Clinical Pharmacology/Pharmacometrics Review	
BLA	125736
Submission Type	Original submission
Submission Date:	8/10/2020
Applicant:	Celgene Corporation
Brand Name:	Idecabtagene Vicleucel
Generic Name:	Ide-cel, bb2121
PM Reviewer:	Yuan Xu
PM Team Leader:	Jiang Liu
OCP Division:	CBER submission
ORM Division:	Oncology

1. BACKGROUND

Ide-cel is a genetically modified autologous T cell immunotherapy product consisting of T cells transduced with an anti-BCMA02 CAR LVV. Autologous T cells transduced ex vivo with the anti-BCMA02 CAR LVV express the anti-human BCMA CAR on the T cell surface. The CAR is comprised of a murine extracellular single-chain variable fragment (scFv) specific for recognizing BCMA followed by a human CD8α hinge and transmembrane domain fused to the T cell cytoplasmic signaling domains of CD137 (4-1BB) and CD3ζ chain, in tandem. Binding of ide-cel to BCMA-expressing target cells leads to signaling initiated by CD3ζ and 4-1BB domains and subsequent CAR+ T cell activation. Antigen-specific activation of ide-cel results in CAR+ T cell proliferation, cytokine secretion, and subsequent cytolytic killing of BCMA-expressing cells.

Ide-cel is prepared from the patient's peripheral blood mononuclear cells (PBMCs), which are obtained via a standard leukapheresis procedure. After transduction, the T cells are expanded, harvested, and formulated as a cell suspension for intravenous administration. The drug product is formulated and cryopreserved in a solution containing Plasma-Lyte A and CryoStor® CS10, resulting in a final dimethyl sulfoxide concentration of 5%. Ide-cel drug product is filled in one or more infusion bags and thawed before infusion. Ide-cel is provided as a single dose for infusion containing a suspension of CAR+ T cells. The target dose is 450 x 10^6 CAR+ T cells, within a range of (b) (4) x 10^6 CAR+ T cells originally proposed by the applicant.

The primary efficacy endpoint was ORR based on the IRC adjudicated assessment of response in 128 patients in the pivotal study B2121-M001. The ORR in the ide-cel-treated population was 73.4% (95% CI: 65.8, 81.1) ($p < 0.0001$) across the target dose levels of 150 to 450 x 10^6 CAR+ T cells. In addition, 31.3% of subjects achieved a response of CR or better and 51.6% of subjects achieved a response of VGPR or better. An ORR of 50.0% was observed at the target dose of 150 x 10^6 CAR+ T cells, 68.6% was observed at the target dose of 300 x 10^6 CAR+ T cells, and 81.5% was observed at the target dose of 450 x 10^6 CAR+ T cells.

2. EXECUTIVE SUMMARY:

FDA's analysis shows there is a positive dose-ORR relationship. Generally female cohort shows better overall response rate (ORR) compared with male cohort who received same dose under same condition. Model predicted ORR at different dose levels are shown below:

	Male	**Female**
DOSE	**Model Predicted ORR (95% CI)**	**Model Predicted ORR (95% CI)**
50 Million Cells	0.44 (0.24, 0.66)	0.49 (0.28, 0.70)
150 Million Cells	0.51 (0.35, 0.67)	0.65 (0.49, 0.79)
300 Million Cells	0.61 (0.52, 0.70)	0.84 (0.73, 0.91)
450 Million Cells	0.71 (0.60, 0.80)	0.94 (0.84, 0.98)
460 Million Cells	0.72 (0.60, 0.81)	0.94 (0.85, 0.98)
520 Million Cells	0.75 (0.61, 0.82)	0.96 (0.88, 0.99)
700 Million Cells	0.83 (0.62, 0.94)	0.988 (0.93, 0.998)
800 Million Cells	0.87 (0.62, 0.96)	0.993 (0.949, 0.999)

Briefly, at the proposed dose level of 450 x 10^6 CAR+ T cells, efficacy (ORR) appears to reach plateau in female patients but may still improve in male patients with increased dose.

Overall, the target dose (450 x 10^6 CAR+ T cells) proposed by applicant is acceptable from the totality of efficacy and safety, however the originally proposed dose range of (b) (4) x 10^6 CAR+ T cells is sub-optimal (especially at the lower end of the dose range).

3. RECOMMENDATION

The proposed target dose of 450 x 10^6 CAR+ T cells, is acceptable from the totality of efficacy and safety. However, the dose range is recommended to be above 300 x 10^6 CAR+ T cells.

SIGNATURE:

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Yuan Xu, DPM Jiang Liu, TL, DPM

4. Question Based Review

4.1 Is There Dose-Efficacy Relationship in Ide-cel Product?

Yes. FDA's analysis shows there is a positive relationship between actual administered dose and response measured as ORR (section 6.3.2) and this is consistent with applicant proposed overall positive dose-efficacy relationship (section 5.2). Notably, there is a difference between male and female cohort. Generally female patients show better overall response (ORR) compared with male under same condition. At the proposed dose level 450 million CAR+ T cells, ORR appears to reach plateau in female patients but may still be improved in male patients by increasing dose.

Additional exploratory analysis of dose efficacy relationship measured as complete response rate (CR) was also conducted. There is no positive or negative trend (Section 6.3.2).

4.2 Is There Dose-Exposure Relationship in Ide-cel Product?

Yes. Ide-Cel pharmacokinetic parameters from study MM-001 and study CRB-401 are pooled and reanalyzed. Overall, a positive dose-exposure relationship as measured by Cmax and T cell expansion rate (defined as Cmax/Tmax) was observed (Section 6.3.1).

4.3 Is There Exposure-Efficacy Relationship in Ide-cel Product?

Yes. A positive exposure-efficacy relationship was identified by both applicant's (Section 5.7) and FDA's analysis (Section 6.3.3). However, consistent with other CAR-T products, there might be confounding effects and it is hard to conclude a causal effect since exposure might also be affected by clinical outcomes.

4.4 Is Dose Adjustment Needed for Specific Population?

No. Multivariable logistic regression was conducted. Age, ethnicity, race had no obvious impact on efficacy. (Section 6.3.3)

Pre LD chemo bone marrow plasma cell percentage (PRBMP) and post LD chemo soluble BCMA level (PLSB) appear to have a negative association on overall efficacy endpoint measured as ORR, VGPR and CR.

As previous described in question 4.1, sex is still a factor after adjusting PRBMP and PLSB in model. It is still unknow whether gender is associated with other baseline factors or it's a risk factor by itself.

Body weight (BW) or body surface area (BSA) appear to have an apparent negative correlation with efficacy (data not shown), however after incorporating sex (male or female), BW/BSA do not further contribute to model prediction. The negative impact of body weight or BSA on efficacy is considered secondary to gender effect. Female patients have lower baseline BW/BSA and their efficacy are generally better than male under same condition.

4.5 Dose tocilizumab and Corticosteroid Have Negative Impact on Efficacy?

It is difficult to evaluate the impact of tocilizumab and corticosteroid use on efficacy base on currently available data. Exposure appears to be higher in subjects treated with tocilizumab or corticosteroids for the occurrence of CRS (section 5.5); it should be noted that these correlations may be driven through a safety exposure-response rather than representing a direct effect of these comedications on PK.

4.6 What Is the Dose-Response-Response Relationship for CRS?

A positive dose-CRS or exposure-CRS relationship was observed. Sex is not a significant predictive marker for CRS. (section 6.3.5)

There is a positive relationship between administered dose and all grade CRS events and a shallow positive relationship with grade 3 and above CRS event. Unlike impact on ORR, there is no difference between male and female cohort in terms of CRS event or GR3+ CRS event rate.

4.7 What Is the Dose-Response Relationship for Neurotoxicity?

No apparent dose-GR2+ NT relationship was observed (Figure 14). This might be due to the overall limited incident rate. Exposure-GR2+ NT relationship is positive but still this might be due to potential confounding effects. Female patients appeared to have higher risk to develop grade 2 and above neurotoxicity (section 6.3.6).

4.8 Is the proposed dose range from (b) (4) x 10^6 CAR+ T Cells optimal?

No. Overall there is a positive dose-efficacy relationship measured by ORR. In the pivotal study B2121-MM001, the observed ORRs are 50%, 68.6% and 81.5% at the dose levels of 150, 300, 450 million cells, respectively. Model predicted ORRs at the dose level of 150 million cells are 0.51 (95% CI: 0.35, 0.67) for male and 0.65 (95% CI: 0.49, 0.79) for female which are much lower than those predicted at the dose level of 450 million cells (0.71 (95% CI: 0.60, 0.80) for male and 0.94 (95% CI: 0.84, 0.98) for female). The dose range is not optimal especially on the lower end.

4.9 What Is the Impact of CD4: CD8 Ratio?

Overall, the initial CD4:CD8 ratio does not have strong impact on efficacy as measured by the ORR or CR rate. The median level of CD4:CD8 ratio is 6, 8 and 7 in dose level 150, 300 and 450 million cells in study BB2121-MM-001. Initial CD4: CD8 seems to have a negative impact on VGPR adjusted with PRBMP, PLSB and sex.

5. SPONSOR'S ANALYSIS

5.1 Dose Exposure Relationship

Samples of whole blood were collected from each subject at pre-specified time points. CD3+ T cells, composed of endogenous and CAR+ T cells, were isolated from the whole blood. DNA was purified from the CD3+ sorted cells. Ide-cel cellular kinetic profile (PK) was then described by time course of transgene copies per microgram (μg) of genomic DNA as measured by (b) (4) method using CD3+ sorted T cells.

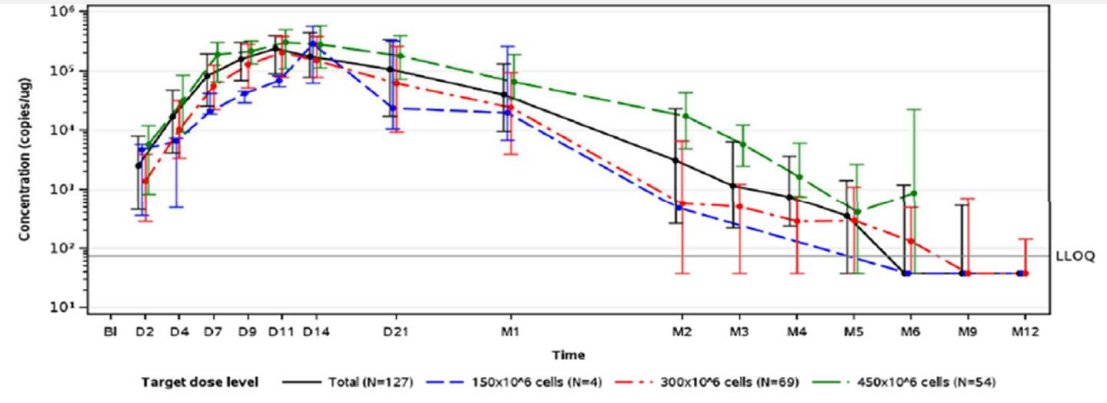
Serial samples for measurement of transgene levels were collected for all subjects at predose and following ide-cel infusion, at Day 2, Day 4, Day 7, Day 9, Day 11, Day 14, Day 21, Month 1, Month 2, Month 3, Month 4, Month 5, Month 6, Month 9, Month 12, Month 15, Month 18, Month 21, and Month 24.

