 (25)
Lymphopenia	27 (20)
Constipation	20 (15)
Headache	14 (11)

Source: FDA analysis of ADAE 3 dataset
**Includes one subject who received non-conforming product*

Reviewer's comment: Toxicity profile is consistent with commonly anticipated adverse events from lymphodepleting chemotherapy. Most of the grade 3 or 4 AEs related to lymphodepletion were cytopenias that either worsened in grade or remained the same grade prior to bb2121. None of these AEs worsened in grade post bb2121 and most resolved after receiving bb2121.This is expected in a heavily pre-treated myeloma population, many of whom had Grade 2 neutropenia and/or thrombocytopenia at the time of study enrollment. Severe and persistent cytopenia is an anticipated safety concern with this product and therefore, will be monitored post-approval in the post-marketing registry protocol. Five subjects developed non-hematological grade 3 or 4 AE after receiving lymphodepletion. These included dyspnea, respiratory tract infection, abdominal pain, hyperuricemia and hypertension. Respiratory tract infection and dyspnea resolved prior to administration of bb2121. The remaining AEs resolved without worsening in grade post bb2121. Two subjects that died after receiving LD and prior to bb2121 have been included in Section 14 of the label to inform prescribers about the risk of the entire investigational therapy including LD.

6.1.12.3 Deaths
While the primary safety analysis was conducted with data cutoff date of October 16, 2019, the reviewer analyzed all deaths with data cutoff date of January 14, 2020. Forty-three out of the 127 bb2121 treated subjects had died at the time of efficacy data cut off (January 14,2020) for BLA submission.

Table 37:Summary of deaths post-bb2121 in Study MM-001 based on FDA adjudication

Death Statistic	Overall N = 127 n (%)
All Deaths	43 (34%)
Disease Progression	23 (18%)
Fatal Adverse Events	7 (5.5%)
Other causes	8 (6%)
Unknown cause	5 (4%)
Fatal AEs ≤ 30 days of bb2121	1 (0.8%)
Fatal AEs > 30 days after bb2121	6 (4.7%)

Source: FDA Analysis at January 14,2020 data cutoff

Table 38:Summary of fatal AEs observed in Study MM-001

USUBJID	Fatal Adverse Event	Dose Regimen	Study day of death
(b) (6)	Cytokine release syndrome and HLH/MAS	300 million	5
	Lower GI bleed and Grade 4 thrombocytopenia	450 million	36
	Bronchopulmonary aspergillosis and HLH/MAS	450 million	55
	Respiratory failure	450 million	56
	CMV* and PCP**	300 million	113
	Pneumonia	450 million	128
	Pneumonia	450 million	182

Source: FDA analysis of ADSL, ADAE3, ADLB datasets; death narratives and autopsy reports

*CMV =cytomegalovirus pneumonia

**PCP=pneumocystis carinii pneumonia

Table 39: Table of Deaths classified as 'other causes 'in Study MM-001:

USUBJID	Cause of death	Assigned Dose Regimen	Study day of death	Reviewer comment
(b) (6)	Subdural hematoma	450 million	264	Pt developed PD on Day 70, was re-treated and then received multiple AMT. He fell and developed subdural hematoma with platelet count=4000.
	Sepsis	450 million	383	PD on Day 29, received subsequent AMT.
	Sepsis	300 million	547	PD on Day 96, received multiple subsequent lines of therapy.
	Euthanasia	300 million	591	Disease progression on Day 411 and received subsequent anti-myeloma therapy with PD.
	Cardiac arrest	300 million	276	Disease progression on Day 89 and treated with subsequent anti-myeloma therapy
	Toxicity to chemotherapy	450 million	388	Disease progression on Day 269. Subject received subsequent anti-myeloma therapy.
	Cerebral hemorrhage	300 million	607	Grade 2 thrombocytopenia at baseline. PD on Day 540. Cerebral bleed occurred in setting of grade 4 thrombocytopenia (Platelet count=17k) and PD.
	Lung adenocarcinoma with brain metastasis	300 million	616	Long term smoker. .

AMT: anti-myeloma therapy, PD: Progressive disease
Source: FDA analysis of ADSL, ADAE3, ADLB datasets; death narratives and autopsy reports

Reviewer's comments:
We reviewed all narratives to confirm the reported causes of death. Reviewer considered the cause of death to be the underlying malignancy when supported by worsening of disease by laboratory data, imaging, biopsy, autopsy, or description of other objective evidence. In this analysis, fatal AEs represent all-cause events that had onset prior to administration of new anti-myeloma therapy for disease progression. In cases where anti-myeloma therapy was initiated after the onset of the AE, the reviewer included these events as fatal AEs

Given the difficulty in ascertaining the baseline incidence of adverse events in a population of advanced myeloma in a single arm trial, the reviewer considered all deaths due to a treatment emergent AE as treatment related unless clearly related to an extraneous cause. If it was not possible to distinguish between AE related to underlying disease versus AE due to the treatment, the reviewer considered the AE as related to investigational therapy.
The leading cause of death in the bb2121 treated population at the data cutoff was disease progression (23 subjects,18 %). All five deaths with an unknown cause occurred >6 months after receiving bb2121 and in the setting of disease progression. The rate of fatal AE was 5.5%% which is not unexpected in a relapsed refractory multiple myeloma population and is similar to non-relapse mortality with other approved CAR T products.

Narratives for subjects who died due to a fatal AE post bb2121 treatment are detailed below:

1. Subject (b) (6) : This subject was a 48 years old white female who died on study day 5 due to cytokine release syndrome (CRS). There was a 2-month delay between the time of enrollment and initiation of lymphodepletion due to development of multiple medical complications including respiratory failure on study day -52 and E. coli bacteremia on study day -15. She developed grade 3 respiratory failure from pleural effusion resulting in altered mental status on study day -2. This was managed with antibiotics and therapeutic thoracentesis. Her functional status had deteriorated to ECOG 2 due to disease related complications at the time of lymphodepletion. She was treated with bb2121 in the 300 x10e6 CAR +T cell dose cohort. Nine hours after receiving bb2121, she developed CRS manifested with tachycardia and hypoxia. On study day 2, CRS progressed to Grade 3 which was accompanied with Grade 2 encephalopathy and Grade 4 cytopenia. She was treated with tocilizumab and dexamethasone. On Day 4, encephalopathy resolved, however, CRS progressed to Grade 4 with symptoms of hypotension, multiple organ dysfunction, acidosis, coagulopathy, cardiomyopathy and Grade 4 hemophagocytic lymphohistiocytosis (HLH). She was treated with tocilizumab, dexamethasone, and anakinra. Despite these interventions, she experienced bradycardic event leading to PEA cardiac arrest on study day 5. The subject underwent an autopsy which demonstrated HLH /MAS of multiple organs including lungs, lymph nodes and bone marrow with depleted marrow cellularity and minimal trilineage hematopoiesis.
   Reviewer's comments: This death prompted changes to study design implemented in Protocol amendment 3.0 requiring that subjects complete baseline assessments 72 hours prior to receiving bb2121 or on the day of lymphodepletion to ensure that study subjects have no intercurrent illness or toxicity that may place them at safety risk from the investigational therapy. This death from CRS and HLH/MAS is related to bb2121.

2. Subject (b) (6) : Subject was a 71-year-old white male diagnosed with myeloma 5 years prior with grade 2 thrombocytopenia at baseline. He developed grade 4 neutropenia and thrombocytopenia on day 1 post bb2121. He developed CRS on day 1 and Grade 4 HLH/MAS on day 9. CRS resolved on day 17 with maximal grade 3. He was diagnosed with Grade 1 encephalopathy from Day 5-6. In the setting of Grade 4 neutropenia and thrombocytopenia, he developed Grade 4 bronchopulmonary aspergillosis and right lower lobe pulmonary emboli on day 29. Antifungal therapy was initiated. His clinical course was further complicated with Grade 4 enterococcal bacteremia. On study day 43, his clinical status deteriorated with worsening renal function, ongoing neutropenia, metabolic acidosis (pH=7.2) and mental status changes with coma requiring intubation and vasopressor therapy. He was treated with

mesenchymal stem cell therapy followed with conditioning therapy with fludarabine and ATG followed by HLA matched sibling allogeneic stem cell transplantation to reconstitute hematopoiesis. He was continued on supportive care with anti-viral, anti-fungal therapy and placed on dialysis. Subject's family decided to limit medical care and withdraw dialysis and subject passed away on day 55. Autopsy indicated that primary cause of death as diffuse pulmonary angioinvasive aspergillosis. Secondary diagnoses included bone marrow aplasia, hemophagocytic lymphohistiocytosis syndrome and foci of brain hemorrhage especially in the pontine area.

Reviewer's comment:

Cause of death is diffuse bronchopulmonary aspergillosis as complication of prolonged neutropenia, HLH/MAS, bone marrow aplasia. Therefore, death is deemed to be related to LD and bb2121. In general, HLH and CRS can overlap and sometimes be indistinguishable. HLH/MAS can be worsened by ongoing or pre-existing systemic infection and can be associated with bone marrow failure causing prolonged neutropenia. Therefore, HLH/MAS and marrow aplasia causing prolonged neutropenia predisposed this subject to an invasive fungal infection. The conditioning therapy was administered to ablate HLH/MAS involving the bone marrow prior to administration of allogeneic stem cell. Therefore, this death is attributed to bronchopulmonary aspergillosis, HLH/MAS and marrow aplasia. Based on this fatal AE, HLH/MAS, prolonged cytopenia and severe infections will also be included in the warning and precautions section of the label. HLH/MAS and prolonged cytopenia has been added to the boxed warning in addition to CRS and neurologic toxicity to alert providers to these toxicities.

3. Subject (b) (6) : 57-year-old white male was diagnosed with myeloma 8 years prior to treatment with bb2121 and had received 7 prior regimens. At baseline, he had Grade 2 cytopenias. Post-treatment (on study day 2), he developed grade 4 neutropenia and thrombocytopenia. Bone marrow biopsy performed on Day 13 revealed a profoundly hypocellular marrow. He developed polymicrobial sepsis and left lower lobe pneumonia in the setting of severe neutropenia from day 22 to 31. Due to ongoing grade 4 neutropenia, subject received an autologous stem cell infusion on study day 30 which was complicated with distributive shock requiring pressor support and intubation. On study day 36, he developed grade 5 lower gastrointestinal bleed in the setting of profound thrombocytopenia (platelet count=4000/mm3). Grade 2 neurotoxicity and Grade 4 neutropenia were ongoing at the time of death.

   Reviewer comment:

   Death from GI bleeding is due to profound thrombocytopenia from lymphodepletion and bb2121. Death is deemed to be related to LD and bb2121. This AE indicates that in heavily pre-treated myeloma population, administration of lymphodepletion and bb2121 can result in prolonged cytopenia resulting in fatal complications such as this GI bleeding event. Subjects post-treatment with bb2121 may require hematopoietic stem cell rescue for prolonged cytopenia. The bone marrow ablative effects of LD and bb2121 in multiple myeloma may be more extensive than observed with other approved CD19 CAR T products in R/R lymphoma.

4. Subject (b) (6) : Subject was 57-year-old white male who was diagnosed with myeloma 8 years prior and had received seven prior antimyeloma regimens. On Study day 98, he was diagnosed with pneumonia in the setting of Grade 3 neutropenia. CT chest revealed left upper and lower lobe infiltrate. A bronchoalveolar lavage (BAL) was performed that revealed CMV (cytomegalovirus) viral load of 46,800 copies. BAL was

also positive for Pneumocystis jirovecii DNA at 41,830 IU/ml. He was treated with antibiotics, antiviral therapy and intravenous immunoglobulin. Despite these interventions, on study day 113, he passed away from CMV/Pneumocystis pneumonia.
Reviewer's comments: Heavily pre-treated multiple myeloma patients are predisposed to infectious complications. However, reviewer cannot rule out the possibility that LD and bb2121 related immunosuppression and cytopenias contributed to CMV pneumonia and PCP (Pneumocystis pneumonia).

5. Subject (b) (6) :
Subject was a 57-year-old black male who had received 8 prior anti-myeloma treatment regimens. He had bone lesions, pulmonary and hepatic extramedullary plasmacytomas at baseline. He had Grade 3 anemia and Grade 4 thrombocytopenia at baseline with hemoglobin of 7gm/dl and platelet count=19,000/mm3. Post-treatment, he required transfusion support for Grade 3 anemia and Grade 4 thrombocytopenia. He developed investigator identified PD on Study day 33. On study day 46, he was admitted with dyspnea. He had severe anemia (Hemoglobin of 4.8gm/dl) and thrombocytopenia with a platelet count of 10,000/mm3. While hospitalized, he developed melena and grade 2 atrial fibrillation with RVR (rapid ventricular response). CT chest showed bilateral pleural effusion, bilateral lung masses, bilateral ground glass opacities possibly pneumonia or hemorrhage, diffuse skeletal metastasis, subcutaneous skin nodules and a large right paraspinal mass in the back. Subject developed progressive respiratory failure and subsequently passed away on Day 56. Grade 4 thrombocytopenia and Grade 3 anemia was ongoing at the time of death.
Reviewer's comment: Given that the patient had EMP involving the lungs at baseline, reviewer agrees that disease progression is most likely etiology for respiratory failure. Secondary pneumonia and/ or hemorrhage contributing to respiratory failure may also be contributory and therefore attribution to investigational therapy cannot be ruled out.

6. Subject (b) (6) : Subject was 70-year-old white male with best response of partial response with disease progression on Day 149. On Day 171, he developed Grade 3 pneumonia requiring hospitalization. He also developed Grade 3 hepatic failure due to disease progression. Day 173, he developed Grade 4 sepsis and blood cultures were positive for Proteus mirabilis. He was subsequently initiated on antimyeloma therapy. On Day 182, he died from pneumonia. An autopsy was performed which revealed that cause of death was bronchopneumonia with transition to consolidated pneumonia. Extensive involvement with myeloma of the liver, solitary nodular metastasis in the left kidney, thyroid gland and left lobe of the lung.
Reviewer's comment: While, the subject clearly had evidence of disease progression, he died from pneumonia. Since symptoms of the AE started prior to administration of anti-myeloma therapy, attribution to investigational therapy cannot be ruled out.

7. Subject (b) (6) : 62-year-old white female with best response of on Day 59. On Day 122, she was noted to have right upper lobe airspace disease/consolidation suspiscious for pneumonia, small to moderate left pleural effusion and underlying lower lung parenchymal disease. This occurred in setting of Grade 3 neutropenia. Subject subsequently entered inpatient hospice and died on Day 128. At the time of death, DVT and Grade 4 neutropenia was ongoing.
Reviewer's comment: Pneumonia in the setting Grade 3 neutropenia may be related to the investigational therapy.

6.1.12.4 Nonfatal Serious Adverse Events

For this review, SAEs were defined as a serious AE that occurred after the bb2121 administration. SAEs occurred in 85 out of 127 (67%) subjects. SAEs were Grade 3-5 in 67/127 (53%) of the subjects. Table 40 summarizes all SAEs and grade ≥3 SAEs.