The PK analyses were performed using a data cutoff date of 19 Apr 2019, corresponding to ≥ 3 months of follow-up after the last subject was infused with ide-cel. The PK analyses were conducted using the PK evaluable population, defined as subjects who received at least one ide-cel infusion and had evaluable transgene levels (ie, at least one measurable timepoint postinfusion). There were 127 subjects who received ide-cel, met this definition and were included in the PK population; there was 1 subject who died on Day 4 and had no evaluable PK samples and therefore was excluded from the evaluable PK population.

Noncompartmental PK parameters such as maximum transgene levels (Cmax), time of maximum transgene levels (Tmax), area under the curve of the transgene level from the time of dose to 28 days postinfusion (AUC0-28days), area under the curve of the transgene level from the time of dose to 3 months postinfusion (AUC0-3M) were calculated and summarized for subjects in the PK evaluable population. The following extrapolation rule was used for calculating AUC0-3M: if time of last observed ide-cel level (Tlast) < 3 month, only if AUCextrap, pred < 35%, AUC0-3M was calculated and included in the PK summaries and subsequent analyses. Longer term exposures including AUC0-6M and AUC0-9M were also calculated, using these prespecified acceptance criteria for these parameters.

Figure 1 shows the time course of ide-cel by target dose levels for the PK population. Following the ide-cel infusion, the CAR+ T cells proliferated and underwent rapid multi-log expansion, followed by a bi-exponential decline. The maximum peak expansion occurred at a median of 11 days across the ide-cel target dose levels, which was consistent across the target dose levels with median of 14 days, 11 days, and 11 days at ide-cel target dose levels of 150, 300, and 450 x 10^6 CAR+ T cells, respectively.

Figure 1: Median (Q1, Q3) Transgene Levels of Ide-Cel by Target Dose Levels Following a Single Infusion (Semi-log Scale): Study BB2121-MM-001



Source: Figure 1 of SCP. Ide-cel = idecabtagene vicleucel; B = baseline; D = day; LLOQ = lower limit of quantification; M = month; Q = quartile. Solid grey horizontal line represents lower limit of quantification (75 copies/µg). Plot shows median time-course profiles: median (Q1, Q3). Data cutoff date: 19 Apr 2019

Ide-cel PK parameters summarized by target dose and across the target dose levels (defined as total) are shown in Table 1. Pharmacokinetic parameters are presented as geometric mean values (geometric %CV), unless otherwise specified.

The median time of last measurable transgene level (Tlast) was 58 days at the dose of 150 × 10^6 CAR+ T cells, 119 days at the dose of 300 × 10^6 CAR+ T cells, and 115 days at the target dose of 450 x 10^6 CAR + T cells, with a median value of 119 days across the dose range. The maximum transgene level (Cmax) was 204,299 copies/µg (169%), 180,185 copies/µg (210%), and 321,117 copies/µg (126%) at ide-cel target doses of 150, 300, and 450 x 10^6 CAR+ T cells, respectively. In addition, the area under the curve of transgene level from time of dosing to 28 days (AUC0-28days) was 1,942,929 days*copies/µg (154%) at target dose of 150 x 10^6 CAR+ T cells; 2,138,414 (215%) days*copies/µg at a target dose of 300 x 10^6 CAR+ T cells, and 4,277,327 (152%) days*copies/µg at target dose of 450 x 10^6 CAR+ T cells. A similar trend in AUC0-3M increase was observed across the target dose levels. These results suggest that cellular expansion parameters increased with increasing ide-cel target dose levels. The inter-subject variability as measured by the geometric %CV was > 100% for all PK parameters, resulting in substantial overlap of ide-cel exposure across the target dose levels.

Longer term exposures as measured by the area under the curve of transgene level from time 0 to 6 months (AUC0-6M) and area under the curve of transgene level from time 0 to 9 months (AUC0-9M) also increased with increasing ide-cel target dose, consistent with trends observed in AUC0-28days and AUC0-3M. Comparing the extent of the CAR + T cell expansion over time, the geometric mean estimates of AUC0-6M and AUC0-9M were similar (within ~ 10%) to AUC0-3M.

Furthermore, the extent of cell expansion during the first month post-infusion (AUC0-28days) represents more than 70% of the cumulative exposure at 3 months (AUC0-3M) postinfusion. These data suggest that following peak expansion at ~ 11 days, the extent of cell expansion during the first month post-infusion (AUC0-28days) represents the majority (65%) of total ide-cel exposure.

Table 1:Summary of Ide-Cel Pharmacokinetic Parameters: Study BB2121-MM-001

Pharmacokinetic Parameter	Ide-cel (CAR+ T cells) Target Dose			
	150×10^6	300×10^6	450×10^6	Total 150 to 450×10^6
C_{max} (copies/µg)	204,229 (169) N = 4	180,185 (210) N = 69	321,117 (126) N = 54	231,278 (178) N = 127
T_{max} (days)	14 (11-14) N = 4	11 (7-30) N = 69	11 (7-28) N = 54	11 (7-30) N = 127
T_{last} (days)	58 (29-142) N = 4	119 (21-365) N = 69	115 (22-184) N = 54	119 (21-365) N = 127
$AUC_{0\text{-}28days}$ (days*copies/µg)	1,942,929 (154) N = 4	2,138,414 (215) N = 68	4,277,327 (152) N = 53	2,860,340 (197) N = 125
$AUC_{0\text{-}3M}$ (days*copies/µg)	4,372,535 (1023) N = 2	2,952,312 (213) N = 62	5,955,266 (170) N = 51	4,057,643 (208) N = 115
$AUC_{0\text{-}6M}$ (days*copies/µg)	4,413,811 (997) N = 2	3,249,486 (214) N = 59	6,528,331 (180) N = 47	4,427,242 (213) N = 108
$AUC_{0\text{-}9M}$ (days*copies/µg)	4,420,074 (993) N = 2	3,276,494 (225) N = 56	6,572,367 (181) N = 47	4,499,940 (219) N = 105

Source: Table 2 of Summary of clinical pharm.

FDA comments: Please refer to FDA's review at section 6.3.1. Ide-Cel pharmacokinetic parameters from study BB2121-MM-001 and study CRB-401 were pooled and reanalyzed. Overall, there is a consistent conclusion between applicant's analysis based on study BB2121-MM-001 and FDA reviewer's analysis based on data from pooled studies. There is a positive dose-exposure relationship as measured by Cmax and T cell expansion rate (defined as Cmax/Tmax).

5.2 Dose Efficacy Relationship

Primary Endpoint: Overall Response Rate (Independent Response Committee Assessment)

The primary efficacy endpoint was ORR based on the IRC adjudicated assessment of response. The ORR in the ide-cel-treated population was 73.4% (95% CI: 65.8, 81.1) ($p < 0.0001$) across the target dose levels of 150 to 450 x 10^6 CAR+ T cells (Table 2). The magnitude of response observed was statistically significant, rejecting the null hypothesis of ≤ 50% and meeting the study's primary endpoint. In addition, 31.3% of subjects achieved a response of CR or better and 51.6% of subjects achieved a response of VGPR or better. An ORR of 50.0% was observed at the target dose of 150 x 10^6 CAR+ T cells, 68.6% was observed at the target dose of 300 x 10^6 CAR+ T cells, and 81.5% was observed at the target dose of 450 x 10^6 CAR+ T cells.

In the enrolled population, the ORR was 67.1% (95% CI: 59.4, 74.9) and additionally, 28.6% of subjects achieved a response of CR or better and 47.1% of subjects achieved a response of VGPR or better (Table 2, Figure 3).

Table 2: Best Overall Response Based on IMWG Criteria by IRC Review (Ide-cel Treated and Enrolled Populations)- Study MM-001

	Ide-cel Treated Population Ide-cel (CAR+ T cells) target dose				Enrolled Population (N = 140)
	150 x 10^6 (N=4)	300 x 10^6 (N=70)	450 x 10^6 (N=54)	150 to 450 x 10^6 (N=128)	
Best Overall Response - n (%)					
sCR	1 (25.0)	19 (27.1)	19 (35.2)	39 (30.5)	39 (27.9)
CR	0	1 (1.4)	0	1 (0.8)	1 (0.7)
VGPR	1 (25.0)	10 (14.3)	15 (27.8)	26 (20.3)	26 (18.6)
PR	0	18 (25.7)	10 (18.5)	28 (21.9)	28 (20.0)
MR	0	2 (2.9)	0	2 (1.6)	2 (1.4)
SD	1 (25.0)	14 (20.0)	7 (13.0)	22 (17.2)	22 (15.7)
PD	1 (25.0)	6 (8.6)	1 (1.9)	8 (6.3)	8 (5.7)
NE[a]	0	0	2 (3.7)	2 (1.6)	14 (10.0)
ORR - n (%)	**2 (50.0)**	**48 (68.6)**	**44 (81.5)**	**94 (73.4)**	**94 (67.1)**
95% CI[b]	(6.8 , 93.2)	56.4, 79.1	68.6, 90.7	65.8, 81.1	59.4, 74.9
p-value[c]	-	-	-	< 0.0001	< 0.0001

Source: Table 10 of summary of clinical efficacy. sCR: stringent complete response. CR: complete response.

Key Secondary Endpoint: Complete Response Rate

As the test for ORR (primary endpoint) was positive, the CR rate was tested against the null hypothesis of ≤ 10% for the key secondary efficacy endpoint.

As of the data cutoff date, the CR or better rate in the ide-cel-treated population based on IRC assessments was 31.3% (95% CI: 23.2, 39.3) across the target dose levels of 150 to 450 x 10^6 CAR+ T cells (Table 2). A CR of 25.0% was observed at the target dose of 150 x 10^6 CAR+ T cells, 28.6% was observed at the target dose of 300 x 10^6 CAR+ T cells, and 35.2% was observed at the target dose of 450 x 10^6 CAR+ T cells.

In the enrolled population, the CR rate based on IRC assessment was 28.6% (95% CI: 21.1, 36.1) (Table 2).