Table 40: Serious Adverse Events in ≥1%of study subjects

Adverse Events	All Grades N (%)	Max toxicity Grade 3-5 N (%)
Infections-pathogen unspecified[!]	24 (18.8)	19 (15%)
Cytokine Release Syndrome	23 (18)	9 (7)
Pneumonia *	15 (12)	12 (9.4)
General physical health deterioration	13 (10)	13 (10)
Viral infectious disorders[1]	12 (9.4%)	11 (8.6%)
Sepsis*	9 (7%)	9 (7%)
Febrile neutropenia	8 (6%)	8 (6%)
Thrombocytopenia*	6 (5%)	6 (5%)
Neutropenia*	6 (5%)	5 (4%)
Basal cell carcinoma	5 (4%)	0
Pyrexia	5 (4%)	2 (1.6)
Investigator identified NT*	4 (3%)	4 (3%)
Musculoskeletal Pain*	3 (2.4)	3 (2.4)
Gastrointestinal Hemorrhage*	3 (2.4)	2 (1.6)
Dyspnea*	3 (2.4)	2 (1.6)
C-reactive protein increased	3 (2.4)	1 (0.8)
Bacterial infectious disorder[1]	5 (4)	5 (4)
Upper respiratory tract infection *	3 (2.4)	2 (1.6)
Hemophagocytic lymphohistiocytosis	2 (1.6)	1 (0.8)
Hepatitis E	2 (1.6)	2 (1.6)
Lower respiratory tract infection*	2 (1.6)	1 (0.8)
Seizure	2 (1.6)	0
Encephalopathy*	2 (1.6)	2 (1.6)
Diarrhea	2 (1.6)	2 (1.6)
Hypotension*	2 (1.6)	0
Hemorrhage*	2 (1.6)	2 (1.6)
Renal failure*	2 (1.6)	2 (1.6)
Tumor flare	1 (0.8)	0
Squamous cell carcinoma	1 (0.8)	0
Peripheral neuropathy*	1 (0.8)	1 (0.8)
Dizziness*	1 (0.8)	1 (0.8)
Spinal cord compression	1 (0.8)	1 (0.8)
Benign prostate hyperplasia	1 (0.8)	0
Upper airway obstruction	1 (0.8)	1 (0.8)

Adverse Events	All Grades N (%)	Max toxicity Grade 3-5 N (%)
Pneumonitis	1 (0.8)	0
Rash*	1 (0.8)	1 (0.8)
Thrombosis*	1 (0.8)	0
Shock	1 (0.8)	1 (0.8)
Lung adenocarcinoma	1 (0.8)	1 (0.8)
Anal carcinoma	1 (0.8)	1 (0.8)
Metabolic acidosis*	1 (0.8)	0
Transaminase increase*	1 (0.8)	1 (0.8)
Blood alkaline phosphatase increased	1 (0.8)	1 (0.8)
Compression fracture	1 (0.8)	1 (0.8)
Foot fracture	1 (0.8)	1 (0.8)
Femoral neck fracture	1 (0.8)	1 (0.8)
Colitis	1 (0.8)	0
Abdominal pain*	1 (0.8)	1 (0.8)
Hyperbilirubinemia	1 (0.8)	1 (0.8)
Tachycardia*	1 (0.8)	0
Cardiac arrhythmia *	1 (0.8)	0
Pericardial effusion	1 (0.8)	1 (0.8)
Myocardial ischemia*	1 (0.8)	0
Device related infection	1 (0.8)	1 (0.8)
Herpes Virus infection*	1 (0.8)	1 (0.8)
Urinary tract infection *	1 (0.8)	1 (0.8)
Infection	1 (0.8)	0
Pain *	1 (0.8)	0
Chills	1 (0.8)	0
Fatigue*	3 (2.4)	2 (1.6)
Anemia	1 (0.8)	1 (0.8)
Disease progression	1 (0.8)	1 (0.8)
Coagulopathy*	1 (0.8)	0
Visual field defect*	1 (0.8)	0
Fungal infectious disorder[1]	1 (0.8)	1 (0.8)

Source: FDA Analysis of ADAE3.xpt.
** Includes grouped terms as detailed in APPENDIX A*
[1] High level grouped term
Febrile neutropenia and neutropenia are considered separately for this analysis.

Reviewer Comment

The label includes nonlaboratory SAEs ≥ 5%. While the preferred term of cytokine release syndrome and neurotoxicity (iiNT) was flagged for SAE, the individual signs and symptoms of these adverse events of special interest were not flagged for SAE in the datasets. Since these AESIs are included in Warning and Precaution section of the label, review team did not consider that additional flagging of these adverse event as SAEs would be informative to the prescribers.

6.1.12.5 Adverse Events of Special Interest (AESI)

Adverse events of special interest for safety analyses included secondary malignancy, auto-immune-like, rheumatologic or hematologic disorder, ≥Grade 3 CRS, macrophage activation syndrome (MAS), neurotoxicity, and infection.

Cytokine Release Syndrome:
CRS occurred in 108/127 (85%) of the bb2121 treated subjects. 12 subjects (9%) experienced grade 3 or higher CRS event. One subject died from CRS (See 6.1.12.3: Deaths for details). Thirty-four of the 108 subjects (31%) with CRS also experienced neurologic toxicity. CRS was graded per modified Lee et al 2014 criteria which excludes neurological AEs as part of CRS.

Table 41: CRS Toxicity Grade: Study MM-001

Worst CRS Toxicity Grade	Subjects N=127 (%)
CRS Any Grade	108 (85%)
Grade 1	58 (46%)
Grade 2	38 (30%)
Grade 3	9 (7%)
Grade 4	2 (1.5%)
Grade 5	1 (0.8%)

Source: FDA Analysis of CRSPRIM Legacy Dataset. This table includes all 5 cases of HLH/MAS which occurred in the setting of CRS.

Table 42: CRS in different dose cohorts in study MM-001

bb2121 Dose Cohort	Number of Subjects	CRS Grade 1-5 N (%)	CRS Grade 1 N(%)	CRS Grade 2 N(%)	CRS Grade 3-5 N (%)
150 million	4	2 (50%)	1 (25%)	1 (25%)	0
300 million	70	55 (79%)	32 (46%)	16 (23%)	7 (10%)
450 million	53	51 (96%)	25 (47%)	21 (40%)	5 (9%)
Total	127	108 (85%)	58 (46%)	38 (30%)	12 (9.4%)

Source: FDA Analysis of CRSPRIM Legacy Dataset

Median time to CRS onset was 1 day (range 1 to 23 days). Median time to CRS maximal toxicity grade was 2 days (Range 1-23 days). CRS resolved at a median of 6.5 days (Range 1-63 days). Median duration of CRS is 6.5 days in all subjects including the subject who died from CRS (range 1 to 63 days). Median duration of CRS was longer in the 450 x10e6 CAR+ T dose cohort compared to the 300 x10e6 CAR+ T dose cohort with median of 7 days (Range 1-63 days) and 6 days (Range 2- 28 days) respectively.

The most common manifestations of CRS (≥10%) included pyrexia, hypotension, tachycardia, chills, hypoxia, fatigue and headache. Notable Grade 3 or higher events associated with CRS include pyrexia, hypotension, hypoxia, dyspnea, tachycardia, ARDS, atrial fibrillation, hypofibrinogenemia, metabolic acidosis, multiple organ dysfunction syndrome, pulmonary edema and hepatocellular injury.

Table 43 summarizes all AEs and Grade 3 and higher-grade AEs observed in subjects with CRS.

Table 43: Symptoms in 108 subjects with CRS

CRS Symptoms/AEs*	All grades n (%)	Max toxicity Grades 3 or higher n (%)
Total	108 (100%)	37 (34%)
Pyrexia	106 (98%)	16 (15%)
Hypotension	44 (41%)	7 (6.4%)
Tachycardia	38 (35%)	2 (1.8%)
Chills	33 (31%)	0
C-reactive protein increased	24 (22%)	2 (1.8%)
Hypoxia	22 (20%)	6 (5.5%)
Fatigue	13 (12%)	0
Headache	11 (10%)	0
Tachypnea	10 (9%)	2 (1.8%)
Alanine aminotransferase increased	8 (7%)	0
Aspartate aminotransferase increased	8 (7%)	2 (1.8%)
Dyspnea	7 (6%)	2 (1.8%)
Serum ferritin increased	7 (6%)	1 (0.9%)
Atrial fibrillation	5 (5%)	1 (0.9%)
Malaise	5 (5%)	0
Hypofibrinogenemia*	5 (5%)	3 (2.7%)
Decreased appetite	4 (4%)	0
Febrile neutropenia	4 (4%)	4 (3.7%)
Nausea	4 (4%)	0
Vomiting	4 (4%)	0
Hyperhidrosis	3 (3%)	0
Hypoalbuminemia	3 (3%)	0
Sinus tachycardia	3 (3%)	0
Activated partial thromboplastin time prolonged	2 (2%)	1 (0.9%)
Asthenia	2 (2%)	1 (0.9%)
Blood bilirubin increased	2 (2%)	2 (1.8%)
Diarrhea	2 (2%)	0
Dizziness	2 (2%)	0
Fibrin D dimer increased	2 (2%)	0
Flushing	2 (2%)	0
Gamma-glutamyl transferase increased	2 (2%)	0
Hepatocellular injury	2 (2%)	1 (0.9%)
Metabolic acidosis	2 (2%)	1 (0.9%)
Musculoskeletal pain	2 (2%)	0

CRS Symptoms/AEs*	All grades n (%)	Max toxicity Grades 3 or higher n (%)
Oxygen saturation decreased	2 (2%)	0
Pulmonary edema	2 (2%)	1 (1%)
Respiratory failure	2 (2%)	0
Blood fibrinogen increased	2 (2%)	0
Abdominal pain	1 (1%)	0
Acute kidney injury	1 (1%)	0
Acute respiratory distress syndrome	1 (1%)	1 (0.9%)
Acute respiratory failure	1 (1%)	0
Aspartate aminotransferase decreased	1 (1%)	0
Blood lactate dehydrogenase increased	1 (1%)	0
Capillary leak syndrome	1 (1%)	0
Chest pain	1 (1%)	0
Electrocardiogram T wave abnormal	1 (1%)	0
Erythema	1 (1%)	0
Fluid retention	1 (1%)	0
Hemophagocytic lymphohistiocytosis	1 (1%)	0
hyperphosphatemia	1 (1%)	0
Hypocalcemia	1 (1%)	1 (0.9%)
Hypokalemia	1 (1%)	0
Hypomagnesaemia	1 (1%)	0
Hyponatremia	1 (1%)	0
Hypothermia	1 (1%)	0
International normalized ratio increased	1 (1%)	0
Lethargy	1 (1%)	0
Multiple organ dysfunction syndrome	1 (1%)	1 (0.9%)
Neutropenia	1 (1%)	1 (0.9%)
Night sweats	1 (1%)	0
Non-cardiogenic pulmonary edema	1 (1%)	0
Edema peripheral	1 (1%)	0
Performance status decreased	1 (1%)	1 (0.9%)
Pleural effusion	1 (1%)	0
Pollakiuria	1 (1%)	0
Portal vein thrombosis	1 (1%)	0
Pulseless electrical activity	1 (1%)	1 (0.9%)

Source: FDA analysis of ADAE3 dataset

- *Includes blood fibrinogen decreased and hypofibrinogenemia, (Adverse events are not grouped terms).

CRS management:
Tocilizumab and/or corticosteroids were used in the management of CRS. Tables 44-47 depict the use of tocilizumab, corticosteroids and other interventions used in study MM-001 in the management of CRS.

Table 44: Tocilizumab and/or Corticosteroid Use in CRS Management

Medication	150 million N=4	300 million N=70	450 million N=53	Overall N=127
Tocilizumab	1(25%)	31(44%)	36 (68%)	68 (53.5%)
Corticosteroids	0	7 (10%)	12 (23%)	19 (15%)

*All 19 subjects that received steroids also received tocilizumab.
Source: FDA analysis of ADAESUM, ADCM dataset and Applicant IR.

Table 45: Tocilizumab use by bb2121 dose and CRS Grade N=68

bb2121 Dose	Grade 1	Grade 2	Grade 3-5	Overall
150 million N=4	0	1 (25%)	0	1 (25%)
300 million N=70	14 (20%)	12 (17%)	5 (7%)	31 (44%)
450 million N=53	13 (24.5%)	18 (34%)	5 (9.4%)	36 (68%)
Total N=127	27 (21%)	31 (24.4%)	10 (7.8%)	68 (53.5%)

FDA analysis of ADAESUM and CRSPRIM dataset

Table 46: Analysis of >1 dose of Tocilizumab by bb2121 dose and CRS Grade

bb2121 Dose	Grade 1	Grade 2	Grade 3-5	Overall
150 million N=4	0	0	0	0
300 million N=70	0	6 (8.5%)	3 (4%)	9 (13%)
450 million N=53	3 (5.6%)	7 (13%)	4 (7.5%)	14 (26%)
Total N=127	3 (2.3%)	13 (10%)	7 (5.5%)	23 (18%)

FDA analysis of CRSPRIM dataset, ADAESUM, clinical study report and Applicant IR.

One subject in 300 million dose cohort received siltuximab and one subject each in the 300 million and 450 million dose cohort received anakinra for the management of CRS.

Table 47: Steroid use by bb2121 dose and CRS Grade

bb2121 Dose	Grade 1	Grade 2	Grade 3-5	Overall
150 million	0	0	0	0
300 million	0	3(4%)	4 (5.7%)	7 (10%)

bb2121 Dose	Grade 1	Grade 2	Grade 3-5	Overall
N=70				
450 million N=53	3 (5.6%)	7 (13%)	2 (3.7%)	12 (22.6%)
Total N=127	3 (2.4%)	10 (7.8%)	6 (4.7%)	19 (15%)

FDA analysis of ADAESUM and CRSPRIM dataset

Table 48: Other Interventions for CRS Management

Intervention	150 million N=4	300 million N=70	450 million N=53	Total N=127
ICU Admission	1 (25%)	10 (14%)	9 (17%)	20 (16%)
Dialysis	0	1 (1.4%)	0	1 (0.8%)
Ventilator Use	0	1 (1.4%)	1(2%)	2 (1.6%)
Vasopressors*	0	6 (8.6%)	1 (2%)	7 (5.5%)

FDA analysis of CRSPRIM dataset, CSR:MM-001 and Applicant IR.
*One subject in 300 million dose cohort received high dose vasopressor. Remaining subjects received low dose vasopressor use.

Reviewer's comments:

- Applicant identified 106/127 bb2121 treated subjects with CRS. Our review strategy of finding additional subjects with CRS included looking for fever, hypotension and hypoxia between day 1 to 30 in the subjects not flagged as having CRS. We additionally looked for subjects not flagged as having CRS that received tocilizumab since tocilizumab is specifically used in the front-line treatment modality for CRS. Corticosteroid use was not used to identify additional CRS cases as it was considered a low yield strategy since corticosteroids are generally used as adjunctive to tocilizumab for CRS management and may also be used for additional indications such as neurotoxicity, treatment of progressive myeloma, hypersensitivity reactions etc. Overall, we identified two new subjects with CRS and upgraded CRS grade in 7 additional subjects. In two subjects, the duration of CRS was increased based on our re-adjudication. Although a dose toxicity relationship was observed with CRS, the absence of substantial differences in ICU and ventilator use between the 300 and 450 million dose cohorts suggests that these toxicities didn't result in a need for critical care interventions.