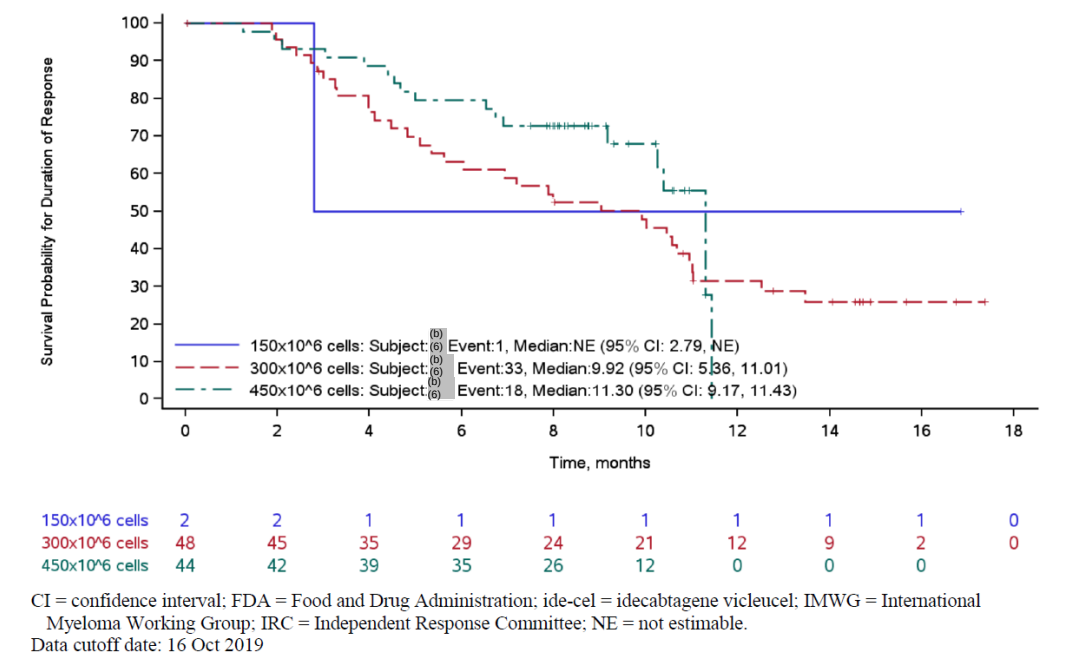
Duration of Response:

Duration of response was defined as the time from the date of the first documented response (PR or better) to the first documentation of PD or death, whichever was earlier. The DoR analysis was based on responders only, and therefore was the same for the ide-cel-treated population and enrolled population.

As of the data cutoff date, 52 (55.3%) of 94 responders had progressed/died and 42 (44.7%) were censored. The Kaplan-Meier (KM) estimate for median DoR among responders was 10.6 months (95% CI: 9.0, 11.3) (Figure 2). Based on KM estimates, 61.9% of responders had responses lasting ≥ 9 months, and 32.7% of responders had responses lasting ≥ 12 months. The median DoR among responders was 9.9 months (95% CI: 5.4, 11.0) at the target dose of 300 x 10^6 CAR+ T cells and 11.3 months (95% CI: 9.2, 11.4) at the target dose of 450 x 10^6 CAR+ T cells. A

majority (59.1%) of responders at the target dose of 450 x 10^6 CAR+ T cells were still progression-free as of the data cutoff date. The median was not estimable (NE) (95% CI: 2.8, NE) at the target dose of 150 x 10^6 CAR+ T cells, although with the small number of responders at this target dose (N = 2), the median should not be over-interpreted for this subgroup. Results in other subgroups were generally similar to that of all responders. The KM curve across the target dose levels in the ide-cel-treated population is shown in Figure 2.

Figure 2: Kaplan-Meier Curve of Duration of Response by Target Dose Based on IMWG Criteria by IRC Review – FDA Censoring Rules (Subjects with at Least a Partial Response, Ide-cel-treated Population) – Study BB2121-MM-001



CI = confidence interval; FDA = Food and Drug Administration; ide-cel = idecabtagene vicleucel; IMWG = International Myeloma Working Group; IRC = Independent Response Committee; NE = not estimable.
Data cutoff date: 16 Oct 2019

Source: Figure 5 of Summary of Efficacy Report

FDA Comments: Overall there is a positive dose-efficacy relationship measured by ORR and duration of response. An ORR of 50.0% was observed at the target dose of 150 x 10^6 CAR+ T cells, 68.6% was observed at the target dose of 300 x 10^6 CAR+ T cells, and 81.5% was observed at the target dose of 450 x 10^6 CAR+ T cells.

Please refer to section 6.3.2 for FDA's analysis. Briefly a univariate regression with administered dose versus ORR is conducted and consistent with applicant's observation there is a positive actual dose-ORR relationship. Notably, there is a difference in the impact of administered dose on ORR in male and female cohort. Generally female showed better overall response compared with male. Model predicted ORR at dose level 300 million cells is 0.61 (95% CI: 0.52, 0.70) for male and 0.84 (95% CI: 0.73, 0.91) for female. Model predicted ORR at dose level 450 million cells is 0.71 (95% CI: 0.60, 0.80) for male and 0.94 (95% CI: 0.84, 0.98) for female. At the proposed dose level 450 million cells, female cohort has already reached plateau of efficacy. However, in male cohort, proposed 450 million cells is still at linear stage and this suggest a better efficacy might be achieved by increasing initial dose.

5.3 Exploratory Biomarker Endpoints

An exploratory analysis evaluating the relationship between 27 immune-related cytokines/chemokines (including biochemical markers of inflammation, C-reactive protein [CRP], and ferritin), and soluble B-cell maturation antigen (sBCMA), as a composite biomarker of disease burden, with efficacy endpoints was conducted pre- and post-ide-cel infusion. A summary of key findings from the exploratory analyses with efficacy endpoints are provided here.

Of the 27 immune-related soluble factors evaluated for possible relationship to efficacy, there were no immune-related soluble factors measured pre-infusion that could stratify subjects by response. Four cytokines (CRP, IFN-γ, IL-10, and IL-6) demonstrated significantly higher peak concentrations post-ide-cel infusion in responders compared to non-responders. No immune-related soluble factors further stratified subjects with CR compared to subjects without CR.

Serum BCMA provides a peripherally accessible biomarker that tracks well with tumor burden and response. At baseline (day of infusion), sBCMA levels were higher in non-responders compared to responders ($p = 0.0002$). Post infusion, subjects who achieved response had a median concentration below the lower limit of quantification (LLOQ) (4.40 ng/mL) at nadir compared to non-responders (283 ng/mL, $p < 0.0001$). The percentage of subjects with elimination of sBCMA to levels below LLOQ at nadir was 81.3% of responders compared to 3% for non-responders. The duration of the elimination of sBCMA from serum trended with the depth of response. The subjects who achieved a PR, VGPR or ≥ CR had a median concentration below LLOQ of 4.40 ng/mL at Month 2; subjects who achieved a VGPR or ≥ CR had a median concentration below LLOQ of 4.40 ng/mL at Month 2 and 3; and the subjects who achieved a ≥ CR had a median concentration below LLOQ of 4.40 ng/mL at Month 2 through Month 6. The median concentration of sBCMA remained below baseline levels in the subjects who achieved a ≥ PR through Month 15 postinfusion.

As sBCMA may serve as a composite biomarker of disease burden, the levels of sBCMA were compared to other markers of tumor burden, including CD138+ plasma cells in the bone marrow biopsy as measured by immune-histochemistry. Serum sBCMA and tumor associated CD138+ plasma cells were correlated as subjects with high tumor burden as measured by ≥ 50% CD138+ plasma cells had significantly higher levels of circulating sBCMA. Importantly, for both groups (those with ≥ 50% and those with < 50% CD138+ plasma cells in bone marrow), median levels of sBCMA at nadir after ide-cel infusion were below the LLOQ and a similar percentage of subjects in both subgroups achieved elimination of sBCMA to levels below LLOQ at nadir indicating resolution of myeloma was achieved in both high and low tumor burden groups.

Subjects with extramedullary disease had higher levels of serum sBCMA at baseline prior to infusion, however there was no difference in median nadir reached (below LLOQ) and a similar percentage of subjects in both subgroups achieved elimination of sBCMA to levels below LLOQ at nadir as both groups were able to achieve complete elimination of sBCMA in > 50% of subjects.

Minimal residual disease measured by (b) (4) on bone marrow aspirates was assessed to evaluate MRD status in relation to efficacy. A total of 34 of 128 subjects (26.6%,) achieved ≥ CR and MRD-negative status within 3 months prior to achieving ≥ CR based on

measurements using (b) (4) at a sensitivity level of 10-5. When considering ≥ CR responders as the denominator, 34 of the 46 ≥ CR responders (73.9%) achieved MRD-negative status within 3 months of achieving ≥ CR response at the 10-5 cutoff level.

FDA Comments: Applicant's analysis seems reasonable.
In summary, Of the 27 immune-related soluble factors evaluated for possible relationship to efficacy, there were no immune-related soluble factors measured pre-infusion that could stratify subjects by response. Four cytokines (CRP, IFN-γ, IL-10, and IL-6) demonstrated significantly higher peak concentrations post-ide-cel infusion in responders compared to non-responders.

Serum BCMA provides a peripherally accessible biomarker that tracks well with tumor burden and response. At baseline (day of infusion), sBCMA levels were higher in non-responders compared to responders (p = 0.0002).

5.4 Dose Safety Relationship

An overview of AEs reported on or after ide-cel infusion in Study MM-001, Study CRB-401, and for the pooled analysis by target doses of 150, 300, and 450 x 10^6 CAR+ T cells and across the target dose levels of 150 to 450 x 10^6 CAR+ T cells, as of the data cutoff dates, is presented in Table 3.

MM-001

All subjects who received ide-cel across the target dose levels of 150 to 450 x 10^6 CAR+ T cells in Study MM-001 had ≥ 1 AE and 127 (99.2%) subjects had ≥ 1 Grade 3 or 4 AE. The frequencies of AEs in these categories were generally similar across the target dose levels, although there were fewer subjects at the target dose of 150 x 10^6 CAR+ T cells compared with subjects at the target doses of 300 and 450 x 10^6 CAR+ T cells. Eighty-six (67.2%) subjects had ≥ 1 SAE and 22 (17.2%) subjects had AEs leading to death.

CRB-401

All subjects who received ide-cel across the target dose levels of 150 to 450 x 10^6 CAR+ T cells in Study CRB-401 had ≥ 1 AE and 55 (98.2%) subjects had ≥ 1 Grade 3 or 4 AE. Forty-one (73.2%) subjects had ≥ 1 SAE, and 7 (12.5%) subjects had AEs leading to death. The frequencies of subjects with any AE, Grade 3 or 4 AEs, and SAEs were generally similar across the target dose levels.

Pooled Analysis (MM-001 and CRB-401)

In the pooled analysis (N = 184), all subjects who received ide-cel across the target dose levels of 150 to 450 x 10^6 CAR+ T cells had ≥ 1 AE and 182 (98.9%) subjects had ≥ 1 Grade 3 or 4 AE. Serious AEs were reported for 127 (69.0%) subjects and 29 (15.8%) subjects had AEs that led to death. The frequency of subjects with any AE and Grade 3 or 4 AEs were generally similar across the target dose levels. The frequency of subjects with SAEs and AEs leading to death varied across the target dose levels.

Table 3: Overall of Adverse Events- Study MM-001, Study CRB-401, and Pooled Analysis (Ide-cel-treated Population)

	Study MM-001				Study CRB-401 (Parts A and B)			Pooled Analysis (MM-001 and CRB-401)			
	Ide-cel (CAR+ T Cells) Target Dose										
Subject with ≥ 1:	**150 x 10^6 (N = 4) n (%)**	**300 x 10^6 (N = 70) n (%)**	**450 x 10^6 (N = 54) n (%)**	**150 to 450 x 10^6 (N = 128) n (%)**	**150 x 10^6 (N = 18) n (%)**	**450 x 10^6 (N = 38) n (%)**	**150 to 450 x 10^6 (N = 56) n (%)**	**150 x 10^6 (N = 22) n (%)**	**300 x 10^6 (N = 70) n (%)**	**450 x 10^6 (N = 92) n (%)**	**150 to 450 x 10^6 (N = 184) n (%)**
Any AE	4 (100)	70 (100)	54 (100)	128 (100)	18 (100)	38 (100)	56 (100)	22 (100)	70 (100	92 (100)	184 (100)
Grade 3 or 4 AE[a]	4 (100)	69 (98.6)	54 (100)	127 (99.2)	18 (100)	37 (97.4)	55 (98.2)	22 (100)	69 (98.6)	91 (98.9)	182 (98.9)
Serious AEs	4 (100)	44 (62.9)	38 (70.4)	86 (67.2)	13 (72.2)	28 (73.7)	41 (73.2)	17 (77.3)	44 (62.9)	66 (71.7)	127 (69.0)
AEs leading to death (Grade 5 AE)[a]	1 (25.0)	13 (18.6)	8 (14.8)	22 (17.2)	4 (22.2)	3 (7.9)	7 (12.5)	5 (22.7)	13 (18.6)	11 (12.0)	29 (15.8)

Source: Table 13 of Summary of Overall Safety

A summary of AEs reported for ≥ 10% of subjects on or after ide-cel infusion in Study MM-001, Study CRB-401, and for the pooled analysis by target doses of 150, 300, and 450 x 10^6 CAR+ T cells and across the target dose levels of 150 to 450 x 10^6 CAR+ T cells, as of the data cutoff dates, is presented in Table 4.

In the pooled analysis, AEs for subjects who received ide-cel across the target dose levels of 150 to 450 x 10^6 CAR+ T cells were most frequently reported (≥ 60%) from the following SOCs: blood and lymphatic system disorders (95.7%), immune systems disorders (84.2%), general disorders and administration site conditions (81.0%), gastrointestinal disorders (78.3%), metabolism and nutrition disorders (76.1%), infections and infestations (70.7%), and musculoskeletal and connective tissue disorders (62.5%).

The most frequently reported (≥ 40%) PTs by decreasing frequency were neutropenia (91.3%), CRS (81.0%), anemia (70.7%), thrombocytopenia (66.8%), and leukopenia (48.4%). Except for CRS, there was no clear evidence of a dose response in the pooled analysis.

Table 4: Adverse Event by System Organ Class and Preferred Term Reported for at Least 10% of Subjects Across the Target Dose Levels of 150 to 450 x 10^6 CAR+ T Cells in the Pooled Analysis – Study MM-001, Study MM-001, Study CRB-401, and Pooled Analysis (Ide-cel-treated Population)

	Study MM-001				Study CRB-401 (Parts A and B)			Pooled Analysis (MM-001 and CRB-401)			
	Ide-cel (CAR+ T Cells) Target Dose										
System Organ Class Preferred Term[a]	150 x 10^6 (N = 4) n (%)	300 x 10^6 (N = 70) n (%)	450 x 10^6 (N = 54) n (%)	150 to 450 x 10^6 (N = 128) n (%)	150 x 10^6 (N = 18) n (%)	450 x 10^6 (N = 38) n (%)	150 to 450 x 10^6 (N = 56) n (%)	150 x 10^6 (N = 22) n (%)	300 x 10^6 (N = 70) n (%)	450 x 10^6 (N = 92) n (%)	150 to 450 x 10^6 (N = 184) n (%)
Subjects with ≥ 1 AE	4 (100)	70 (100)	54 (100)	128 (100)	18 (100)	38 (100)	56 (100)	22 (100)	70 (100)	92 (100)	184 (100)
Blood and lymphatic system disorders	**4 (100)**	**67 (95.7)**	**53 (98.1)**	**124 (96.9)**	**17 (94.4)**	**35 (92.1)**	**52 (92.9)**	**21 (95.5)**	**67 (95.7)**	**88 (95.7)**	**176 (95.7)**
Neutropenia	4 (100)	62 (88.6)	51 (94.4)	117 (91.4)	16 (88.9)	35 (92.1)	51 (91.1)	20 (90.9)	62 (88.6)	86 (93.5)	168 (91.3)
Anaemia	4 (100)	51 (72.9)	34 (63.0)	89 (69.5)	11 (61.1)	30 (78.9)	41 (73.2)	15 (68.2)	51 (72.9)	64 (69.6)	130 (70.7)
Thrombocytopenia	4 (100)	42 (60.0)	35 (64.8)	81 (63.3)	13 (72.2)	29 (76.3)	42 (75.0)	17 (77.3)	42 (60.0)	64 (69.6)	123 (66.8)
Leukopenia	2 (50.0)	34 (48.6)	18 (33.3)	54 (42.2)	12 (66.7)	23 (60.5)	35 (62.5)	14 (63.6)	34 (48.6)	41 (44.6)	89 (48.4)
Lymphopenia	2 (50.0)	19 (27.1)	14 (25.9)	35 (27.3)	7 (38.9)	16 (42.1)	23 (41.1)	9 (40.9)	19 (27.1)	30 (32.6)	58 (31.5)
Febrile neutropenia	2 (50.0)	11 (15.7)	8 (14.8)	21 (16.4)	3 (16.7)	5 (13.2)	8 (14.3)	5 (22.7)	11 (15.7)	13 (14.1)	29 (15.8)
Immune system disorders	**2 (50.0)**	**58 (82.9)**	**52 (96.3)**	**112 (87.5)**	**8 (44.4)**	**35 (92.1)**	**43 (76.8)**	**10 (45.5)**	**58 (82.9)**	**87 (94.6)**	**155 (84.2)**
Cytokine release syndrome	2 (50.0)	53 (75.7)	52 (96.3)	107 (83.6)	7 (38.9)	35 (92.1)	42 (75.0)	9 (40.9)	53 (75.7)	87 (94.6)	149 (81.0)
Hypogammaglobulinaemia	1 (25.0)	14 (20.0)	11 (20.4)	26 (20.3)	4 (22.2)	5 (13.2)	9 (16.1)	5 (22.7)	14 (20.0)	16 (17.4)	35 (19.0)
General disorders and administration site conditions	**4 (100)**	**60 (85.7)**	**37 (68.5)**	**101 (78.9)**	**15 (83.3)**	**33 (86.8)**	**48 (85.7)**	**19 (86.4)**	**60 (85.7)**	**70 (76.1)**	**149 (81.0)**
Fatigue	1 (25.0)	28 (40.0)	14 (25.9)	43 (33.6)	9 (50.0)	20 (52.6)	29 (51.8)	10 (45.5)	28 (40.0)	34 (37.0)	72 (39.1)
Pyrexia	0	17 (24.3)	15 (27.8)	32 (25.0)	6 (33.3)	15 (39.5)	21 (37.5)	6 (27.3)	17 (24.3)	30 (32.6)	53 (28.8)
Oedema peripheral	1 (25.0)	12 (17.1)	6 (11.1)	19 (14.8)	5 (27.8)	13 (34.2)	18 (32.1)	6 (27.3)	12 (17.1)	19 (20.7)	37 (20.1)
Chills	1 (25.0)	10 (14.3)	3 (5.6)	14 (10.9)	4 (22.2)	9 (23.7)	13 (23.2)	5 (22.7)	10 (14.3)	12 (13.0)	27 (14.7)

	Study MM-001				Study CRB-401 (Parts A and B)			Pooled Analysis (MM-001 and CRB-401)			
	Ide-cel (CAR+ T Cells) Target Dose										
System Organ Class Preferred Term[a]	150 x 10^6 (N = 4) n (%)	300 x 10^6 (N = 70) n (%)	450 x 10^6 (N = 54) n (%)	150 to 450 x 10^6 (N = 128) n (%)	150 x 10^6 (N = 18) n (%)	450 x 10^6 (N = 38) n (%)	150 to 450 x 10^6 (N = 56) n (%)	150 x 10^6 (N = 22) n (%)	300 x 10^6 (N = 70) n (%)	450 x 10^6 (N = 92) n (%)	150 to 450 x 10^6 (N = 184) n (%)
Subjects with ≥ 1 AE	4 (100)	70 (100)	54 (100)	128 (100)	18 (100)	38 (100)	56 (100)	22 (100)	70 (100)	92 (100)	184 (100)
Blood and lymphatic system disorders	**4 (100)**	**67 (95.7)**	**53 (98.1)**	**124 (96.9)**	**17 (94.4)**	**35 (92.1)**	**52 (92.9)**	**21 (95.5)**	**67 (95.7)**	**88 (95.7)**	**176 (95.7)**
Neutropenia	4 (100)	62 (88.6)	51 (94.4)	117 (91.4)	16 (88.9)	35 (92.1)	51 (91.1)	20 (90.9)	62 (88.6)	86 (93.5)	168 (91.3)
Anaemia	4 (100)	51 (72.9)	34 (63.0)	89 (69.5)	11 (61.1)	30 (78.9)	41 (73.2)	15 (68.2)	51 (72.9)	64 (69.6)	130 (70.7)
Thrombocytopenia	4 (100)	42 (60.0)	35 (64.8)	81 (63.3)	13 (72.2)	29 (76.3)	42 (75.0)	17 (77.3)	42 (60.0)	64 (69.6)	123 (66.8)
Leukopenia	2 (50.0)	34 (48.6)	18 (33.3)	54 (42.2)	12 (66.7)	23 (60.5)	35 (62.5)	14 (63.6)	34 (48.6)	41 (44.6)	89 (48.4)
Lymphopenia	2 (50.0)	19 (27.1)	14 (25.9)	35 (27.3)	7 (38.9)	16 (42.1)	23 (41.1)	9 (40.9)	19 (27.1)	30 (32.6)	58 (31.5)
Febrile neutropenia	2 (50.0)	11 (15.7)	8 (14.8)	21 (16.4)	3 (16.7)	5 (13.2)	8 (14.3)	5 (22.7)	11 (15.7)	13 (14.1)	29 (15.8)
Immune system disorders	**2 (50.0)**	**58 (82.9)**	**52 (96.3)**	**112 (87.5)**	**8 (44.4)**	**35 (92.1)**	**43 (76.8)**	**10 (45.5)**	**58 (82.9)**	**87 (94.6)**	**155 (84.2)**
Cytokine release syndrome	2 (50.0)	53 (75.7)	52 (96.3)	107 (83.6)	7 (38.9)	35 (92.1)	42 (75.0)	9 (40.9)	53 (75.7)	87 (94.6)	149 (81.0)
Hypogammaglobulinaemia	1 (25.0)	14 (20.0)	11 (20.4)	26 (20.3)	4 (22.2)	5 (13.2)	9 (16.1)	5 (22.7)	14 (20.0)	16 (17.4)	35 (19.0)
General disorders and administration site conditions	**4 (100)**	**60 (85.7)**	**37 (68.5)**	**101 (78.9)**	**15 (83.3)**	**33 (86.8)**	**48 (85.7)**	**19 (86.4)**	**60 (85.7)**	**70 (76.1)**	**149 (81.0)**
Fatigue	1 (25.0)	28 (40.0)	14 (25.9)	43 (33.6)	9 (50.0)	20 (52.6)	29 (51.8)	10 (45.5)	28 (40.0)	34 (37.0)	72 (39.1)
Pyrexia	0	17 (24.3)	15 (27.8)	32 (25.0)	6 (33.3)	15 (39.5)	21 (37.5)	6 (27.3)	17 (24.3)	30 (32.6)	53 (28.8)
Oedema peripheral	1 (25.0)	12 (17.1)	6 (11.1)	19 (14.8)	5 (27.8)	13 (34.2)	18 (32.1)	6 (27.3)	12 (17.1)	19 (20.7)	37 (20.1)
Chills	1 (25.0)	10 (14.3)	3 (5.6)	14 (10.9)	4 (22.2)	9 (23.7)	13 (23.2)	5 (22.7)	10 (14.3)	12 (13.0)	27 (14.7)