Brief narratives are summarized below:

1. Subject (b) (6) : Subject had fever on Day 1 and Day 9 without alternative explanation. Subject was treated with acetaminophen on Day 1 and Day 9. Therefore, although the T max did not meet protocol specified threshold of 38.5 degree Celsius, these two febrile episodes were classified as Grade 1 CRS.

2. Subject (b) (6) : Subject developed febrile neutropenia on Study Day 23 and Grade 1 intermittent confusion on Day 24. On Day 25, she developed Grade 3 hypoxia. CT chest

revealed increase in the size of a right pleural effusion. Tocilizumab was administered on Day 26. In addition, subject was also treated with diuretics, blood transfusion and antibiotics. Thoracentesis was not performed due to thrombocytopenia. Subjects' lowest oxygen saturation was 70% and she required 60% Fi02 and BIPAP. Hypoxia resolved on Day 31. Subject required care in the ICU. Overall clinical picture of fever and hypoxia prompting the use of tocilizumab was considered in classifying this subject as Grade 3 CRS.

In the following cases, the CRS grade and/or duration was modified based on the review of narratives, ADAE, ADCE and ADCM datasets. We specifically reviewed vasopressor and oxygen use in the ADCM dataset, vital signs in ADVS dataset and grade 3 and higher organ toxicities in the ADAE/ADCE dataset to identify subjects with a higher CRS grade than the one assigned.

3. Subject (b) (6) : Applicant assigned Grade 1 CRS was increased to Grade 2 due to occurrence of hypotension which required administration of normal saline. The duration of CRS was increased from Days 2-5 to Days 1-5 as subject developed fever and hypotension as symptoms of CRS without an alternative explanation on Day 1.

4. Subject (b) (6) : Applicant assigned Grade 2 CRS was increased to Grade 4. Subject developed Grade 4 dyspnea secondary to metabolic acidosis which was multifactorial from diarrhea, fluid overload and acute kidney injury. On Day 3, in the setting of significant metabolic acidosis (bicarbonate=14), subject was intubated for dyspnea. This is considered life threatening toxicity requiring mechanical ventilation.

5. Subject (b) (6) : Applicant assigned Grade 2 CRS was increased to Grade 3. During CRS episode, subject developed fever and tachypnea on Day 3 requiring 6 L/minute of oxygen (Fi02=44%). Oxygen requirement of ≥40% is considered Grade 3 CRS per Lee Criteria 2014.

6. Subject (b) (6) : Applicant assigned Grade 1 was increased to Grade 3: Subject was administered oxygen at 6L/minute (Fi02=44%) for tachypnea and comfort on Day 8.

7. Subject (b) (6) : Applicant assigned Grade 1 was increased to Grade 2. During CRS, subject developed hypoxia with oxygen saturation of 86% on Day 3. Subject was subsequently administered oxygen at 2L/minutes which meets criteria for Grade 2 CRS.

8. Subject (b) (6) : Applicant assigned Grade 1 was increased to Grade 2. Subject had CRS from Days 1-3. From Days 2-5, subject was administered norepinephrine @1 mg/hour from days 2-5 for presumed sepsis. Blood cultures were positive for streptococcus gallolyticus on Day 1. Due to the overlap between CRS and sepsis, the contribution of CRS towards hypotension and vasopressor use could not be ruled out resulting in upgrading of CRS event.

9. Subject (b) (6) : Applicant assigned Grade 2 was upgraded to Grade 3 as subject developed Grade 3 atrial fibrillation (cardiac end organ toxicity) during CRS.

10. Subject (b) (6) : CRS Grade 2 duration was Days 1-5. Subject was administered norepinephrine on Days 4-9 for the indication of CRS. Given the ongoing need for vasopressor use until Day 9, CRS duration was increased from Day 1-9.

- Dose toxicity relationship for CRS:
  In general, the overall incidence of CRS was higher in 450 million dose cohort compared to 300 million dose cohort (96% versus 79%). This was driven specifically by the incidence of Grade 2 CRS. There was no significant difference in the rate of Grade ≥ 3 CRS in between the two dose cohorts. The median duration of CRS was longer in the 450 million dose cohort compared to 300 million dose cohort (7 days versus 6 days). The overall rate of tocilizumab and steroid use for the management of CRS was higher in the 450 million dose cohort compared to 300 million dose cohort. This dose toxicity relationship has been added to the Warning and Precautions Section of the label to inform the prescribers. This higher risk of toxicity should be considered in the risk benefit assessment with the dose of bb2121 that is selected by prescribers.

- Despite a higher incidence of Grade 2 CRS in the 450 million dose cohort, the shift from Grade 2 to Grade 3 CRS in the 450 million dose cohort could have been mitigated by the earlier use of tocilizumab which may support the conclusion that earlier intervention may limit progression of CRS. Therefore, the labeling considerations reflect this approach of earlier initiation of tocilizumab and in fact support extending tocilizumab use to Grade 1 CRS not responding to supportive care measures.

- In general, rate of grade 3 and higher CRS was low. Interventions like ventilatory support, vasopressors and ICU stay as outlined in Table 48 were required in a small proportion of subjects corresponding to the low rate of grade 3 and higher CRS. Lower rate of severe CRS is likely due to early recognition and intervention preventing serious toxicity and end organ damage.

- The majority of vasopressor use was low dose with CRS which may explain a similar rate of ICU admissions between the 300 and 450 million dose cohort despite a higher vasopressor use in the 300 million dose cohort.

- One subject treated within 300 million dose cohort had fatal CRS. For details regarding this subject, please refer to narrative under Section 6.1.12.3 (Deaths).

- Duration of CRS was defined as the number of days from onset to when the last CRS event ended including the intervening non-event days which is consistent with the calculation of CRS duration across multiple CAR T applications.

- End-organ toxicity observed with CRS included transaminase elevation, atrial fibrillation, respiratory failure, hypofibrinogenemia and acute kidney injury. (See Table 43 which summarizes signs and symptoms of CRS)

- Five subjects with CRS Grades 2-5 also developed HLH/MAS. For details regarding the HLH/MAS, please see section under Hemophagocytic lymphohistiocytosis/ Macrophage activation syndrome.

Neurotoxicity:

Thirty-six subjects (28%) experienced one or more events of neurologic toxicity (NT) including Grade 3 events in 4% (5/127) of subjects. One subject had Grade 2 neurologic toxicity (encephalopathy, delirium and urinary incontinence) ongoing at the time of death from a lower

GI bleed (See Section 6.1.12.3 Deaths). Two subjects had neurologic toxicity of grade 1 tremor ongoing at the time of data cut off.

Table 49: Neurologic Toxicity Grade

Worst Neurological Toxicity Grade	Subjects N (%)=127
Neurological Toxicity Any Grade	36 (28%)
Grade 1	21 (16.5%)
Grade 2	10 (8%)
Grade 3	5 (4%)
Grade 4	0
Grade 5	0

Source: FDA Analysis of ADAE 3 Dataset
NT Grading is based on CTCAE version 4.07

The most common neurological toxicities include 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 subjects with NT had neurologic events start within 60 days of bb2121 infusion. The median time to onset of the first event was 2 days (range 1 to 42 days). Median time to onset of maximum NT grade was 1 day (range 1 to 3 days). Neurologic toxicities resolved in 33 of 36 subjects (92%). Median time to neurotoxicity resolution was 5 days (range 1 to 61 days). Median duration of NT in all subjects including those with ongoing events at death or data cut off was 5.5 days (range 1 to 578 days).

Table 50 : Neurologic Events in 127 subjects in study MM-001

Characteristic	Grade 1-5 N (%)	Max toxicity Grade 3 or higher (%)
Total number of subjects with NT		
All	36 (28%)	5 (4%)
Encephalopathy*	26 (20.4%)	5 (4%)
Tremor*	12 (9.4%)	0
Aphasia*	9 (7%)	1 (0.8%)
Delirium*	7 (5.5%)	0
Motor dysfunction*	4 (3%)	0
Headache*	4 (3%)	0
Ataxia*	3 (2%)	0
Paresis*	2 (1.6%)	1 (0.8%)
Dizziness*	2 (1.6%)	0
Fatigue *	2 (1.6%)	0
Visual field defect*	1 (0.8%)	0
Vision blurred*	1(0.8%)	0
Urinary incontinence	1(0.8%)	0
Seizure	1(0.8%)	0
Reflexes abnormal*	1(0.8%)	0
Nystagmus	1(0.8%)	0

Source: FDA analysis of ADAE 3 dataset

NT: Neurological Toxicity; multiple events could have contributed to NT in subjects
**GT: grouped term; See APPENDIX A for Preferred terms and Grouped Terms used*
Source: adae 3.xpt,

Table 51: Neurologic Toxicity in Different Dose Cohorts in study MM-001

bb2121 Dose Cohort (CAR+ T cells)	Number of Subjects	NT Grade 1-5 N (%)	NT Grade 3-5 N (%)
150 million	4	1 (25%)	0
300 million	70	19 (27%)	1 (1.4%)
450 million	53	16 (30%)	4 (7.5%)

Source: FDA analysis of ADAE 3 dataset

Neurologic toxicity and CRS:
Thirty-four subjects (94%) with NT had CRS. Neurologic toxicity with onset during CRS occurred in 29/34 subjects. The onset of any NT event was after onset of CRS in 2 subjects and before CRS onset in three subjects.
Management of Neurologic Toxicity:
Corticosteroids, antiepileptics and anti-cytokine agents were used in neurotoxicity management.

Table 52: Medications in Management of Neurologic Toxicity

Medication	150 million N=4	300 million N=70	450 million N=53	Overall N=127
Corticosteroids	0	6 (8.5%)	10 (19%)	16 (12.5%)
Tocilizumab	0	0	3 (5.6%)	3 (2.3%)
Anakinra	0	0	1 (2%)	1 (0.8%0

Source: FDA analysis of ADCM, ADESSUM and Applicant IR

Anti-seizure prophylaxis was recommended for subjects considered high risk for neurotoxicity, experiencing neurotoxicity or CRS. Anti-seizure prophylaxis was used in 42/127 (33%) of the bb2121 treated subjects. All 42 subjects who were treated with anti-seizure prophylaxis received levetiracetam. None of the four subjects treated at 150 $x10^6$ CAR+ T cells received antiseizure prophylaxis. 27% of the subjects (19/70) in the 300$x10^6$CAR + T cell dose cohort and 43%(23/53) of the subjects in the 450 $x10^6$ CAR + T cell cohort received anti-seizure prophylaxis.

Reviewer's comments:
FDA's neurotoxicity analysis was based on the MedDRA system organ classes and included all preferred terms that could be indicative of neurotoxicity regardless of the applicant's attribution as "investigator identified neurotoxicity" (ii NT). All events from the nervous system disorders and psychiatric disorders that had onset within 60 days after the administration of bb2121 were analyzed. In addition, the analysis included preferred terms that were misclassified under other system organ classes that could be indicative of neurotoxicity and occurred within 60 days after bb2121 treatment.
These preferred terms and the SOC are summarized below in Table 53

Table 29
Preferred Terms Analyzed for Neurotoxicity from SOCs Other than Nervous System Disorder and Psychiatric Disorders

AESOC	Preferred Term
Gastrointestinal disorders	anal incontinence
Eye disorders	diplopia, eyelid ptosis, pupillary reflex impaired, vision blurred and visual impairment.
Respiratory, thoracic and mediastinal disorders	dysphonia
General disorders and administration site conditions	gait disturbance, feeling jittery,
Ear and labyrinth disorders	hypoacusis, vertigo
Gastrointestinal disorders	hypoesthesia oral
Musculoskeletal and connective tissue disorders	muscle spasms, muscle weakness
Investigations	Romberg test positive
Renal and urinary disorders	urinary incontinence

Source : FDA analysis of ADAE3

1. Adverse events of special interest for NT included grouped terms of encephalopathy, delirium, aphasia, tremor, dizziness, motor dysfunction, headache and paresis as these are considered a part of the global constellation of ICANS (immune effector cell associated neurotoxicity). Neurologic toxicity consisted of different neurologic and/or psychiatric manifestations with or without overlapping time courses. Duration of NT was calculated from time of onset of the first event until resolution of the last event.

2. The clinical team grouped several AEs (AEDECOD terms in the dataset) under a single term (FDA Group term) as outlined in APPENDIX A when applicable. Grouping was performed to maintain consistency across CAR T applications and to classify similar adverse events under a unifying term which would accurately estimate the rate of neurological toxicity. For example; confusional state and memory impairment were grouped under encephalopathy. Some of the FDAs group and preferred terms did differ from the Applicant's which explains the difference in incidence of certain AEs. However, Applicant was provided with the FDA's list of group and preferred terms for the label.

3. Applicant considered 91 iiNT (investigator identified neurotoxicity events) in 23 subjects (23/127) as neurotoxicity events. The reviewer identified 24 neurotoxicity events in 13 new subjects and 18 additional neurotoxicity events in 8 subjects already flagged as having iiNT using the strategy outlined above. Majority of these events were low grade events (< Grade 3) events. Overall, 36 subjects had 133 neurotoxicity events.
The timing of onset of the adverse event relative to the administration of bb2121, the duration of the toxicity, occurrence of multiple neurological symptoms as opposed to an isolated AE, absence of other competing causes such as concurrent illness, concomitant medications with overlapping side effects, and current understanding of immune effector cell associated neurotoxicity were all considered in making assessment of attribution.

4. The applicant had misclassified some neurotoxicity events such as encephalopathy and tremor under signs and symptoms of CRS. These were reclassified as neurotoxicity. Headaches

that preceded or overlapped with a CNS toxicity such as encephalopathy, delirium or aphasia were reclassified as NT. Non-specific symptoms such as insomnia and anxiety that may be associated with inpatient hospital stay and underlying diagnosis and treatment of a relapsed/refractory hematological malignancy were not considered as bb2121 related neurotoxicity in general.

5. Though the overall rate of Grade 3 or higher neurotoxicity was low in the study (See Table 49), it was higher in the 450 million dose cohort compared to 300 million dose cohort. (7.5% vs. 1 % respectively). This dose toxicity relationship will be included in the Warnings and Precautions section of the label to inform prescribers.
It is noted that all Grade 3 neurotoxicity events occurred in subjects 65 years or older. Please see Section 6.1.11.3 for details. The incidence and severity of neurotoxicity in the older adults will be captured in the PMR registry study.

5. No case of cerebral edema was reported this this study. One subject developed Grade 1 seizure.

6. According to the Applicant's analysis, ten subjects with NT were treated with corticosteroids. However, six additional subjects who received corticosteroids for management of CRS and had overlapping neurotoxicity while receiving steroids were not included in this analysis. Since corticosteroid use in these six subjects treated both ongoing concurrent CRS and NT, the reviewer considered that these subjects as treated for neurotoxicity and CRS with steroids. The use of steroid use for NT was higher in the 450 million dose cohort compared to 300 million dose cohort (19% vs. 9%). Only 3 subjects received tocilizumab for NT which is in keeping with current management guidelines that tocilizumab should be used in subjects with NT only with concurrent CRS.

7. Since 24/42(57%) subjects received anti-seizure prophylaxis while CRS was ongoing in the absence of any concurrent neurotoxicity, reviewer recommends that label include the recommendation to consider anti-seizure prophylaxis in subjects with CRS even in the absence of NT as a preventative strategy.