System Organ Class Preferred Term[a]	Study MM-001				Study CRB-401 (Parts A and B)			Pooled Analysis (MM-001 and CRB-401)			
	Ide-cel (CAR+ T Cells) Target Dose										
	150 x 10^6 (N = 4) n (%)	300 x 10^6 (N = 70) n (%)	450 x 10^6 (N = 54) n (%)	150 to 450 x 10^6 (N = 128) n (%)	150 x 10^6 (N = 18) n (%)	450 x 10^6 (N = 38) n (%)	150 to 450 x 10^6 (N = 56) n (%)	150 x 10^6 (N = 22) n (%)	300 x 10^6 (N = 70) n (%)	450 x 10^6 (N = 92) n (%)	150 to 450 x 10^6 (N = 184) n (%)
Subjects with ≥ 1 AE	4 (100)	70 (100)	54 (100)	128 (100)	18 (100)	38 (100)	56 (100)	22 (100)	70 (100)	92 (100)	184 (100)
Blood and lymphatic system disorders	**4 (100)**	**67 (95.7)**	**53 (98.1)**	**124 (96.9)**	**17 (94.4)**	**35 (92.1)**	**52 (92.9)**	**21 (95.5)**	**67 (95.7)**	**88 (95.7)**	**176 (95.7)**
Neutropenia	4 (100)	62 (88.6)	51 (94.4)	117 (91.4)	16 (88.9)	35 (92.1)	51 (91.1)	20 (90.9)	62 (88.6)	86 (93.5)	168 (91.3)
Anaemia	4 (100)	51 (72.9)	34 (63.0)	89 (69.5)	11 (61.1)	30 (78.9)	41 (73.2)	15 (68.2)	51 (72.9)	64 (69.6)	130 (70.7)
Thrombocytopenia	4 (100)	42 (60.0)	35 (64.8)	81 (63.3)	13 (72.2)	29 (76.3)	42 (75.0)	17 (77.3)	42 (60.0)	64 (69.6)	123 (66.8)
Leukopenia	2 (50.0)	34 (48.6)	18 (33.3)	54 (42.2)	12 (66.7)	23 (60.5)	35 (62.5)	14 (63.6)	34 (48.6)	41 (44.6)	89 (48.4)
Lymphopenia	2 (50.0)	19 (27.1)	14 (25.9)	35 (27.3)	7 (38.9)	16 (42.1)	23 (41.1)	9 (40.9)	19 (27.1)	30 (32.6)	58 (31.5)
Febrile neutropenia	2 (50.0)	11 (15.7)	8 (14.8)	21 (16.4)	3 (16.7)	5 (13.2)	8 (14.3)	5 (22.7)	11 (15.7)	13 (14.1)	29 (15.8)
Immune system disorders	**2 (50.0)**	**58 (82.9)**	**52 (96.3)**	**112 (87.5)**	**8 (44.4)**	**35 (92.1)**	**43 (76.8)**	**10 (45.5)**	**58 (82.9)**	**87 (94.6)**	**155 (84.2)**
Cytokine release syndrome	2 (50.0)	53 (75.7)	52 (96.3)	107 (83.6)	7 (38.9)	35 (92.1)	42 (75.0)	9 (40.9)	53 (75.7)	87 (94.6)	149 (81.0)
Hypogammaglobulinaemia	1 (25.0)	14 (20.0)	11 (20.4)	26 (20.3)	4 (22.2)	5 (13.2)	9 (16.1)	5 (22.7)	14 (20.0)	16 (17.4)	35 (19.0)
General disorders and administration site conditions	**4 (100)**	**60 (85.7)**	**37 (68.5)**	**101 (78.9)**	**15 (83.3)**	**33 (86.8)**	**48 (85.7)**	**19 (86.4)**	**60 (85.7)**	**70 (76.1)**	**149 (81.0)**
Fatigue	1 (25.0)	28 (40.0)	14 (25.9)	43 (33.6)	9 (50.0)	20 (52.6)	29 (51.8)	10 (45.5)	28 (40.0)	34 (37.0)	72 (39.1)
Pyrexia	0	17 (24.3)	15 (27.8)	32 (25.0)	6 (33.3)	15 (39.5)	21 (37.5)	6 (27.3)	17 (24.3)	30 (32.6)	53 (28.8)
Oedema peripheral	1 (25.0)	12 (17.1)	6 (11.1)	19 (14.8)	5 (27.8)	13 (34.2)	18 (32.1)	6 (27.3)	12 (17.1)	19 (20.7)	37 (20.1)
Chills	1 (25.0)	10 (14.3)	3 (5.6)	14 (10.9)	4 (22.2)	9 (23.7)	13 (23.2)	5 (22.7)	10 (14.3)	12 (13.0)	27 (14.7)
Vascular disorders	**1 (25.0)**	**23 (32.9)**	**13 (24.1)**	**37 (28.9)**	**7 (38.9)**	**18 (47.4)**	**25 (44.6)**	**8 (36.4)**	**23 (32.9)**	**31 (33.7)**	**62 (33.7)**
Hypotension	0	12 (17.1)	9 (16.7)	21 (16.4)	5 (27.8)	4 (10.5)	9 (16.1)	5 (22.7)	12 (17.1)	13 (14.1)	30 (16.3)
Hypertension	1 (25.0)	7 (10.0)	6 (11.1)	14 (10.9)	2 (11.1)	7 (18.4)	9 (16.1)	3 (13.6)	7 (10.0)	13 (14.1)	23 (12.5)
Psychiatric disorders	**0**	**33 (47.1)**	**12 (22.2)**	**45 (35.2)**	**4 (22.2)**	**11 (28.9)**	**15 (26.8)**	**4 (18.2)**	**33 (47.1)**	**23 (25.0)**	**60 (32.6)**
Confusional state	0	10 (14.3)	7 (13.0)	17 (13.3)	0	3 (7.9)	3 (5.4)	0	10 (14.3)	10 (10.9)	20 (10.9)
Cardiac disorders	**1 (25.0)**	**23 (32.9)**	**9 (16.7)**	**33 (25.8)**	**6 (33.3)**	**13 (34.2)**	**19 (33.9)**	**7 (31.8)**	**23 (32.9)**	**22 (23.9)**	**52 (28.3)**
Tachycardia	1 (25.0)	14 (20.0)	4 (7.4)	19 (14.8)	2 (11.1)	6 (15.8)	8 (14.3)	3 (13.6)	14 (20.0)	10 (10.9)	27 (14.7)

AE = adverse event; CAR = chimeric antigen receptor; CSR = clinical study report; ide-cel = idecabtagene vicleucel; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term;

Source: Table 15 of Summary of Clinical Safety

FDA comments: Applicant's analysis seems reasonable. The most frequently reported (≥ 40%) PTs by decreasing frequency were neutropenia (91.3%), CRS (81.0%), anemia (70.7%), thrombocytopenia (66.8%), and leukopenia (48.4%). Except for CRS, there was no clear evidence of a dose response in the pooled analysis.

5.5 Effect of Baseline and Demographic Characteristics on the Pharmacokinetic Parameters.

Several pre-specified covariates were explored for graphical trends with cellular expansion parameters. Briefly, the evaluated covariates were in the following major categories:

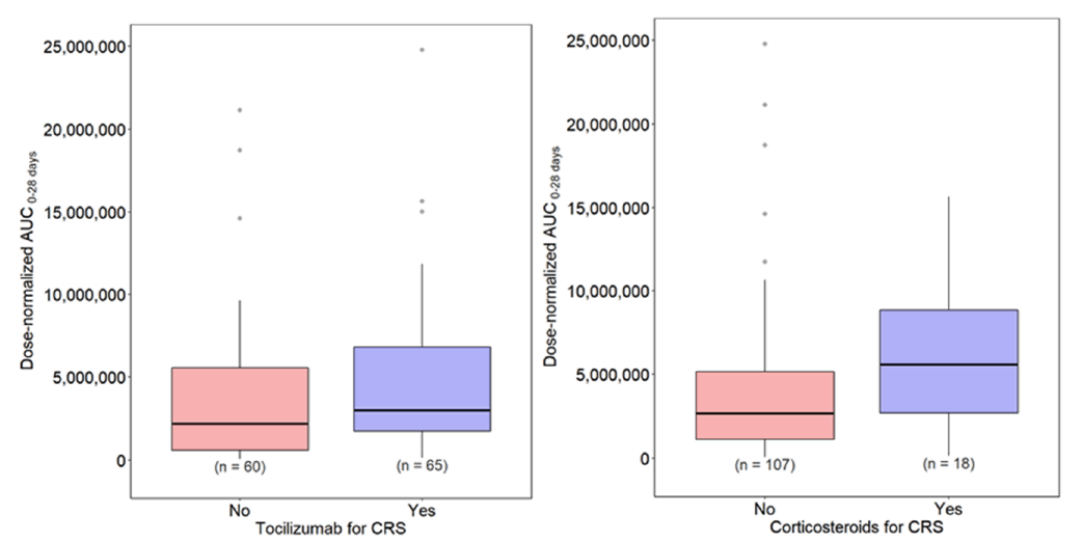
- Baseline demographic factors, including sex, age, body weight, body surface area (BSA), race, and ethnicity;
- Disease factors, such as number of prior MM regimens, last prior MM therapy (such as corticosteroids), extramedullary disease, Eastern Cooperative Oncology Group (ECOG) performance status, concomitant medications of tocilizumab or corticosteroids administered to manage CRS, bridging therapy
- Baseline/Preinfusion variables, for instance, serum sBCMA1 levels, urine monoclonal protein (m-protein); serum m-protein;
- Antidrug antibody (ADA) status: Development of postinfusion ADAs (as binary variable) was evaluated on cell expansion kinetics.