Brief narrative of new subjects identified with NT are outlined below:

1. Subject ID (b) (6) : Grade 1 disturbance in attention from Days 1-2, Grade 1 tremor on Days 1-3,Grade 1 dizziness on Days 1-5 and Grade 1 diplopia on Days 4-5 were considered NT. Subject had ongoing Grade 1 CRS from Days 2-5.
2. Subject ID (b) (6) : Grade 2 confusional state on Days 2-3, Grade 1 tremor on Days 1-3 and Grade 1 dizziness on Days 1-2 were considered NT. Subject had E coli bacteremia on Days 1-9 which could be contributory to the symptoms of confusion. Subject had CRS from Days 1-2.
3. Subject ID (b) (6) : Grade 1 cognitive disorder from Days 2-3 was considered NT. Subject had CRS from Days 1-4 and Days 4-5.
4. Subject ID (b) (6) : Grade 1 nystagmus on Day 2 and Grade 1 intermittent hand tremors from Days 2-14 were considered NT. Grade 1 CRS was from Days 1-4.
5. Subject ID (b) (6) : Grade 1 Romberg test positive Day 12-13 was considered NT. Subject had CRS from Days 1-3.

6. Subject (b) (6) : Grade 1 expressive aphasia and Grade 1 right hand asterixis on Days

18- 22 was considered NT. This subject did not developed CRS.

7. Subject (b) (6) : Grade 2 somnolence on Days 31-34, Grade 1 dysarthria on Days 32, 36-37 and Grade 1 seizure on Day 43 was considered NT. This subject had CRS from Day 1-2.
8 Subject (b) (6) : Grade 1 confusional state from Days 24-30 was considered NT. This subject was also re-adjudicated as having Grade 3 CRS from Day 23-31. See narrative under Section on CRS for details.
9. Subject (b) (6) : Grade 1 tremor from Day 5 to ongoing at the time of data cut off was considered NT. This subject had CRS from Days 5-8.
10. Subject (b) (6) : Grade 1 tremor from Day 42 to ongoing at the time of data cut off was considered NT. This subject received subsequent anti-myeloma therapy on Day 41 with cisplatin, Bortezomib, Cytoxan, dexamethasone, etoposide, thalidomide and doxorubicin. Given that the onset of tremor was 1 day after the initiation of anti-myeloma therapy and since tremor is one of the characteristic toxicities from CAR T cell therapy, this toxicity was considered neurotoxicity from bb2121. This subject did not developed CRS.

Reviewer's comment: Grade 1 tremor for subjects outlined above in #9 and 10 are ongoing without any worsening of severity at the 90-day safety update with a duration of follow up of 747 days for Subject (b) (6) and 752 days for Subject (b) (6) respectively. Therefore, development of post treatment tremors may indicate chronic neurotoxicity albeit of low grade.

11. Subject (b) (6) : Applicant assessed Grade 1 confusional state and Grade 1 depressed level of consciousness from Days 2-3 as signs and symptoms of CRS. We re-adjudicated these as NT.
12. Subject (b) (6) : Applicant considered Grade 1 tremor on Day 3 as a sign and symptom of CRS which occurred on Days 1-4. We re adjudicated this event as NT.
13. Subject ID (b) (6) : We re-adjudicated Grade 1 tremor on Day 1 as NT. This subject had CRS from Day 2-8.

Additional reviewer identified NT events in subjects with ii NT are summarized below:

1. Subject (b) (6) : Grade 1 impaired pupillary reflex from Days 5-8 and Grade 1 somnolence from Days 33-35 is adjudicated as NT. This subject had iiNT of mental status changes from Day 2-3 and asthenia Grade 1 from Days 2-3.
2. Subject (b) (6) : Grade 2 lethargy from days 15-18 is adjudicated as NT. In addition, this subject had Grade 2 confusional state on Day 5 and Grade 3 toxic encephalopathy on Days 6-8 listed as CRS signs and symptoms. These were re-adjudicated as NT events.
This subject had multiple iiNT events including aphasia, ataxia, cognitive disorder, confusional state, delirium, encephalopathy, hallucination, hemiparesis, hypotonia, lethargy, mental status changes and metabolic and toxic encephalopathy occurring from days 5- 15.
3. Subject (b) (6) : Applicant considered lethargy Grade 2, Days 2-3 as a part of CRS. Neurotoxicity symptoms occurring during CRS are considered a part of NT. Therefore, this event is re-adjudicated as NT. Grade 2 somnolence from Days 26-28 is also adjudicated as NT. This subject had iiNT events of Grade 1 confusional state from Days 2-3, Grade 1 tremor from Days 1-3 and Grade 1 vision blurred from Days 1-2.
4. Subject (b) (6) : Grade 1 left foot tremor from Days 3-63 and Grade 1 right great toe tremor on Days 13-14 are adjudicated as NT. This subject had iiNT of Grade 1 aphasia, eyelid ptosis and hallucination from Days 6-13.

5. Subject (b) (6) : This subject had ii NT of Grade 1 hallucination and Grade 1 confusional state on Days 10-11. Grade 1 headache on Day 6 and Days 7-11 preceded and overlapped with iiNT and therefore was adjudicated as NT.
6. Subject (b) (6) : Applicant classified the following symptoms as CRS related: Grade 1 dysarthria from days 5-7 and days 8-9, Grade 1 headache from Days 2-7 and Grade 1 muscular weakness from Days 2-7. All these events were re-classified as NT. In addition, Grade 2 muscular weakness from Days 14-40 was adjudicated as NT. This subject had multiple iiNT events including amnesia, confusional state, delirium, dysarthria, encephalopathy and muscular weakness from Days 4-14 and 14-25.
7. Subject (b) (6) : Applicant considered Grade 1 headache on Days 6-7 as a symptom of CRS. This event was re-adjudicated as NT since it overlapped with iiNT (aphasia, and encephalopathy) from Days 2-10. .
8. Subject (b) (6) : Applicant considered Grade 1 headache on Days 1-6 as a symptom of CRS. This event was re-adjudicated as NT since it overlapped with encephalopathy occurring on Days 5-6 (iiNT).

Events that were examined and not considered as NT:
1. Subject (b) (6) : Grade 1 confusional state from Days 20-21 was further examined. This subject had grade 4 airway obstruction from plasmacytoma from Day 14 to ongoing at the time of data cut-off. A tracheotomy was performed on Day 18 for airway obstruction. This episode of confusion occurred in setting of ICU stay post-tracheotomy, while the subject was being administered tramadol. Given the overall picture of a low grade and transient event of confusional state which could be explained by ICU admission and concomitant medications, this event was not adjudicated as NT.
2. Subject (b) (6) : This subject developed transient Grade 1 somnolence on Day 1 after receiving Benadryl. Given the transient nature of somnolence and an alternative explanation, this event was not adjudicated as NT.

Infections:
Infection of any grade occurred in 89/127 (70%) subjects treated with bb2121.
Grade 3 or higher infections occurred in 29/127 (23%) of the subjects treated with bb2121.
Sepsis occurred in 12/127 (9.4%) subjects treated with bb2121.

Table 54: Infections by pathogen class in Study MM-001; N=127

Infections (High Level Group Term)	Any Grade N= 89/127 (70%)	Max Grade 3 or higher N=29/127 (23%)
Infections: pathogen unspecified	65 (51%)	19 (15%)
Bacterial infectious disorder	19 (15%)	5 (4%)
Viral infectious disorder	34 (27%)	12 (9.4%)
Fungal infectious disorder	10 (8%)	1 (0.8%)

Source: FDA analysis: ADAE 3 Dataset

Table 55: Infection by select sites in Study MM-001; N=127

Site of Infection*	Any grade n (%)	Max Grade 3 or higher n (%)
Upper respiratory tract	43 (34%)	2 (1.6%)
Lower Respiratory tract	7 (5.5%)	1 (0.8%)
Urinary tract	10 (7.8%)	1 (0.8%)
Pneumonia	21 (16.5%)	12 (9.4%)

Source: FDA analysis of adae3.xpt
* Includes group terms; see APPENDIX A for preferred terms included in specific group terms

Grade 5 infections with bb2121 occurred in 4 subjects (3%) and included two cases of bacterial pneumonia, a case of CMV and Pneumocystis pneumonia (in the same subject) and bronchopulmonary aspergillosis respectively. Please see Section: 6.1.12.3 Deaths for narratives of these subjects.
Febrile neutropenia occurred in 20/127 subjects (16%) treated with LD and bb2121.

Reviewer's comment:
1. In addition to the infections captured under SOC of Infections and Infestations, the reviewer identified 8 additional infections in 7 subjects that were mis-classified under various SOCs; Respiratory, thoracic and mediastinal disorders, Investigations and General disorders & administration site conditions. These events were reclassified under infections-pathogen unspecified and viral infectious disorders.

2. Applicant grouped infections based on pathogen class reflected in high-level grouped term (AEHLGT) in ADAE3 dataset. To analyze infections based on location, the reviewer grouped infections according to the site of occurrence (such as pneumonia, urinary tract infection etc.). If an infection could either be grouped under a specific pathogen class or a specific site, the reviewer prioritized grouping under site of infection since applicant's grouping (AEHLGT) captured classification based on pathogen class. This strategy allowed for analysis of infections based both on the pathogen type and site of infection.

3. Febrile neutropenia rate of 16% is expected given the population and toxicity profile of LD followed with bb2121. One subject with febrile neutropenia was incorrectly graded as grade 2. By CTCAE v 4.03, since febrile neutropenia is at a minimum classified as grade 3.

4. This analysis does not include febrile neutropenia events (eight events in 4 subjects) that were classified as signs and symptoms of CRS. These events were misclassified as febrile neutropenia and were indicative of fever as manifestation of CRS with concurrent neutropenia. None of these events were associated with culture positive or other clinical evidence of infection. Based on the review of the narratives including the timing of the onset of fever relative to administration of bb2121 and the overall clinical course, the reviewer concluded that these events indicated neutropenia in setting of CRS with manifestation of fever instead of febrile neutropenia.

5. The review team grouped bacteremia and sepsis under GT-sepsis to capture severe and life-threatening infections. This grouping from different from the Applicant's approach of grouping bacteremia under bacterial infections and sepsis under infections-pathogen unspecified.

6. Notable infections included Grade 5 bronchopulmonary aspergillosis and Grade 5 CMV and Pneumocystis pneumonia.

7. The fatal infection rate with bb2121 is 4/127(3%). This rate does not include fatal cases of sepsis that occurred in two subjects after receiving subsequent anti-myeloma therapy for disease progression.

Persistent Cytopenia:
Persistent cytopenia was defined as Grade 3 or 4 neutropenia or thrombocytopenia at the last assessment within 1 month of receiving bb2121. Recovery of cytopenia from bb2121 infusion was defined as first time return to Grade ≤2 after Month 1. These analyses were based on cytopenias as determined by laboratory values rather than as reported in ADAE dataset.
Out of the 127 bb2121 treated subjects, Grade 3 or higher anemia occurred in 77%, Grade 3 or higher neutropenia occurred in 98% and Grade 3 or higher thrombocytopenia occurred in 66%.
Overall, 77/127(61%) of bb2121 treated subjects had any persistent cytopenia.
24/77 (31%) of the subjects with persistent cytopenia had not recovered from either persistent neutropenia, persistent thrombocytopenia or both as of the safety data cut off (10/16/2019).

Persistent neutropenia:
Fifty two out of 127 (41%) subjects had persistent neutropenia; 24/70 (34%) subjects in 300 million dose cohort and 26/53 (49%) subjects in 450 million dose cohort respectively had persistent neutropenia.
In the 300 million dose cohort: 3 subjects died with ongoing persistent neutropenia.
In the 450 million dose cohort: 4 subjects died with ongoing persistent neutropenia and one subject was lost to follow up.
Overall, 43/52 (83%) subjects had neutropenia recovery and median time to recovery from persistent neutropenia was 1.9 months

Persistent thrombocytopenia:
Sixty two out of 127 subjects (49%) had persistent thrombocytopenia; 34/70 (48.5%) subjects in 300 million dose cohort and 26/53 (49%) subjects in 450 million dose cohort respectively had persistent neutropenia.
In the 300 million dose cohort: 6 subjects died with ongoing persistent thrombocytopenia, two subjects were lost to follow up and one subject had this AE ongoing at the time of data cut off.
In the 450 million dose cohort: 5 subjects died with ongoing persistent thrombocytopenia, one subject was lost to follow up and 5 subjects had ongoing AE at the time of data cut off.
Overall, 40/62 (64.5%) subjects had thrombocytopenia recovery with median time to recovery of 2.1 months.

Table 56 below outlines selected supportive care for cytopenia in the bb2121 treated population:

Table 56 :

Concomitant Medication or Intervention of Interest	bb2121 treated population N=127 N(%)
White cell Colony stimulating factors	111 (87%)
Filgrastim	104 (81%)
Filgrastim-sndz	15 (12%)
Peg filgrastim	11 (9%)
Erythropoietin stimulating agents	7 (5.5%)
***Thrombopoietin mimetics**	4 (3%)
Intravenous Immunoglobulin	77 (61%)
Transfusion support:	91 (71%)
Packed red cells	90 (71%)
Platelets	61 (48%)
Stem cell Transplant for Hematopoietic Reconstitution	3 (2.3%)

- *Includes Romiplostim and Eltrombopag

Source: Applicant analysis

Table 57: Summary of the three subjects that required rescue stem cell transplantation

USUBJID/ Age (yrs.)	Dose Cohort Million CAR+T cells	Prior lines of therapy	Type of transplant	Hematopoietic reconstitution ;/Cause of death
(b) (6) / 57	450	7	Autologous	No .Death from GI bleed
(b) (6) / 60	300	6	Autologous	Yes, Death from disease progression
(b) (6) /71	450	3	Allogeneic	No Death from BP aspergillosis, HLH/MAS

Source: FDA analysis of ADAE3 dataset and subject narratives

To further evaluate risk of persistent cytopenia, we evaluated the number of prior lines of therapy and risk of persistent cytopenia. This is summarized below in Table 58 and 59.

Table 58: Persistent cytopenia and Prior lines of therapy

Total N=127	Grade 3/4 neutropenia N(%)	Grade 3/4 thrombocytopenia N(%)	Persistent neutropenia	Persistent thrombocytopenia	Any persistent cytopenia
<6 prior lines of therapy N=55	54 (98%)	32 (58%)	23 (42%)	23 (42%)	31(56%)
≥6 prior lines of therapy N=72	71 (99%)	52 (72%)	29 (40%)	39 (54%)	46 (64%)

Source: Applicant analysis IR dated March 2, 2021

Table 59: Persistent cytopenia: Duration and Recovery and Prior lines of therapy

Total N=127	Median duration of persistent neutropenia (months)	Median duration of persistent thrombocytopenia (months)	Subjects who did not recover from persistent cytopenia		
			Neutropenia	Thrombocytopenia	Any or both cytopenia
<6 prior lines of therapy N=55	1.9	2.4	2 (9%)	9 (39%)	10(32%)
≥6 prior lines of therapy N=72	1.9	2.0	7 (24%)	13 (33%)	14 (30%)

Source: Applicant analysis, IR dated March 2, 2021.

Reviewer comment:
1.Since the study allowed Grade 2 neutropenia and thrombocytopenia at the time of enrollment and given the heavily pre-treated nature of the study population, the definition of cytopenia recovery (recovery to ≤Grade 2) is appropriate for this study population.