Based on these evaluations, covariates, such as age, race, ethnicity, sex, ADA status, and number of prior anti-MM therapies were not found to influence the cell expansion parameters.

Covariates that were significantly associated with $AUC_{0\text{-}28days}$ (and Cmax) were: body weight, body surface area, baseline soluble BCMA, and medications (tocilizumab or corticosteroids) to manage CRS. Exposures appeared to decrease with increasing body weight and body surface area and showed an increasing trend with baseline sBCMA.

Exposures appeared to be higher in subjects treated with tocilizumab or corticosteroids for the occurrence of CRS (Figure 3); it should be noted that these latter two correlations may be driven through a safety exposure-response rather than representing a direct effect of these comedications on PK.

Figure 3: Correlations between Dose-normalized $AUC_{0\text{-}28days}$ and Concomitant Medication to Manage CRS: Graphical Evaluation from Study MM-001



Source: Figure 7 of Summary of Clinical Pharm.

Correlations between AUC0-28days, and Statistically Selected Continuous Covariates

Table 5 shows the results of statistically significant (continuous) covariates for $AUC_{0\text{-}28days}$, for each attempted functional form of the model. Since BSA is highly correlated with body weight, these effects are considered secondary to the effects of body weight, and any further assessment of the clinical relevance of these effects focused on body weight.

Table 5: Univariate Correlations between Dose-Normalized AUC0-28days, and Statistically Selected Continuous Covariates: Study MM-001

Covariate	Model	AIC	Estimate (%RSE)	P-value[a]
Body weight	Linear	4179.2	-57427 (43.6%)	0.0235*
	Exponential	4178.3	-0.0165 (38.5%)	0.0105*
	Power	4176.9	-1.309 (32.0%)	0.0022*
Body Surface Area	Linear	4091.0	-3088725 (50.6%)	0.0506
	Exponential	4090.2	-0.922 (42.2%)	0.0195*
	Power	4089.3	-1.858 (36.7%)	0.0074*
Baseline Soluble BCMA	Linear	4149.4	2093 (62.5%)	0.1125
	Exponential	4150.0	0.00035 (74.6%)	0.1828
	Power	4146.7	0.197 (47.0%)	0.0353*

Source: Table 5 of Summary of Clinical Pharm.

Based on the AIC criteria, the power model appeared to provide marginally better description of both covariates on $AUC_{0\text{-}28days}$.

Based on the estimated power model of body weight on AUC0-28days, relative to a subject with a median weight of 76.4 kg, the effect of body weight would be predicted to translate into a 46% higher AUC0-28days in a subject of 58 kg, representing the 10th percentile of weight distribution in Study MM-001, and a 28% lower AUC0-28days in a subject of 97 kg, reflecting the 90th percentile of weight distribution in Study MM-001. In the context of the overall variability observed in ide-cel exposures (geometric %CV > 100%) across the population, these effects are considered relatively modest.

Using the established power model the effect of baseline soluble BCMA on AUC0-28days, relative to a subject with median baseline soluble BCMA of 329 ng/mL would be predicted to translate into a 31% lower AUC0-28days in a subject at the 10th percentile of the baseline soluble BCMA distribution (37 ng/mL), and a 25% higher AUC0-28days in a subject at the 90th percentile (751.6 ng/mL). Similar as for the effect of body weight, these effects are considered relatively modest in the context of the overall variability observed in ide-cel exposures.

Exposure Summaries in Subgroups of Body Weight and Soluble BCMA

To further understand the relevance of exposure changes for statistically significant covariates, subgroups were created by dividing each of these covariates into quartiles. A tabular presentation showing descriptive statistics of normalized AUC0-28days by these subgroups of body weight and sBCMA is shown in Table 6.

Point estimates of the normalized exposure metrics (mean and median) by quartiles of covariates generally confirm the overall trends in the identified relationships. However, the trends are

consistently modest; as an example, the point estimates (median) of Q1 to Q4 of each covariate (including body weight) for $AUC_{0\text{-}28days}$ are within 35% of each other. In contrast, the variability in $AUC_{0\text{-}28days}$ within each of the covariate quartiles is consistently at least ~ 80% (and greater than 100% across all covariate quartiles), thus considerably larger than the effect size associated with the overall trend.

Additionally, for baseline soluble BCMA the trends in the mean and median exposure parameters appear inconsistent between the quartiles, but since the identified relationship for this covariate is biologically plausible (baseline soluble BCMA is a surrogate measure of tumor burden prior to treatment and higher tumor burden may predict an increased drive for cellular expansion), this may be attributed to the small sample size of the quartile subsets.

Relative to covariate evaluation on $AUC_{0\text{-}3M}$, baseline soluble BCMA but not weight was found to be a statistically significant predictor on $AUC_{0\text{-}3M}$. As a statistically significant effect of body weight was identified on $AUC_{0\text{-}28days}$ (and Cmax.), but not on $AUC_{0\text{-}3M}$; this may indicate that body weight is specifically a predictor of the initial cellular expansion, but less so of longer-term persistence.

Table 6:Summary of Normalized $AUC_{0\text{-}28days}$ (days*copies/µg) by Quartiles of Covariates: Study MM-001

Covariate	Covariate Range	n	Mean	SD	CV%	Median	Min	Max
Body weight (kg)	[42.6,66.7]	32	5,207,890	5,746,972	110.4	3,011,296	340,061	24,783,686
	(66.7,76.4]	31	4,287,824	4,033,298	94.1	2,881,264	412,809	15,027,195
	(76.4,85.6]	31	3,794,636	3,374,992	88.9	2,930,610	91,119	11,864,226
	(85.6,125.6]	31	3,769,549	4,130,870	109.6	1,950,595	75,404	18,729,398
Baseline sBCMA (ng/mL)	[24,91]	31	2,809,867	2,207,046	78.5	2,677,110	75,404	9,927,968
	(91,231]	31	3,495,232	3,182,866	91.1	2,074,347	152,876	11,765,526
	(231,428.8]	31	5,283,623	5,052,418	95.6	4,519,139	135,958	21,154,118
	(428.8,1310]	31	5,496,591	5,857,697	106.6	3,020,105	91,119	24,783,686

Source: Table 6 of Summary of Clinical Pharm.

Summary of PK Characterization Analyses

Ide-cel cellular expansion kinetics were characterized by an increase in cell expansion parameters across the target dose levels; a high degree of between-subject variability (%CV ≥ 100%) was observed. Body weight and baseline sBCMA were identified as statistically significant covariates for AUC0-28days and Cmax; the magnitude of these effects (up to 46% change) is considered relatively modest in consideration of the overall exposure variability.

Baseline sBCMA was identified as statistically significant covariate for AUC0-3M. Weight was not found to be a statistically significant covariate for this exposure parameter. Age, race, ethnicity, sex, and ADA status were not found to be significant covariates on cell expansion parameters. No association was found between number of prior anti-MM therapies and cell expansion parameters.

FDA Comments: Applicant's covariate evaluation for PK seems reasonable. However, consistent with other CAR-T products, there might be confounding effects and it is hard to conclude a causal effect since exposure might also be affected by clinical outcomes. This confounding effect may also affect the evaluation of covariates effect on PK.

5.6 Persistence

Persistence of ide-cel (measured as detectable transgene level) over time is summarized in Table 7. Approximately 59% and 36% of ide-cel treated subjects had measurable CAR+ T cell levels at 6 months and 12 months postinfusion, respectively. These available PK data thus demonstrate that ide-cel can persist in peripheral blood for up to 1year post infusion.

Table 7: Pharmacokinetic Persistence of Ide-cel Over Times: Study MM-001

Visit	Total Number of Observations	Number of Observations with Measurable Values (%)	Number of Observations BLQ (%)
Month 1	118	117 (99.2%)	1 (0.8%)
Month 3	100	75 (75.0%)	25 (25.0%)
Month 6	49	29 (59.2%)	20 (40.8%)
Month 9	27	10 (37.0%)	17 (63.0%)
Month 12	11	4 (36.4%)	7 (63.6%)

Source: table 3 of summary of clinical pharm.

FDA Comments: applicant's analysis seems reasonable. Approximately 59% and 36% of ide-cel treated subjects had measurable CAR+ T cell levels at 6 months and 12 months postinfusion, respectively.

5.7 Exposure Response for Efficacy

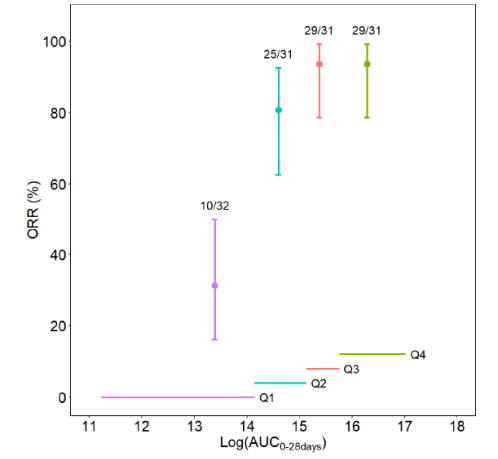
The ER analyses characterized the relationship between individual observed exposures (and other covariates) and efficacy endpoints from Study MM-001. The exposure-efficacy analyses were performed using a data cutoff date of 19 Apr 2019, corresponding to ≥ 3 months of follow-up after the last subject was infused with ide-cel. Subject-level exposures were calculated through noncompartmental methods. Only subjects included in the analysis population were included in the ER analyses. A total of 127 subjects had both evaluable PK parameters and efficacy endpoints.

The objective of these analyses was to evaluate the ER of ide-cel efficacy endpoints and characterize established ER relationships through model-based simulations and provide support for the proposed dose range. The key efficacy endpoints examined for relationship to exposure parameters summarized in this document include ORR, VGPR or better, CR rate, and PFS.

Overall Response Rate

The overall response rate, defined as proportion of subjects who experience a PR or better based on IRC-adjudicated assessment, was explored with log (AUC0-28days). Figure 4 visualizes the proportion of responders for ORR within each of the quartiles of log (AUC0-28days). The graphical evaluation suggested the presence of an exposure-response relationship, with a lower proportion of responders in the lowest exposure quartile and a numerical increase across higher quartiles; highest proportions were associated with the two highest quartiles. The ORR was approximately 31% in the lowest exposure quartile which increased to an ORR ≥ 80% in the higher three quartiles.