2. Across the dose cohorts, the Grade ≥3 neutropenia or thrombocytopenia toxicity predominantly included Grade 4 events whereas Grade ≥3 anemia toxicity was primarily Grade 3.Rate of persistent neutropenia was higher in the 450 million dose cohort compared to 300 million dose cohort (49% versus 34%), however, the median time to recovery was similar across the 2 dose cohorts for both persistent neutropenia and thrombocytopenia. The risk of persistent thrombocytopenia and neutropenia for approximately 2 months increased risk of infection and bleeding.

3. While, the pattern of supportive care outlined in Table 56 is not unusual for a heavily pre-treated myeloma population, it is notable that three subjects were treated with rescue stem cell therapy (two subjects with autologous and one subject with allogeneic stem cells transplantation) for prolonged cytopenia post-treatment with bb2121. Two subjects died from complications of persistent cytopenia despite the rescue transplantation including one subject with a fatal AE of GI bleeding in the setting of prolonged grade 4 thrombocytopenia (platelet count=4000/mm3) and another subject who developed fatal bronchopulmonary aspergillosis due to prolonged neutropenia in the setting of ongoing HLH/MAS(Please see Section 6.1.12.3 ;Deaths for details). The third subject recovered from neutropenia after receiving autologous CD34+ stem cell infusion. This information was added to the label to inform prescribers regarding the risk of prolonged cytopenia in this population. Prolonged cytopenia has been added to the boxed warning in the label.

4. Analysis of the risk of persistent cytopenia based on the number of prior lines of therapy indicates that subjects who had received ≥6 prior lines of therapy were more likely to develop ≥Grade 3 thrombocytopenia post bb2121compared to <6 prior lines of therapy (72% vs. 58%) with a higher proportion developing persistent thrombocytopenia (54% vs. 42%). While the median duration of cytopenia was similar in between the two groups, more subjects with ≥6 prior lines of therapy did not recover from persistent neutropenia (24% vs. 9%) at the time of data cut

off. Therefore, the overall risk of persistent thrombocytopenia and lack of neutropenia recovery may be associated with the number of prior lines of therapy in this population.

Hypogammaglobulinemia:

Newly diagnosed hypogammaglobulinemia based either on laboratory value defined as IgG <500 mg/dl post-bb2121 infusion or on adverse event (defined by FDA GT) in ADAE 3 dataset was reported in 41% (52/127) of bb2121 treated subjects. This included 43% (30/70) of subjects treated in 300 million dose cohort and 40% of subjects (21/53) treated in 450 million dose cohort. Overall, 77/127 (61%) bb2121 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. This includes 38/70 (54%) subjects treated in the 300 million dose cohort and 37/53 (70%) of the subjects treated in 450 million dose cohort.

Reviewer's comment:

The PI will reflect a combination of adverse event and laboratory based hypogammaglobulinemia. IVIG therapy was administered in the study for subjects with serum IgG levels less than 400 mg/dl. The recommendation to administer IVIG to maintain IgG level above 400 mg/dl will be included in the label as it may have reduced the overall rate of infection post bb2121 in study MM-001.

Secondary Malignancies

Risk of insertional mutagenesis resulting in secondary malignancies is a concern with CAR-T therapy. Secondary malignancies were defined as newly diagnosed reports of cancer not representing relapse of the underlying disease for which the subject received study treatment. Nine subjects (7%) had secondary malignancies reported after treatment with bb2121 of which one subject had plasmablastic lymphoma that developed after retreatment with bb2121. This case of plasmablastic lymphoma was evaluated and deemed not related to the CAR T product. Other malignancies included basal cell carcinoma, lung adenocarcinoma (in a smoker), anal cancer and squamous cell carcinoma of the skin. The 90-day safety update included one case of myelodysplastic syndrome (USUBJID: (b) (6)) summarized below.
Overall, the vector integration site analysis from Study MM-001 demonstrated insertion sites with clonal heterogeneity which does not support monoclonality.

Reviewer's comment:

1. Subject (b) (6) was diagnosed with EBV negative plasmablastic lymphoma 3.6 months after retreatment with bb2121. This subject was treated with 300 $x10^6$ million CAR+ T cells for initial treatment and 450 $x10^6$ million CAR+ T cells at the time of retreatment. No insertional analysis could be performed as all available tumor specimen was exhausted at the clinical site for diagnostic purposes. Peripheral blood expansion analysis did not demonstrate clonal expansion of bb2121.Prior to the diagnosis of plasmablastic lymphoma, subject experienced disease progression and pathology from the plasmablastic lymphoma demonstrated similar histological and immunophenotypic features as the subject's known myeloma. This malignancy is likely an evolution of subject's myeloma to a plasmablastic form of the disease as opposed to a true secondary malignancy.
2. Subject (b) (6) : This 55-year-old subject was diagnosed with refractory anemia with excess blasts (5% blasts) approximately 1 year after treatment with bb2121. FISH analysis showed presence of monosomy 7, monosomy 5 and deletion 20q. NGS showed p53 variant pCys176Gly with variant allele frequency (VAF) of 49%. The bone marrow sample was negative for the CAR transgene. A pre-treatment bone marrow was analyzed which revealed deletion

5q,20q and 7q on FISH and p53 variants pCys176Gly at VAF of 2% and pLys132Thr at VAF of 1% respectively on NGS. The presence of the clonal abnormalities prior to treatment with bb2121 and absent CAR transgene in the dysplastic marrow makes it unlikely that this malignancy is related to bb2121.

Hemophagocytic Lymphohistiocytosis (HLH)/Macrophage activation syndrome:
Five out of 127 (4%) subjects treated with bb2121 developed HLH. This included one subject (1/70=1.4%) treated in 300 million dose cohort and four subjects (4/53=7.5%) treated in 450 million dose cohort. One subject treated in the 300 million dose cohort had fatal HLH/MAS with CRS. Another subject in the 450 million dose cohort with fatal bronchopulmonary aspergillosis had HLH/MAS ongoing at the time of death that contributed to the fatal event.
For narratives on the two cases of fatal HLH/MAS, please see Section 6.1.12.3; Deaths.
Three out of five subjects had Grade 2 HLH/MAS events which resolved.
All events of HLH had onset within 10 days of receiving bb2121 (median onset was 7 days; range: 4-9 days) and occurred in the setting of ongoing or worsening CRS. Max CRS grade was Grade 5 in one subject, Grade 4 in one subject, Grade 3 in one subject and Grade 2 in two subjects. Two subjects had concurrent or overlapping NT with HLH/MAS. The manifestations of HLH/MAS include hypotension, hypoxia, multiple organ dysfunction, renal dysfunction and cytopenias.
Two of the five subjects had bone marrow biopsy demonstrating HLH/MAS. All subjects had elevation of IL-2 RSA (receptor subunit alpha) with mean level of 12,005 pg/ml (range 5535-30,850 pg/ml). The peak ferritin level was a mean of 34,798 microgram/l (range 3073-95,207microgram/L).

Reviewer's comment:
1. HLH/MAS is a rare but serious safety risk observed with bb2121. This life-threatening toxicity may be clinically overlooked as it occurs in the setting of ongoing CRS frequently presenting as refractory CRS. The Prescriber information would include consideration of HLH in the setting of CRS not responsive to CRS management. Therefore, it has been included under boxed warning and Section 5; Warning and Precautions as a separate entity to alert prescribers.
2. Given the limitation of small sample size, HLH/MAS appears to be a dose dependent toxicity seen more frequently in 450 million dose cohort. However, the fatal case of HLH/MAS and CRS occurred in the 300 $x10^6$ CAR+ T cell dose cohort.
3. There is lack of standardized management guidelines for HLH/MAS. Therefore, management of this toxicity has been left to the institutional guidelines in the label.

Infusion Related Reaction:
Infusion related reaction occurred in 2 subjects (1.5%) on the study. No event was grade 3 or higher and both events occurred on the same day as bb2121 infusion.

Subpopulation Analyses; Safety:
Subpopulation: 65 years and older:
Thirty six out of the 100 subjects treated at the recommended dose of 300-460 million CAR+ T cells were ≥65 years of age (Range 65-78 years). Four subjects (4%) of the subjects were ≥75 years of age. Overall, rates of ≥ Grade 3 CRS, infection, HLH/MAS and fatal AE were comparable between subjects ≥65 years and < 65 years subgroups. It is noted that all five subjects with grade 3 neurotoxicity events were ≥65 years of age (range 66-74 years). This information will be included in the label to inform prescribers.
Reviewer's comment: Given that all Grade 3 neurotoxicity events occurred in 65 years or older population, clinical team recommends that the primary safety endpoint of the post-marketing

registry trial include the incidence and severity of neurotoxicity in the older adults (≥65 years of age).

Subpopulation: Creatinine clearance <45 ml/minute:

Nine subjects (9/127) treated in the study had creatinine clearance of <45 ml/minute (Range: 30 ml/minute to 45 ml/minute) which was lower than protocol specified threshold of 45 ml/minute. Three subjects had creatinine clearance <35 ml/minute. The fludarabine was dose reduced for all of these subjects. Overall, no obvious safety concerns were observed in this population. Three out of the nine subjects (33%) had Grade 5 general physical health deterioration in the setting of progressive myeloma.

6.1.12.6 Clinical Test Results

Table 60: Laboratory abnormalities in ≥10% of subjects treated with bb2121

Laboratory Based Abnormality	All grades n(%)	Grade 3-4 n(%)
Hematology		
Leukopenia	124/127 (98%)	122/127 (96%)
Lymphopenia	117/127 (92%)	117/127 (92%)
Neutropenia	124/127 (98%)	122/127 (96%)
Thrombocytopenia	111/127 (87%)	80/127 (63%)
Anemia	103/127 (81%)	80/127 (63%)
Chemistry		
Hypophosphatemia	113/126 (90%)	57/126 (45%)
Hypoalbuminemia	108/127 (85%)	10/127 (8%)
Serum Creatinine increased	13/127 (10%)	0
Serum ALT increased	89/127 (70%)	11/127 (9%)
Serum Alkaline Phosphatase increased	81/127 (64%)	9/127 (7%)
Serum Bilirubin increased	53/127 (42%)	7/127 (6%)
Serum AST increased	80/127 (63%)	10/127 (8%)
Hypercalcemia	15 (6)	0
Hyperglycemia	61/127 (48%)	9/127 (7%)
Hypomagnesemia	46/126 (37%)	0
Hypocalcemia	82/120 (68%)	4/120 (3%)
Alkaline phosphatase increased	81/127 (64%)	9/127 (7%)
Hyponatremia	73/127 (57%)	13/127(10%)
Hypokalemia	69/127 (54%)	9/127 (7%)
Hypoglycemia	67/127 (53%)	1/127 (0.8%)
Creatine kinase increased	22/123 (18%)	3/123 (2%)
Hypernatremia	19/127 (15%)	0
Hyperkalemia	13/127(10%)	0
Coagulation		
a PTT increased (seconds)	78/124 (63%)	12/124 (10%)
Prothrombin INR increased	69/127 (54%)	1/127 (0.8%)
Fibrinogen decreased	32/126 (25%)	6/126 (5%)

Denominators for laboratory analyses are based on patients with a baseline and at least one on-study value. Patients must have had at least one grade worsening on study to be counted in analyses and only worst grade will be included in the analyses.

Source: FDA analysis; adlb.xpt, adsl.xpt

Reviewer's comment:

- Laboratory data (ADLB dataset) was used to generate incidence of laboratory- based AEs since this is more accurate as opposed to using the adverse event dataset (ADAE dataset).
- A "lab-shift" analysis was carried out wherein baseline laboratory abnormalities that worsened following treatment were recognized i.e. shift of a laboratory grade from a lower to higher grade.
- Cytopenias of all grades were the most common laboratory abnormalities as expected and reflect toxicity of the entire investigational protocol including lymphodepleting chemotherapy.
- Hypophosphatemia was the most common overall and the most common grade 3-4 chemistry laboratory abnormality.
- Increase in a PTT and PT/INR were the most common coagulation abnormality. Hypofibrinogenemia was noted in 25% of the evaluable subjects with 5% Grade 3-4 events.

6.1.12.7 Dropouts and/or Discontinuations

Among the 140 subjects who were enrolled in MM-001 and underwent leukapheresis, 132 subjects received the conditioning regimen and 128 subjects were treated with bb2121. Of the twelve subjects who did not receive bb2121, 8 subjects discontinued prior to receiving conditioning. The reasons for discontinuation were physician decision (n=3), disease progression (n=1), withdrawal by patient (n=2), AE (n=1) and manufacturing failure (n=1), two subjects died prior to bb2121 and four subjects withdrew from the study. Four subjects discontinued after receiving conditioning due to death (n=2) and patient withdrawal (n=2).The primary reason for study discontinuation following bb2121 was death followed by patient withdrawal.

6.1.13 Study Summary and Conclusions

Efficacy:

MM-001 is a Phase 2, single arm, international study which provided data for the efficacy analysis in this BLA. Patients with relapsed/refractory multiple myeloma who had previously received a proteasome inhibitor, an immunomodulatory drug and an anti-CD 38 antibody were enrolled by undergoing leukapheresis. During product manufacturing, subjects could receive bridging therapy at the discretion of the investigator. All subjects were then treated with lymphodepletion followed by single infusion of bb2121.The pre-defined primary endpoint agreed to by the FDA was ORR, as assessed by IRC applying 2016 IMWG Uniform Response Criteria for multiple myeloma. As of the January 14, 2020 data cut off, 140 subjects had been enrolled, and 127 subjects were treated with bb2121 at the dose range of 150.5 $x10^6$ to 518.4 x 10^6CAR + T cells. The dose range of 300-460 $x10^6$CAR+ T cells is the recommended regimen of dose for this BLA approval. The majority of the subjects (79%) received the study drug at the recommended dose range. By the FDA assessment, ORR was 72% {95% CI (62%, 80%)}. The lower limit of the 95% confidence interval was greater than the pre-specified null hypothesis rate of 50. The stringent complete response rate (s CR) was 28% {95% CI (19%, 37%)}. The lower limit of the 95% CI was greater than the prespecified null hypothesis rate of 10% for CR. The median time to first response was one month. Of the 72 subjects who achieved a response, median duration of response was 11 months {95% CI (10.3, 11.4)} and an estimated 35%

maintained a response for at least 12 months. At a median follow up of 10.7 months, the estimated median duration of response in sCRs was 19 months {95% CI (11.4, NE)}. An estimated 65% of the sCRs maintained a response for 12 months. An estimated 22% of the VGPRs maintained response at 12 months. The median duration of response for PR+VGPR was 9.2 months {95% CI (5, 10.6)}
Within the dose range of 300-460 x 10^6 CAR+T cells, there is a dose response relationship noted with numerically higher ORR, sCR rate and median DOR with 440-460 x 10^6 CAR+ T cells compared with 300-340 x 10^6 CAR+ T cells.
Study MM-001 was an adequate and well controlled study that met the study objective that ORR was statistically significantly greater than the pre-specified null hypothesis rate of 50%. In addition, the s CR was statistically significantly greater that the pre-specified null hypothesis rate of 10% Based on the magnitude of the overall and stringent complete response rate with median duration of response that exceeds 12 months in the sCR subjects , the clinical team recommends traditional approval for bb2121 in patients who have received at least 4 prior lines of therapy including a proteasome inhibitor, an IMiD and anti-CD38 antibody therapy. The clinical benefit observed in the overall population was also observed in the triple class refractory subset which constituted 85% of the overall population. This indicates that the response rate and durability data observed are robust and reproducible in a high-risk population with limited therapeutic options. 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 R/R myeloma patients who have received at least 4 prior lines of therapy. Overall, only 5% of the safety population and 6% of the efficacy population were black or African American though 73% of the study population was enrolled from the US indicating underrepresentation of this racial minority in the study. To address this issue, the 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.

Because MM-001 was a single arm trial without a control arm, we evaluated the efficacy data for bb2121 in the context of approved therapies. Belantamab has accelerated approval and was evaluated in triple class refractory myeloma population with 7 median prior lines of therapy. In a single arm trial of 97 subjects, an ORR of 31% and CR rate of 3% was observed with belantamab. 73% of the responders had at least 6 months duration of response with median follow up of 6.3 months. Melphalan flufenamide in combination with dexamethasone recently received accelerated approved. It was evaluated in a single arm trial in a triple class refractory population with median 6 prior lines of therapies. ORR was 24%, no CRs were observed and median duration of response was 4.2 months. Selinexor in combination with dexamethasone has regular approval in penta-refractory population with median 8 prior lines of therapy. In a single arm trial of 83 patients, an ORR of 25% and CR rate of 1% was demonstrated with a median DOR of 3.8 months. The magnitude of benefit primarily driven by durable stringent CRs in a disease setting where durable complete response rates are dismal with approved therapies supports traditional approval for bb2121.

Safety:
Of the 127 subjects evaluable for safety, grade 3 or higher toxicities for the AEs of concern are as follows:

- CRS occurred in 9.4%.
- Neurologic toxicities in 4%.
- Hemophagocytic lymphohistiocytosis in 1.6%.

- Febrile neutropenia occurred in 16%.
- Persistent cytopenia occurred in 61%.
- Infections occurred in 23% .

The 30-day fatal AE rate was 0.8% and overall fatal AE rate was 5.5%. Cytokine release syndrome, hemophagocytic lymphohistiocytosis (HLH/MAS), bronchopulmonary aspergillosis, CMV and Pneumocystis pneumonia, bacterial pneumonia, lower GI bleeding in the setting of persistent severe thrombocytopenia and respiratory failure were the cause of fatal AEs. There is a dose toxicity relationship with higher rate of Grade 2 CRS, median duration of CRS, Grade 3 neurotoxicity, and HLH observed in 450 million dose cohort compared to 300 million dose cohort. The median time to recovery from persistent cytopenia was approximately 2 months which increased the risk of bleeding and infection. Subjects that had received ≥6 lines of therapies were more likely to have persistent thrombocytopenia compared to <6 lines of therapy (54% vs. 42%) and less likely to recover from persistent neutropenia (24% vs.9%) by the data cut off.

The toxicity profile of bb2121 is similar to other CAR T products except for HLH/MAS and prolonged cytopenia requiring stem cell rescue which are new safety signals with this product .Three subjects required rescue hematopoietic stem cell transplantation due to persistent cytopenia and two died from complications of persistent cytopenia despite the rescue stem cell therapy. While, the toxicity profile is not unexpected in a heavily pre-treated myeloma population, it requires careful monitoring and intervention. While high grade neurologic events were infrequent in Study MM-001, other studies with bb2121 have reported a Grade 3 event of myelitis which was unresponsive to standard therapy and a case of Grade 3 parkinsonism which improved to Grade 1 with dopaminergic agents.

During MM-001 study, life-threatening and fatal adverse reactions caused by bb2121 were mitigated by mandated site and investigator training, careful site selection and monitoring, instructions for early detection and management of the most serious complications, and close monitoring following bb2121 infusion. Inpatient hospitalization for 14 days after receiving bb2121 was mandated. The life-threatening and fatal adverse reactions warrant warnings, including a boxed warning for CRS, neurotoxicity, prolonged cytopenia requiring rescue stem cell transplantation and hemophagocytic lymphohistiocytosis and a REMS. The clinical review team determined, in consultation with OBE and CDER DRISK, that a REMS with ETASU is the appropriate approach. The focus of the REMS with ETASU are site preparation, patient education, and risk mitigation strategies, with emphasis on early recognition and treatment of CRS and neurotoxicity. The clinical team recommends that REMS training materials and knowledge assessment be modified to include HLH/MAS and persistent cytopenia requiring rescue stem cell transplantation to educate health care providers.

Long-term safety after treatment with bb2121 especially for secondary malignancies remains a concern. None of the secondary malignancies during this trial at time of primary data cutoff were attributed to the study product but concern for insertional mutagenesis and secondary malignancies remain. Due to the lack of long-term safety data in the BLA, additional post-marketing registry has been mandated. This study will collect the incidence and severity of AEs such as all secondary malignancies, ≥Grade 3 CRS, ≥Grade 3 neurologic toxicities; including the incidence and severity of neurologic toxicity in 65 years and older population, prolonged cytopenia including the need for rescue transplantation and HLH/MAS.

6.2: Study CRB:401

Study CRB-401 is a Phase 1 trial of bb2121 in BCMA expressing multiple myeloma.
This was a first in human, open-label, multicenter, dose escalation plus dose expansion study to determine the recommended Phase 2 dose of bb2121.CRB-401 consisted of dose escalation (Part A) and dose expansion (Part B). The enrollment is complete, and subjects are in post-treatment follow up. Part A evaluated various dose levels ranging from 50, 150, 450 and 800 $x10^6$CAR+ T cells in 21 relapsed or refractory MM subjects whose tumors expressed ≥50% BCMA. Part B treated 41 relapsed and refractory myeloma subjects at 150 and 450 $x10^6$ CAR+ T cell dose cohorts. Thirteen subjects had <50% BCMA expression and 21 subjects had ≥50% BCMA expression within Part B.

Efficacy Results:
Overall, 56 subjects were treated at RP2D; 18 subjects were treated at $150x10^6$CAR+ T cells and 38 subjects at $450x10^6$CAR+T cells. 87.5% were CD38 antibody refractory, 75% were triple refractory and 80% were refractory to the last regimen. Median prior lines of therapy are 6 (Range 3-18). 26.5% (13/49) of the evaluable subjects had <50% BCMA expression. 54% of the population received bridging therapy.
In summary, the key efficacy results as follows:
At the $150x10^6$CAR+T cell dose (Range from 140.8- 178.3 $x10^6$ CAR+ T cells) : The ORR was 56% {95% CI (31%, 78.5%)}, CR rate was 33% {95% CI (13%, 59%)}.
At the $450x10^6$CAR+T cell dose (Range from 205.4-498.6 x 10^6CAR+T cells): The ORR was 84% {95% CI(69%, 94%)}, CR rate was 37% {95% CI (22%, 54%)}.
DOR for the $450x10^6$CAR+T cell dose (updated at data cutoff date of 7 April 2020) was 10 months {95% CI: 7.2, 14.8)} with a median follow up of 8.5 months (Range: 0.7, 37). Out of the 32 responders at this dose level, 78% (25 subjects) had an event and 16% (five responders) were at risk and censored at >12 months.

Reviewer's comment: The efficacy results presented above are based on Applicant's analysis. Despite pooling of the efficacy results across MM-001 and CRB-401 at $150x10^6$ CAR+T dose cohort, the ORR did not support efficacy at this dose level. (See Section 6.1.11.1 Analyses of Primary Endpoint(s) for details).
The DOR data at the $450x10^6$CAR+T cell dose are similar to the efficacy results from Study MM-001.

Safety Results:
Despite CMC confirmation that the product used in this study was comparable with the product used in MM-001 , the review team did not perform an integrated safety and efficacy analysis given the differences in the eligibility criteria, definition of measurable disease, the schedule of assessment and data collection for safety analysis.. The summary of clinical safety and the datasets were scanned to assess for any additional safety signals. This identified a subject treated at 450 $x10^6$ CAR +T cell dose cohort who developed cerebral edema in the setting of Grade 4 neurotoxicity. This was included in the safety information of the label.
Two subjects treated with bb2121 developed myelodysplastic syndrome. These are briefly summarized below:

a) Subject (b) (6) had received nine prior regimens including two autologous stem cell transplants with melphalan conditioning. Other prior therapies include thalidomide, lenalidomide and cyclophosphamide. Subject developed MDS approximately 368 days after receiving bb2121.Bone marrow biopsy revealed 5q and 7q deletion. A pre-treatment bone marrow biopsy revealed hyper diploidy, detection of 13q14 and unbalanced rearrangement of IGH on FISH analysis.
b) Subject (b) (6) had received 6 prior regimens including autologous transplantation with melphalan conditioning, lenalidomide, pomalidomide and cyclophosphamide. This subject was diagnosed with MDS 14 days after receiving bb2121.Bone marrow biopsy revealed 5q and 7q deletions. A pre-treatment bone marrow biopsy revealed gain of 6p, 18q and t(11;14).

Reviewer's comment: According to the Applicant, both these subjects died prior to an amendment to the CRB-401 protocol that allowed for testing of tissue from secondary malignancy. Therefore, no samples are available for transgene or insertional analysis. The prior alkylator exposure and the presence of the cytogenetic abnormalities in chromosome 5 and 7 typically seen in alkylator therapy related MDS indicates that both of these cases of MDS are likely related to prior cytotoxic therapy

7. Integrated Overview of Efficacy:

No integrated analysis of efficacy was performed. See Section 6.1 and 6.2

8. Integrated Overview of Safety

To facilitate assessment of dose toxicity relationship, the Agency reviewed a pooled safety analyses from clinical studies CRB-401, MM-001, MM-002 (Cohort 1), and MM-001 Japan using the data cut off dates for the 3-month safety update. (See 5.3 Table of Studies/Clinical Trials for information about these studies) This pooled analyses compared the rates of adverse events of special interest: CRS, neurotoxicity, HLH/MAS and disseminated fungal infections based on the dose of bb2121 across these studies.
1. CRS rate for Study MM-001 used in the pooled analyses are based on Agency's adjudication.
2. Given that Cohort 2 of Study MM-002 is for the treatment of subjects to receive an earlier line myeloma population (second line and high-risk front line), safety data from this cohort was not pooled with the other studies to ensure that similar population was combined for this analysis. For example, pre-treatment cytopenias which are impacted by lymphodepletion and ABECMA are more prevalent in patients who receive multiple lines of therapy as is reflected in MM-001 (median of 6 prior lines of therapy) whereas MM-002 enrolled patients who received second line therapy. Pooling patients across studies with differences in baseline risk factors may result in lower frequency of adverse events. These issues are also applicable to MM-003 a study where enrolled patients received 2-4 lines of antimyeloma therapy.
3. Safety data from Study MM-003 a randomized controlled trial is not included in the pooled analyses as it is submitted as aggregate data across the two treatment arms to protect the integrity of the ongoing study.
4. Neurotoxicity: Instead of the iiNT events, applicant identified NT events (NT-focused) were included in the analyses for the studies. For study MM-001, FDA adjudicated NT events were also included. This strategy was used to facilitate pooled analyses from Study CRB-401 in which NT was captured as focused NT events and iiNT flag was not applicable. This analyses

included all neurotoxicity events that started on the day of bb2121 infusion and up to and including day 60 post-treatment.

Table 61: Pooled analysis for Adverse Events by Dose Cohort of bb2121

Dose	CRS All grades n(%)	CRS Grades 3-5 n(%)	HLH All grades n(%)	NT [c] All grades n(%)	NT [c] Grades 3-5 n(%)	Disseminated fungal infection n(%)	Time to recovery from prolonged cytopenia(≥Grade 3)	
300 million [a] N =70	55 (79%)	7 (10%)	1 (1.4%)	25 (36%)	1 (1.4%)	1 (1.4%)	1.9 months	2.1 months
450 million [b] N=141	135 (96%)	9 (6%)	7 (5%)	53 (38%)	10 (7%)	3 (2%)	1.9 months	2.2 months

a : Only Study MM-001 included subjects treated with bb2121 in the 300x 10^6CAR+ T cell dose cohort.
b: Includes Studies CRB-401 (n=38), MM-001 (N=53), MM-001-Japan (n=9), MM-002 Cohort 1 (N=41)
c: Includes NT-focused events. FDA adjudicated NT events from Study MM-001 are included.
Data cutoff date=5 June 2020 for Study MM-002 and 7 April, 2020 for Studies CRB-401,MM-001 and MM-001 Japan.
Source: Applicant analysis.

Reviewer's comment: The pooled safety analyses demonstrated a higher overall rate of CRS, HLH and Grade 3 or higher neurotoxicity in the 450 million dose cohort compared to the 300 million dose cohort. These findings are generally consistent with the safety findings observed in the pivotal study MM-001.

<u>New safety signals identified from the other studies included in the submission:</u>
Two AEs reported in Study MM-002 are considered novel safety signals and included in the safety information of the label. These are summarized below:

1. Subject (b) (6) : 73-year-old male was treated in Cohort 2a of study MM-002 following early relapse (within 18 months) of initial therapy. He had received 2 prior anti-myeloma regimens including autologous stem cell transplantation. He was treated with 301 million CAR+T cells. On Study day 68, he presented with back pain, lower extremity weakness, loss of sensation, inability to walk and subsequently developed neurogenic bladder. He was diagnosed with Grade 3 myelitis . MRI showed extensive edema from medulla to thoracic spine with intramedullary lesions. A PET/CT scan showed no evidence of metabolically active myeloma. CSF analysis was negative for viral, fungal or bacterial infectious etiology and paraneoplastic autoantibodies. Due to concern of malignant involvement of the spinal cord, he was treated with palliative radiation, however, given the lack of clinical benefit, a presumed diagnosis of transverse myelitis was made, and he was subsequently treated with high dose steroids and plasma exchange. On Study day 91, this subject died from pneumonia. Transverse myelitis was unresolved at the time of death.

2. Subject (b) (6) : 60-year-old subject was treated in Cohort 2c with one prior anti-myeloma therapy of autologous transplantation and inadequate response (partial response) between 70-100 days after transplantation. He was treated with 412 million CAR+ T cells and developed symptoms of expressive aphasia, decreased mentation, bradykinesia, parkinsonian-like reflexes, rigidity and tremor (all Grade 3) on Study day 18. He was treated with steroids, keppra and carbidopa/levodopa. Subsequently, memantine was added and he received cyclophosphamide and plasma exchange. On Study Day 120, bradykinesia resolved, other

symptoms of parkinsonism improved to Grade 1 but did not resolve. Carbidopa-levodopa was stopped on Study day 120.

8.1 Safety Assessment Methods
N/A

8.2 Safety Database
N/A

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials
N/A

8.4 Safety Results
N/A

8.5 Additional Safety Evaluations
N/A

8.6 Dose Dependency for Adverse Events:
In Study MM-001, 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%). See Section 6.1.13 : Safety and Table 62 under Section 8.