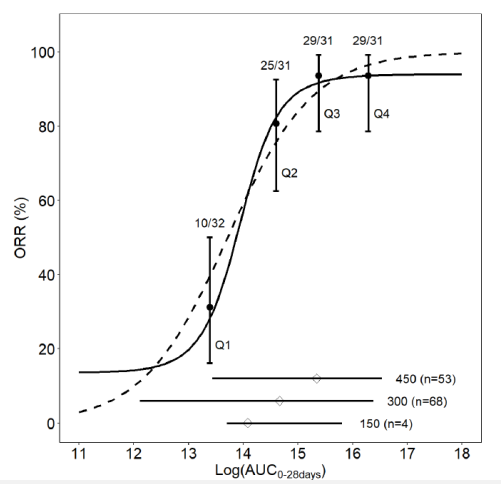
Figure 4: ORR as a Function of Log (AUC0-28days): Study MM-001



Source: Figure 8 of Summary of Clinical Pharm

Based on this trend, logistic regression evaluations were performed. Both a linear and sigmoid Emax functional form was attempted in the logistic regression framework. Figure 5 shows observed mean ORR at each quartile of log (AUC0-28days) along with model predicted curves from linear and sigmoid Emax models.

Figure 5: Observed and Model-predicted ORR by Log (AUC0-28days): Study MM-001



Source: Figure 9 of Summary of Clinical Pharm.

Both linear (dashed lines) and sigmoid Emax (solid lines) models showed reasonable fits to the data. However, the sigmoid Emax model predictions provide an improved fit to the observed mean ORR as seen in Figure 5. The sigmoid Emax model was therefore selected as the final model to perform the model-based ORR simulations.

Sex (M/F) was included as a covariate into the final ER model for ORR because it was identified as a statistically significant predictor of ORR from the stepwise covariate selection process. The interaction between sex and exposure log (AUC0-28 days) was not significant (p = 0.26) and therefore not incorporated in both linear and Emax models. The parameter estimates from the final ORR model are presented in Table 8. The model indicates a higher ORR for females than males.

Table 8: Parameter Estimates from the Final ORR Exposure-Response Model using Log ($AUC_{0\text{-}28\ days}$) as Exposure Metric: Study MM-001

Parameter	Estimate (%RSE) in the Logit Domain
Eo	-2.83 (43.0%)
E_{max}	5.12 (31.8%)
EC_{50} (log(AUC))	14.0 (0.96%)
H	3.25 (19.7%)
Sex (female versus male)	1.78 (38.3%)

Source: Table 8 of clinical pharm summary.

FDA Comments:

1. **Please refer to 6.3.3 to see FDA's analysis of the covariates impact on efficacy.**

   Briefly, Multivariable logistic regression was conducted. Age, ethnicity, race had no obvious impact on efficacy.

   Pre LD chemo bone marrow plasma cell percentage (PRBMP) and post LD chemo soluble BCMA level (PLSB) had negative impact on overall efficacy endpoint measured as ORR, VGPR and CR. Sex is a risk factor after adjusting PRBMP and PLSB in model. It is still unknow whether gender is associated with other baseline factors or it's risk factor by itself.

   Body weight or BSA showed an apparent negative correlation with efficacy, however after incorporating sex (male or female), their impact did not further contribute to model prediction. The negative impact of body weight or BSA on efficacy is considered secondary to gender effect. Female has lower baseline body weight/BSA and their efficacy are generally better than male under same condition.

2. **The effect of tocilizumab and corticosteroid on efficacy:**
   Exposures appeared to be higher in subjects treated with tocilizumab or corticosteroids for the occurrence of CRS; it should be noted that these latter two correlations may be driven through a safety exposure-response rather than representing a direct effect of these comedications on PK.

6. REVIEWER'S ANALYSIS:

6.1 Objectives

- To explore the potential dose-exposure-response relationships for efficacy and safety

6.2 Software

(b) (4)

6.3 Result

6.3.1 Dose-Exposure Relationship

Due to the limited number of applicant's analysis, we re-analysis dose-exposure relationship with pooled population from both study B2121-MM-001 (n=128) and study B2121-CRB-401 (n=62) with each dose listed in Table 9. The distribution of PK parameters across all planned dose levels are shown below (Table 10 - Table 12 and Figure 6).

Table 9: Summary of Patients Number in Each Dose Level in Study BB2121-CRB-401 and Study BB2121-MM-001

Dose	Study BB2121-CRB-401	Study BB2121-MM-001
50	3	-
150	18	4
300	-	70
450	38	54
800	3	-

Source: Adapted from Applicant's submission.

Higher CAR+ T cell exposure was observed in patients with higher doses. For low dose (50 million cells), patient cannot achieve a comparable Cmax compared with higher dose such as 450 million cells (2783 vs. 32370) although Tmax was achieved early at day 7 (compared with 11 days at dose level 450 million cells). The dose level of 150 million cells also had a slightly lower Cmax and longer Tmax (12.5 days) compared to the dose levels of 300 and 450 million cells (11 days).

Among all these PK parameters, CAR+ T cell expansion rate (defined by Cmax/Tmax) was considered a most relevant predictive factor for efficacy and has close association with actual administered dose. Altogether, CAR+ T cell expansion rate represents both maximum CAR+ T cell level and days achieved maximum levels. A histogram distribution of PK parameters was shown in Figure 6. Higher CAR+ T cell expansion rate was observed in patients with higher doses.

Table 10: Summary of Tmax Across All Dose Levels

DOSE	N	Tmax Median (5%-95% percentile)
50M	3	7 (7, 9.7)
150M	22	12.5 (9, 15)
300M	70	11 (7, 21)
450M	92	11 (7, 21)
800M	3	11 (10.1, 13.7)

Source: Adapted from Applicant's submission.

Table 11: Summary of Cmax Across All Dose Levels

DOSE	N	Expansion Rate Median (5%-95% percentile)
50M	3	2783 (478, 4134)
150M	22	12612 (588, 47215)
300M	70	18763 (1245, 87614)
450M	92	32670 (4501, 100424)
800M	3	27855 (18662, 72943)

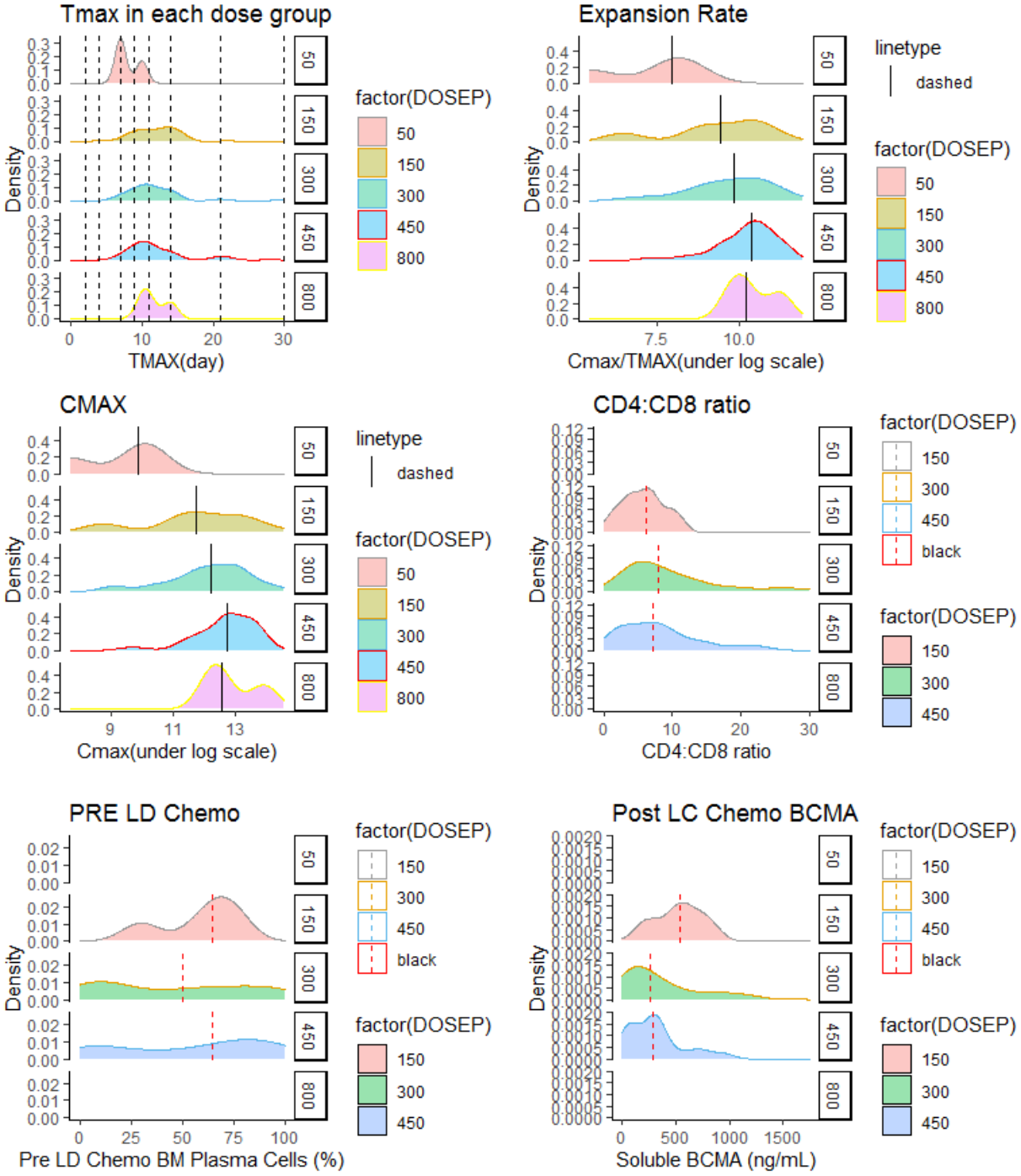
Source: Adapted from Applicant's submission.

Table 12: Summary of Expansion Rate Across All Dose Levels

DOSE	N	Cmax Median (5%-95% percentile)
50M	3	19470 (3946, 28938)
150M	22	125818 (6396, 706010)
300M	70	203721 (9190, 1217959)
450M	92	341146 (62332, 1046307)
800M	3	278550 (202498, 1010073)

Source: Adapted from Applicant's submission.

Figure 6: Dose-Exposure Relationship in Patients Who Received Ide-Cel



Source: Reviewer's analysis. Dashed vertical lines in Tmax figure indicate the PK sampling time which is at day 2, day 4, day 7, day 9, day 11, day 14, day 21, day 30. Vertical line in other figures indicates median level in each sub-group.