8.5.2 Time Dependency for Adverse Events
N/A
8.5.3 Product-Demographic Interactions
N/A
8.5.4 Product-Disease Interactions
N/A
8.5.5 Product-Product Interactions
N/A
8.5.6 Human Carcinogenicity
N/A
8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound
N/A
8.5.8 Immunogenicity (Safety)
N/A
8.5.9 Person-to-Person Transmission, Shedding
N/A

8.6 Safety Conclusions
See above.

9. Additional Clinical Issues

9.1 Special Populations

Thirty six out of the 100 subjects treated at the recommended dose of 300-460 million CAR+ T cells were ≥65 years of age (range 65-78 years). Four out of 100 subjects (4%) were ≥ 75 years of age. Within the subgroup of subjects ≥ 65 years of age, the ORR was 83% with stringent CR rate of 30%. Therefore, efficacy of bb2121 in this subpopulation was comparable to the efficacy noted in population <65 years of age. Overall, rates of ≥ Grade 3 CRS, infection, HLH/MAS and fatal AE were comparable between ≥ 65 years and < 65 years subgroups. It is noted that all five subjects with grade 3 neurotoxicity events were ≥ 65 years of age (range 66-74 years). This information will be included in the label to inform prescribers.

Nine subjects treated in the study had creatinine clearance of <45ml/minute (Range: 30 ml/minute to 45ml/minute) which was lower than protocol specified threshold of 45ml/minute. Three subjects had creatinine clearance <35 ml/minute. ORR in this subgroup was 60% (5/9). No s CR were reported in this group. Given the limitation of a small sample size no conclusions can be made about the efficacy of bb2121 in this subgroup. Overall, the safety concerns observed in patients with creatinine clearance of 35-45 ml/min were not different either in severity or frequency than in patients with creatinine clearance of >45 ml/minute. Three out of the nine subjects (33%) had Grade 5 general physical health deterioration in the setting of progressive myeloma.

9.1.1 Human Reproduction and Pregnancy Data

No animal studies of reproduction or developmental toxicity have been performed, and bb2121 has not been studied in pregnant women.

Clinical reviewer comment

Effective contraception was required for clinical trial participation of bb2121.For information regarding the need for contraceptive use among patients treated with cyclophosphamide and fludarabine lymphodepleting conditioning chemotherapy, please see the respective agents' prescribing information.

9.1.2 Use During Lactation

There are no data on use of bb2121 during lactation.

9.1.3 Pediatric Use and PREA Considerations

There are no pediatric data in the intended population. The application does not trigger PREA, as Idecabtagene vicleucel (bb2121) is a new molecular entity (NME) with orphan designation.

9.1.4 Immunocompromised Patients

N/A

9.1.5 Geriatric Use:

Safety:

Of the 127 subjects, 45 (35%) subjects were 65 years of age or older and 4(3%) were 75 years of age or older. Overall, rates of ≥Grade 3 CRS, infection, HLH/MAS and fatal AE were comparable between ≥65 years and < 65 years. However, all events of grade 3 neurotoxicity in five subjects occurred in subjects ≥65 years of age (range 66-74 years). This information will be included in the label to inform prescribers.

Efficacy: Of the 100 subjects in the efficacy population, 36 subjects were 65 years of age or older. The ORR was 83% (30/36) and s CR rate was 11/36 (30%) in this subpopulation. No

relevant clinical difference in the effectiveness was observed in those older than 65 years compared to younger population.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

Study NDS-MM-003 (Retrospective Observation Study using Real-World Data):
The Applicant conducted a global non-interventional retrospective study (NDS-MM-003) to compare the outcome of MM-001 study with a real-world cohort of relapsed and refractory myeloma patients treated with standard therapies. Patient level data from clinical sites, registries and research database was collated into a single data model using data cut off of October 30, 2019. From a relapsed refractory multiple myeloma cohort of 1949 patients who had received at least three prior lines of therapy including IMiD, PI and anti CD38 antibody, 190 patients (Eligible RRMM cohort) were identified who were refractory to the last antimyeloma regimen, had received further antimyeloma therapy after progression and who met the eligibility criteria for MM-001 in terms of comorbidities, renal dysfunction, bone marrow reserve, ECOG functional status. Subjects in the eligible RRMM cohort received approximately 90 different treatment regimens predominantly as a combination of 3 or more drug regimens. These treatment regimens included combinations of IMiD, PI, corticosteroids, monoclonal antibodies and cytotoxic agents. This eligible RRMM cohort was compared with bb2121 treated subjects in Study MM-001 using trimmed stabilized inverse probability of treatment weighted propensity score (IPTW PS) for efficacy endpoints of ORR, VGPR or better and PFS. The results are summarized below:

Table 62: Comparison of the study population in MM-001 and the eligible cohort from NDS-MM-003.

Baseline Characteristic	Eligible RRMM Cohort N=190	MM-001 * N=128
Median age	64 years	61 years
R-ISS Disease Stage III, %	4%	16%
High risk cytogenetics, %	30%	35%
Triple class refractory	43%	84%
Extramedullary plasmacytoma	11%	39%
Efficacy		
ORR % (95% CI)	32% (24-42)	76% (69- 86)
≥ VGPR % (95% CI)	14% (9-22)	57% (47-70)
Duration of response (Months) Median (95% CI)	9 (7.5, 10.4)	11 (10.7, 11.3)
Median PFS (months) 95% CI	3.5 months (3.2, 3.7)	11.3 months (9.5, 13)

Source: *Applicant's analysis Clinical Study Report NDS-MM-003; BLA 125736

Reviewer's comments:
This RWE study characterizes the outcome of subjects with relapsed and refractory multiple myeloma previously treated with a PI, an IMiD and anti-CD38 antibody therapy and was conducted to provide context to the efficacy data from Study MM-001. Based on the applicant's analysis outlined above, treatment with bb2121 results in improved ORR, ≥VGPR rate, median DOR and median PFS compared to a real-world population treated with available therapies. However, there are several methodological limitations of this comparative analysis outlined below that impact the interpretability of the study results.

- There was significant amount of missing data for baseline prognostic features such as ECOG performance status, revised ISS, cytogenetics and LDH in the eligible RRMM cohort which required imputation.
- The results of NDS-MM-003 are based on data that is collected and merged from multiple sources such as registries, clinical trial sites and external research databases. Differences in follow up and response assessment of subjects from these different sources may impact the interpretability of the study results.
- Subjects in the eligible RRMM cohort were treated with 90 different treatment regimens with differing toxicities and efficacy. This creates significant heterogeneity in the RWE population limiting its utility as a control arm.
- The follow up schedule for response assessment in myeloma patients treated in the real-world setting and subjects treated in a clinical trial may be different. Subjects treated in MM-001 had a fixed schedule for response assessment (every month for the first 6 months and then every 3 months for 24 months) whereas follow up for efficacy assessment of NDS-MM-003 population was at the discretion of the treating physician. This can result in potential bias in the estimate of duration of response.
- Response assessment in MM-001 was based on the IMWG 2016 criteria which incorporates serum and urine chemistry, imaging and bone marrow results. However, disease assessment in the NDS-MM-003 cohort was based on either M spike or free light chain if M spike was not available. Most subjects in the eligible RRMM cohort did not have bone marrow biopsy performed for response assessment in keeping with clinical practice. Therefore, CR was not an efficacy endpoint in this study while CR was key secondary endpoint in study MM-001. Such differences in response assessment that occur in clinical practice versus clinical trial can introduce potential bias in comparison of overall response rate and PFS analysis.
- The comparative efficacy results of the eligible RRMM cohort (N=190) and MM-001 based on the trimmed IPTW are only relevant in the context of the applicant's efficacy adjudication of 128 subjects treated in Study MM-001.The efficacy results from the RWE study population are uninterpretable as compared to efficacy evaluable population determined by the Agency (N=100) and based on FDA adjudicated efficacy results.

  Given the methodological limitations discussed above, we conclude that the evidence generated from the RW analysis is not adequate to provide context or comparison for the outcome of MM-001 study. While it reiterates the challenges of an appropriate choice of a treatment in the control arm and supports the approach of considerations for a single arm study design in support of a primary study intended for marketing purposes, an alternative approach may be to consider a randomized controlled trial with investigator's choice of treatment from prespecified therapeutic options as the control arm.

Systemic Literature Review/ Available therapies:
The Applicant has provided a comparative analysis of relative effectiveness of bb2121 versus 1) selinexor and dexamethasone (STROM trial); and 2) belantamab (DREAMM-2 trial) using a matching-adjusted indirect treatment comparison (MAIC) to adjust for differences in patient characteristics from the clinical trials. The goal of this MAIC was to reduce bias in the treatment effect estimates which can occur with comparison of efficacy data across clinical trials. The applicant concluded from the MAIC analyses that bb2121 was associated with higher overall response rate and median DOR compared with selinexor/dexamethasone and belantamab.
Reviewer's comment:
This analysis is limited in that for the STORM and DREAMM-2 trials, patient level data was not available and therefore, only study-level data was analyzed. Given the differences in the patient characteristics, the definitions of outcomes, and other unreported differences across the studies, the treatment effect estimate may be biased limiting the utility of this analysis.

10. Conclusions:

Efficacy:
The efficacy of bb2121 is based on ORR, s CR and DOR in a multicenter, open label, single arm clinical trial in adults with relapsed and refractory multiple myeloma after at least three lines of systemic regimens including a proteasome inhibitor, an immunomodulatory agent and anti-CD38 antibody. The majority of subjects (79%) received the study drug at the recommended dose schedule of 300-460 million CAR+T cells. By independent response committee (IRC) assessment, ORR was 72% (95% CI: 62%, 80%). The lower limit of the 95% confidence interval was greater than the pre-specified null hypothesis rate of 50%. The stringent complete response rate (CR) was 28% (95% CI: 19%, 37%). The lower limit of the 95% confidence interval was greater than the pre-specified null hypothesis rate of 10% for CR. Of the 72 subjects who achieved an objective response, an estimated 35% maintained response for at least 12 months. Out of the 28 subjects who attained stringent CR, an estimated 65% maintained response at 12 months. Similar efficacy was observed in the triple class refractory subpopulation which constitutes 85% of the population indicating that the efficacy data are robust. The basis of FDA's conclusion of substantial evidence of effectiveness is the magnitude of benefit primarily driven by durable complete response rate.

Safety:
Severe CRS, neurotoxicity and hemophagocytic lymphohistiocytosis associated with bb2121 therapy are serious and life-threatening adverse events which require supportive measures. Severe and prolonged cytopenia that may require rescue stem cell therapy is another safety concern with this product. In addition to the immune effector cell- associated neurotoxicity, additional neurological safety signals identified include Grade 3 myelitis and Grade 3 parkinsonism . Treatment algorithms to mitigate these AEs as implemented in the study permit the benefits of treatment to outweigh these risks. In addition, there is the potential for insertional mutagenesis and resultant secondary malignancies. To enhance safety, the following measures should be followed:
1. The product label will allow for a boxed warning for CRS, NT ,HLH/MAS and prolonged cytopenia, and the warnings and precautions will convey a treatment algorithm for CRS and NT
2. REMS with ETASU will be implemented to assure the safe use of bb2121.

3. PMR study that is a requirement to follow recipients of the commercial product for short term and long-term toxicity.

In summary, Study MM-001 represents an adequate and well controlled study that provided substantial evidence of effectiveness in the context of an acceptable safety profile.

11. Risk-Benefit Considerations and Recommendations

The following table summarizes the risk/benefit considerations for bb2121(ABECMA) for the treatment of adult patients with relapsed or refractory myeloma, after four or more lines of systemic therapy including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody.

11.1 Risk benefit considerations in bb2121 (ABECMA) approval

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Multiple myeloma (MM) is the second most common hematologic malignancy and accounts for 1.8% of all cancers and 17% of all hematologic malignancies. • Therapy for patients with relapsed or refractory myeloma has improved considerably over the past three years with approval of multiple new therapies with improvement in response rate and progression free survival. • However, relapsed and refractory myeloma remains incurable with a 5-year survival rate of 52%.	Relapsed or refractory multiple myeloma is a serious and life-threatening condition with need for effective and safe salvage therapies.
Unmet Medical Need	• Patients with relapsed or refractory myeloma have unmet medical need.	Patient with relapsed or refractory myeloma have unmet medical need.
Clinical Benefit	• In this single arm multicenter study for patients with relapsed and refractory myeloma, lymphodepleting chemotherapy followed by bb2121 (ABECMA) administered at dose range of 300-460 x10^6 CAR + T cells produced: • Stringent CR rate of 28% {95% CI:19%,37%} according to IMWG 2016 criteria, with estimated median DOR of 19 months {95% CI:11.4, NE}. • ORR, by independent review committee (IRC) assessment, of 72% (95% CI: 62%, 80%) with median duration of response of 11 months {95% CI:10.3, 11.4}.	Based on the ORR,CR rate and DOR, bb2121 (ABECMA) at the recommended dose range has clinically meaningful activity in relapsed and refractory myeloma who have received a proteasome inhibitor, an IMID and an anti-CD38 antibody therapy.
Risk	• Major AEs associated with bb2121 (ABECMA) were cytokine release syndrome, neurologic toxicities, prolonged cytopenias; with some cases requiring stem cell rescue , infectious complications, hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) and hypogammaglobulinemia.	All the evidence indicates that the risk of bb2121 (ABECMA), while substantial, does not outweigh the benefit to adult patients with relapsed and refractory myeloma.
Risk Management	• The most substantial risks of bb2121 (ABECMA) are CRS, neurologic toxicity and HLH/MAS. These were mitigated in the trial by careful site selection and training of investigators. • There are theoretical risks of secondary malignancy with this genetically modified immunotherapy based on the potential for replication competent lentivirus due to the risk of insertional mutagenesis.	The risks associated with bb2121 (ABECMA) warrant boxed warnings, a REMS particularly for CRS,NT HLH/MAS and prolonged cytopenia requiring stem cell rescue therapy and a long term follow up study for risk assessment of subsequent malignancy attributable to insertional mutagenesis

11.2 Risk-Benefit Summary and Assessment

The risks of bb2121) are associated with its mechanism of action. CRS, HLH/MAS and neurotoxicity can be life-threatening or fatal. Prolonged cytopenia can last for months and result in increased risk of bleeding or infection. It may also require stem cell rescue therapy. However, the risks may be managed with appropriate risk mitigation strategies in place.
bb2121 is associated with a favorable risk/benefit balance for the recommended indication. A summary of the key efficacy and safety results is provided in Section 1.

11.3 Discussion of Regulatory Options

Safety:
The safety profile of bb2121 warrants a REMS with ETASU. In the IND phase, the applicant selected sites for expertise, conducted site training, and had close medical monitoring to assure that the unique adverse events were treated appropriately, and that patients and medical staff were educated on the risks, particularly of CRS ,neurotoxicity, HLH/MAS and prolonged cytopenia. There are additional long-term safety concerns due to the use of a lentiviral vector. We have asked the applicant to comply with an observational PMR study for short- and long-term toxicities. Additionally, the label will be inclusive of the risks and risk mitigation strategies for CRS, neurotoxicity and HLH/MAS , including a requirement to monitor patients at the certified healthcare facility daily for at least seven days following infusion of bb2121.

Efficacy:
Three regulatory options exist: regular approval, accelerated approval, and denial of approval. Approval requires substantial evidence of effectiveness, with accelerated approval accepting demonstration of a positive effect on a surrogate or intermediate endpoint reasonably likely to predict clinical benefit. Denial of approval results when a product fails to fulfill criteria for either type of approval. Key elements of effectiveness or clinical benefit are magnitude and persistence of response. The submitted MM-001 data demonstrated a significant degree of efficacy by overall and complete response rates after treatment with bb2121 in an adequate number of relapsed and refractory multiple myeloma subjects who had received at least three prior regimens and were exposed an IMiD, a PI and anti-CD38 antibody therapy which is a group with an unmet medical need for safe, effective therapies. Duration of response data based on 10.7 months (median) of follow-up after first response in the overall population and particularly in the sCR subset suggest meaningful clinical benefit.

11.4 Recommendations on Regulatory Actions

The review team recommends regular approval of bb2121 for the treatment of adults with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including an IMID, a PI and an anti CD38 antibody.
Although subjects with R/R myeloma who had received at least three prior lines of therapy including an IMID, a PI and an anti CD38 antibody were eligible for study MM-001, 88% of the efficacy evaluable population had received four or more lines of therapy with a median of 6 prior lines of therapy. Since the risk and benefit of bb2121 has been evaluated primarily in this later line population, the indication is revised to include patients with 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 bb2121 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.

In consideration of granting regular approval for bb2121 in relapsed or refractory myeloma population, the clinical review team considered the limitations and strengths of the data:
Limitations of data:

- The durability of DOR was driven by the stringent CRs, however, the sample size for s CR was limited to 28 subjects resulting in wide confidence intervals.
- 64% (18/28) of the ongoing stringent CRs were censored with 25% (7/28) censored prior to 12 months (10.4 to 11.2 months). This raises concerns about the maturity of the follow up for the stringent CR population.
- bb2121 is associated with toxicities such as CRS and neurotoxicity including Grade 3 myelitis and Grade 3 parkinsonism which will require risk mitigation with REMS and ETASU to maintain favorable risk benefit profile.
- New safety signal of hemophagocytosis lymphohistiocytosis (HLH/MAS) has been identified which will be included in the boxed warning and has also been included in the REMS training program
- Severe prolonged cytopenia requiring stem cell rescue in three subject indicates that marrow toxicity with LD and bb2121 may be more severe than observed with CD 19 CAR T therapy in R/R lymphoma. Therefore, we have modified boxed warning to include prolonged cytopenia . This safety concern will also be included in the REMS training program to educate providers.
- Absence of a randomized controlled trial requiring reliance on historical control data to assess the magnitude of benefit with bb2121.
- None of the subjects treated in Study MM-001 were exposed to belantamab, a BCMA directed antibody and microtubule inhibitor conjugate which is an approved therapy under accelerated approval. It is therefore difficult to extrapolate that population with disease progression post BCMA directed antibody will have the same robust response as observed in BCMA antibody naïve population, especially if the BCMA expression is low or absent post-exposure to belantamab.

Strengths of data:

- bb2121 is a first in class autologous anti-BCMA CAR T therapy with a novel mechanism of action.
- This product was administered as a single dose eliminating cumulative toxicity with repeated administrations while improving patient compliance and convenience.
- The efficacy population included refractory myeloma population with an unmet medical need. Eighty-eight% of the population had received four prior lines of therapy, 85% of the population was triple class refractory and 95% were anti-CD38 antibody refractory.
- We reviewed the historical control data for outcomes in anti-CD38 antibody refractory myeloma population treated with available standard therapies. Outcomes of 38% ORR in the “not triple refractory” and 29% ORR in the triple refractory subgroups were observed (Gandhi et al, 2019). In a triple class refractory myeloma population with 7 median prior lines of therapy, Belantamab received accelerated approval based on ORR of 31%, CR rate of 3% with 73% of responders having DOR of ≥6 months with median follow up of 6.3 months. Melphalan flufenamide in combination with dexamethasone recently received accelerated approval in R/R myeloma patients who have received at least four prior therapies and are triple class refractory. The approval was based on ORR of 24% and median duration of response of 4 months. No CRs were observed in the study.
- 26% of the efficacy evaluable population was penta-refractory. In a penta-refractory population with median 8 prior lines of therapy, Selinexor and dexamethasone has full approval with ORR of 25%, CR rate of 1% and median DOR of 3.8 months.

- In Study MM-001, ORR observed with bb2121 was statistically significant rejecting the null hypothesis of ≤50%. ORR of 72%, sCR rate of 28% with an estimated 35% of all responders and an estimated 65% of s CR subjects in response at 12 months indicates that the magnitude of treatment effect is substantial translating into clinical benefit. A similar clinical benefit was observed in the triple class refractory population.

11.5 Labeling Review and Recommendations

The key labeling negotiations included:
Boxed Warning updated to include HLH/MAS and prolonged cytopenia.
Dosing and Administration:
Narrowing of the dose range (300-460 CAR+ T cells) and removal of target dosing to facilitate a dose range supported by efficacy.
Safety:
Modifications to the warnings and precautions section.
Section 2.3 ; Management of severe adverse reactions updated to align with other approved labels of CAR T products.
Update to Table 3 Under Section 6.1: Clinical trials experience in reflect Agency's safety analysis.
Efficacy:
Section 14 updated to include efficacy for subjects in the recommended dose range.

Reviewer Comment:
The labeling negotiations with the Applicant are ongoing at the time of completion of this review.

11.6 Recommendations on Post-marketing Actions

The Applicant is planning to conduct a post-marketing registry study which we will consider a PMR. This study is observational and focuses on short-term toxicity such as Grade ≥3 CRS, neurologic toxicity, prolonged cytopenia, pregnancy outcome and other AEs considered related to bb2121 such as hypogammaglobulinemia, tumor lysis syndrome, infections and organ toxicities, and long-term follow-up for evaluation of secondary malignancies. The plan is to enroll approximately 1500 patients and follow each patient for 15 years.
The Applicant submitted a REMS that consisted of a communication plan and medication guide. We determined in consultation with the OBE and CDER DRISK that a REMS with ETASU is the most appropriate approach. The focus of the REMS ETASU is site preparation, patient education, and assessment of risk mitigation strategies on the recognition and treatment of CRS and neurotoxicity.
The REMS ETASU should be reviewed, approved, and implemented by the Applicant at participating treatment sites prior to the distribution of bb2121 (ABCEMA)to the site. See Section 4.6 Pharmacovigilance for specific details of the REMS ETASU.
Reviewer's comment:
Given the additional safety signals of HLH/MAS and prolonged cytopenia requiring stem cell rescue therapy, we recommend the following:
1. Education of health care providers regarding these adverse events be included in the REMS training materials and knowledge assessment.
2. The post marketing registry study be modified to include the following additional primary safety endpoints:
1. Prolonged cytopenia requiring stem cell rescue therapy including the timing of transplant and the outcome in terms of hematopoietic reconstitution and survival.
2. Incidence and severity of HLH/MAS

3. The incidence and severity of neurotoxicity in the older adults (age ≥65 years) given that all Grade 3 neurotoxicity events occurred in older adults though the median age of the safety population was 61 years(See Section 6.1.11.3 for details).

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 compared to the whites and the secondary objective is safety.

Appendix 1:

TABLE 1
STUDY MM-001:RESPONDERS WHO RECEIVED BRIDGING THERAPY WITH MISSING ASSESSMENT AT BASELINE:

SUBJECT ID	MISSING ASSESSMENT AT BASELINE	BASELINE MEASURABLE DISEASE PARAMETERS
(b) (6)	URINE M PROTEIN*	SERUM M PROTEIN
	SERUM FREE LIGHT CHAIN#	SERUM AND URINE M PROTEIN
	BONE MARROW	SERUM AND URINE M PROTEIN, SERUM FREE LIGHT CHAIN
	BONE MARROW	SERUM M PROTEIN, SERUM FREE LIGHT CHAIN
	BONE MARROW	SERUM AND URINE M PROTEIN
	Plasmacytoma	SERUM M PROTEIN
	PLASMACYTOMA	URINE M PROTEIN , SERUM FREE LIGHT CHAIN
	PLASMACYTOMA	SERUM M PROTEIN, SERUM FREE LIGHT CHAIN
	PLASMACYTOMA	SERUM M PROTEIN

*NOT MEASURABLE ON SCREENING
measurable on screening .

FDA grouped and preferred terms used in review of BLA 125736 is presented in table format below.

Grouped Term	Preferred terms
Abdominal pain	abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness
Anxiety	Anxiety, feeling jittery, nervousness
Aphasia	*aphasia,* disorganized speech, *dysarthria*, speech disorder, slow speech, aphonia, communication disorder
Ataxia	ataxia, balance disorder, coordination abnormal, dysmetria, dyskinesia, gait disturbance, hand-eye coordination impaired, Romberg test positive
Bacterial infection	Arthritis infective, cellulitis, clostridium difficile infection, clostridium difficile colitis, diverticulitis, enterococcal infection, erysipelas, impetigo, pseudomonal infection, staphylococcal infection, ear infection
Bradycardia	bradycardia, sinus bradycardia
Cardiac Arrhythmias	arrhythmia, atrial fibrillation, atrioventricular block complete, atrioventricular block second degree, extrasystoles, supraventricular tachycardia, ventricular tachycardia
Cardiomyopathy	Stress cardiomyopathy, Ventricular hypertrophy
Chest pain	chest pain, chest discomfort
Coagulopathy	coagulopathy, international normalized ratio increased, activated partial thromboplastin time prolonged, Anticoagulation drug level above therapeutic, Disseminated intravascular coagulation
Conjunctivitis	conjunctivitis, conjunctivitis bacterial

Grouped Term	Preferred terms
Cough	cough, productive cough, upper-airway cough syndrome
Decreased appetite	Decreased appetite, hypophagia
Delirium	agitation, delirium, delusion, disorientation, hallucination; hallucination, visual; irritability, restlessness
Diplopia	Visual field defect
Dizziness	dizziness, presyncope, syncope, vertigo
Dyspnea	acute respiratory failure, dyspnoea, dyspnoea exertional, respiratory failure, acute respiratory distress syndrome
Ecchymosis	ecchymosis, catheter site bruise, contusion, eye contusion
Edema	fluid overload, fluid retention, generalized oedema, oedema, oedema peripheral, peripheral swelling, swelling, scrotal edema, face oedema
Encephalopathy	amnesia, bradyphrenia, cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, dyscalculia, dysgraphia, encephalopathy, lethargy, memory impairment, mental impairment, mental status changes, somnolence, metabolic encephalopathy, toxic encephalopathy
Fatigue	asthenia, fatigue, malaise
Fungal infection	candida infection, oral candidiasis, skin candida, onychomycosis
Gastroenteritis	Enteritis, gastroenteritis
Gastrointestinal hemorrhage	gastrointestinal haemorrhage, haemorrhoidal haemorrhage, melaena
Headache	headache, head discomfort, sinus headache

Grouped Term	Preferred terms
Hemorrhage	conjunctival haemorrhage, epistaxis, haematuria, hyphaema, post-procedural haemorrhage, mouth haemorrhage
Herpes viral infection	herpes simplex oesophagitis, herpes zoster, oral herpes
Hyperammonemia	hyperammonaemia,
Hyperbilirubinemia	blood bilirubin increased, hyperbilirubinaemia, jaundice
Hyperferritinemia	Serum ferritin increased
Hyperglycemia	hyperglycaemia,
Hyperphosphatemia	blood phosphorus increased, hyperphosphataemia
Hypofibrinogenemia	hypofibrinogenaemia, blood fibrinogen decreased
Hypogammaglobulinemia	Hypogammaglobulinaemia, hypoglobulinaemia
Hypoosmolality	Hypoosmolar state
Hypotension	hypotension, orthostatic hypotension
Hypoxia	hypoxia, oxygen saturation decreased
Insomnia	Insomnia, sleep deficit, sleep disorder
Leukopenia	Leukopenia, white blood count decreased
Lower respiratory tract infection	bronchitis, bronchitis haemophilus, tracheitis, lower respiratory tract infection viral
Lymphopenia	lymphopenia, CD4 lymphocytes decreased
Metabolic acidosis	acidosis, acidosis hyperchloraemic, lactic acidosis
Metabolic alkalosis	alkalosis
Motor dysfunction	muscle spasms, muscular weakness, eyelid ptosis, motor dysfunction, muscle twitching, restless leg syndrome, hypotonia, dysphonia

Grouped Term	Preferred terms
Mucositis	Mucosal inflammation, stomatitis, odynophagia, oral mucosal blistering, oral mucosal erythema, laryngeal inflammation
Musculoskeletal pain	musculoskeletal pain, musculoskeletal discomfort, musculoskeletal stiffness, musculoskeletal chest pain, arthralgia, back pain, bone pain, myalgia, neck pain, spinal pain
Myocardial ischemia	Angina pectoris
Neuropathy peripheral	neuropathy peripheral, paraesthesia, hypoaesthesia, hypoaesthesia oral peripheral sensorimotor neuropathy, peripheral sensory neuropathy, sciatica, neuralgia, carpal tunnel syndrome
Neutropenia	neutropenia, neutrophil count decreased
Oral Pain	oropharyngeal pain, oral pain, toothache
Pain	Pain, breast pain, ear pain, flank pain, groin pain, non-cardiac chest pain, pain in jaw, pelvic pain, bladder discomfort, pain in extremity, pain of skin, cancer pain
Pneumonia	bronchopulmonary aspergillosis, lung infection, pneumonia, pneumonia aspiration, pneumonia cytomegaloviral, pneumonia pneumococcal, pneumonia pseudomonal
Pulmonary edema	Pulmonary oedema, non-cardiogenic pulmonary oedema
Rash	Acne, dermatitis, erythema, rash, rash macular, rash papular, dermatitis bullous, urticaria
Reflexes abnormal	Pupillary reflex impaired
Renal failure	acute kidney injury, blood creatinine increased, renal failure, renal impairment, chronic kidney disease
Seizure	seizure
Sepsis	sepsis, septic shock, enterococcal bacteraemia, streptococcal bacteraemia,

Grouped Term	Preferred terms
	serratia bacteraemia, Escherichia bacteraemia, bacteraemia
Shock	Distributive shock
Skin lesion	Skin lesion, skin papilloma
Tachycardia	sinus tachycardia, tachycardia
Thrombosis	deep vein thrombosis, jugular vein thrombosis, pulmonary embolism, portal vein thrombosis
Thrombocytopenia	Thrombocytopenia, platelet count decreased
Transaminase elevation	alanine aminotransferase increased, aspartate aminotransferase increased, transaminases increased, hepatocellular injury, hepatotoxicity
Tremor	Asterixis, tremor
Upper respiratory tract infection	laryngitis, upper respiratory tract infection, sinusitis, nasopharyngitis, respiratory tract congestion, rhinovirus infection, rhinitis, pharyngitis, pharyngeal erythema, pharyngitis, respiratory tract infection, upper respiratory tract infection bacterial, rhinitis
Urine output decreased	Oliguria, urinary retention, urine output decreased
Urinary tract infection	escherichia urinary tract infection, urinary tract infection, urinary tract infection bacterial
Viral infection	parainfluenzae virus infection, corona virus infection, influenza, corona virus test positive, enterovirus infection, H1N1 influenza, influenza, respiratory syncytial virus infection, influenza like illness.
Vision blurred	vision blurred, visual impairment
Weight loss	Weight decreased
Xerosis	dry eye, dry skin, dry mouth, lip dry

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.

Marc Theoret, MD