6.3.2 Dose-Efficacy Relationship

Dose-ORR Relationship:

We have conducted dose-response analysis for efficacy for Ide-Cel. The relationships between administered cell number and overall response efficacy endpoints were evaluated for subjects in 62 patients in study BB2121-crb-401 and 128 patients in study BB2121-MM-001. There is a positive relationship between administered dose and response (Table 13). Notably, there is a different between male and female cohort.

Table 13: Estimated Parameters in Logistic Regression for Dose Response Relationship for ORR Stratified by Gender

		Estimate	Std. Error	P value
ORR ~ Gender: Dose	Intercept	-0.40	0.53	0.45
	Male: Dose Slope	0.002877	0.0014	0.049*
	Female: Dose Slope	0.006878	0.0018	0.00023***

Source: FDA's analysis

A summary of male or female patients' number in each dose level of the two studies were listed in Table 14.

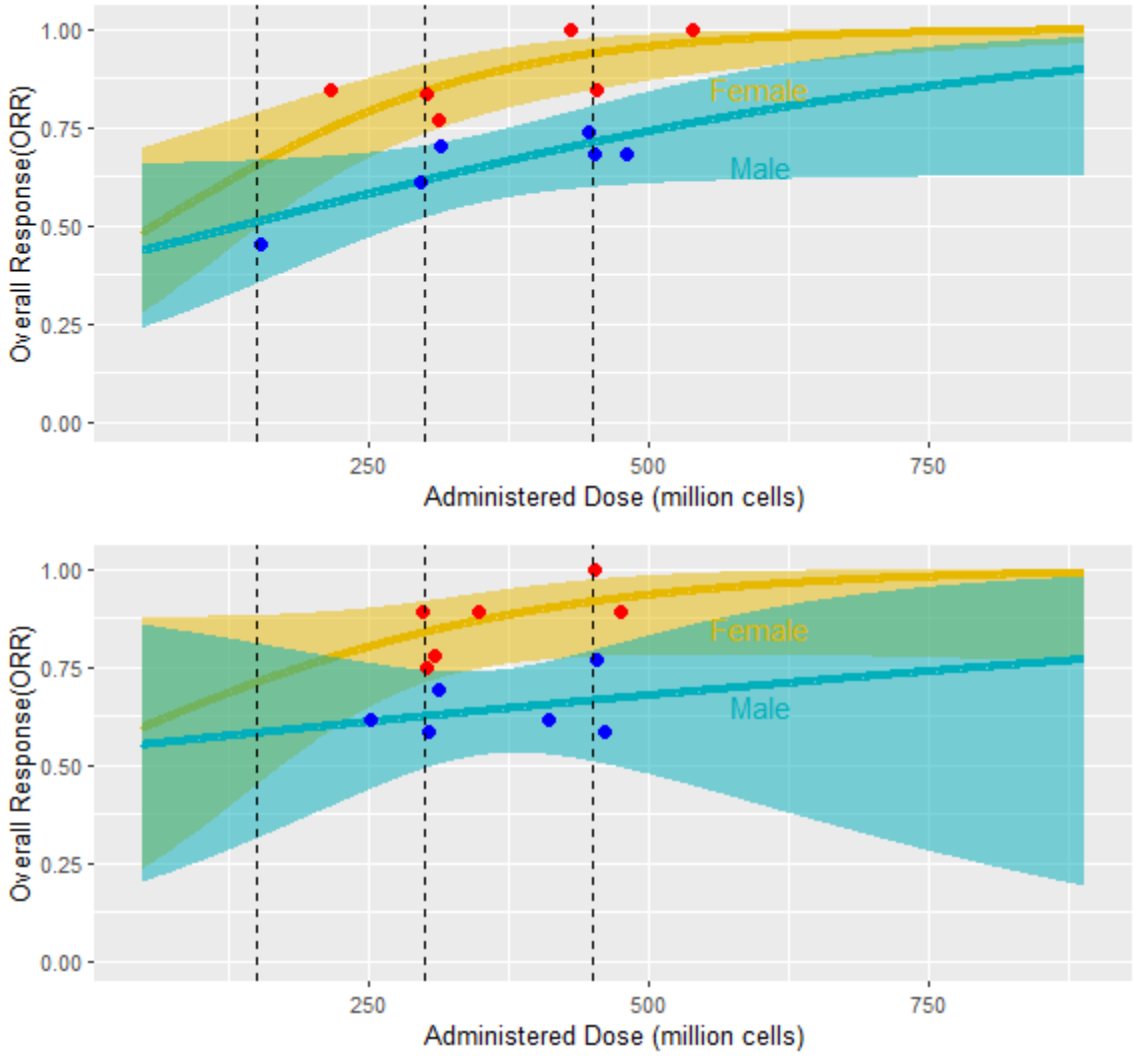
Table 14: Summary of Patients Number in Each Dose Level in Study BB2121-CRB-401 and Study BB2121-MM-001

N	**Study BB2121-CRB-401**		**Study BB2121-MM-001**	
Dose	**Male**	**Female**	**Male**	**Female**
50	2	1	-	-
150	13	5	4	0
300	-	-	38	32
450	23	15	34	20
800	1	2	-	-
Total	39	23	76	52

Source: Adapted from Applicant's submission.

A simulation of model predicted ORR in male (blue) and female (yellow) cohort were shown in Figure 4. Generally female showed better overall response compared with male. The red dots and blue dots represented the observed ORR in each sextile of patients at mean actual dose level. They generally fall into the 95% confident interval zone. A simulated ORR at different dose level were shown in Table 15. Model predicted ORR at dose level 300 million cells is 0.61 (95% CI: 0.52, 0.70) for male and 0.84 (95% CI: 0.73, 0.91) for female. Model predicted ORR at dose level 450 million cells is 0.71 (95% CI: 0.60, 0.80) for male and 0.94 (95% CI: 0.84, 0.98) for female. There are very limited patients received dose above 540 million cells (Table 14). ORR predicted by model for dose above 540 million cells especially in male cohort will need additional clinical data to verify.

Figure 7: Dose Response Relationship for ORR Stratified by Gender in Pooled Studies (Upper) and Pivotal Study BB2121-MM-001 Alone (Lower)



Source: Reviewer's independent Analysis based on a pooled study of study BB2121-MM-001 and study BB2121-CRB-401 (upper) and pivotal study BB2121-MM-001 alone (lower). X axis is administered actual dose of CAR+ Cells (million cells). Y axis is overall response rate in male (blue) and female (yellow) cohort. Dashed lines are targeted three dose levels (150, 300, 450 million cells). Solid line is the logistic regression of the predicted ORR. The area is the 95% CI. For each dose sextile, the observed response rate is plotted as blue circle (male) and red circle (female) vs the mean dose. Each dot represents observed result in 12-13 individuals in female and 18-20 individuals in male.

Table 15: Model Predicted ORR in Ide-Cel Dose-ORR Relationship Stratified by Gender

	Male	Female
DOSE	**Model Predicted ORR (95% CI)**	**Model Predicted ORR (95% CI)**
50 Million Cells	0.44 (0.24, 0.66)	0.49 (0.28, 0.70)
150 Million Cells	0.51 (0.35, 0.67)	0.65 (0.49, 0.79)
300 Million Cells	0.61 (0.52, 0.70)	0.84 (0.73, 0.91)
450 Million Cells	0.71 (0.60, 0.80)	0.94 (0.84, 0.98)
520 Million Cells	0.75 (0.61, 0.82)	0.96 (0.88, 0.99)
700 Million Cells	0.83 (0.62, 0.94) *	0.988 (0.93, 0.998)
800 Million Cells	0.87 (0.62, 0.96) *	0.993 (0.949, 0.999)

Source: Reviewer's Independent Analysis. * There are very limited patients received dose above 540 million cells. ORR predicted by model for higher doses especially in male cohort will need additional clinical data to verify.

Regression of Dose-CR relationship:

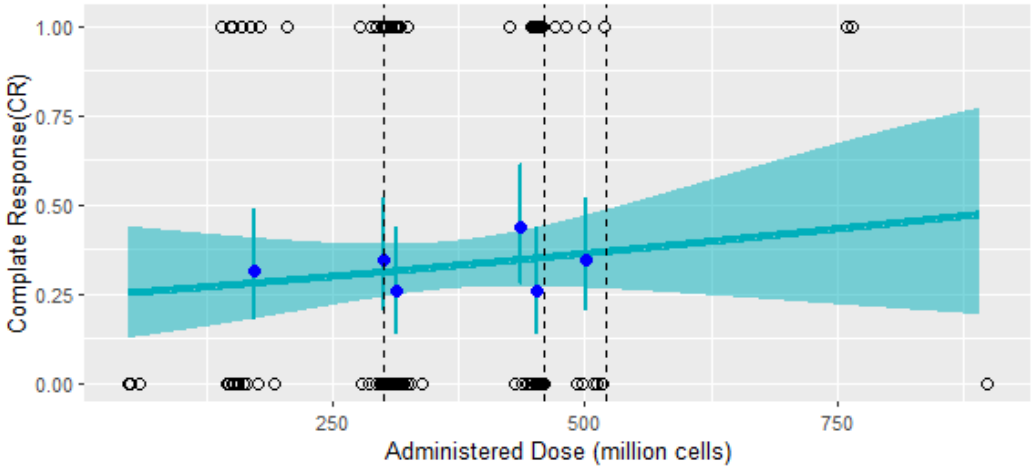
We have conducted dose-CR analysis for efficacy for Ide-Cel. The relationships between administered cell number and complete response efficacy endpoints were evaluated for subjects in 62 patients in study BB2121-crb-401 and 128 patients in study BB2121-MM-001. There is flat relationship between administered dose and CR rate (Table 16). Notably, there is no different between male and female cohort.

Table 16: Estimated Parameters in Logistic Regression for Dose Response Relationship for ORR Stratified by Gender

		Estimate	Std. Error	P value
ORR ~ Dose	Intercept	-1.15	0.49	0.0187 *
	Dose Slope	0.001	0.0012	0.3562

Source: FDA's analysis

Figure 8: Dose Response Relationship for CR Rate in Pooled Studies



Source: Reviewer's independent Analysis based on a pooled study of study BB2121-MM-001 and study BB2121-CRB-401 (upper). X axis is administered actual dose of CAR+ Cells (million cells). Y axis is complete response rate. Dashed lines are dose levels (300, 450 and 520 million cells). Solid line is the logistic regression of the predicted CR. The area is the 95% CI. For each dose sextile, the observed response rate is plotted as blue circle vs the mean dose. Each dot represents observed result in 31-32 individuals.

Observed Dose-Efficacy Relationship:

To verify the impact of gender on overall efficacy, observed ORR, VGPR and CR were shown in male and female cohort at different dose level (Table 17).

Table 17: Observed Efficacy Result of Efficacy Stratified by Gender and Dose in Pooled Study BB2121-MM-001 and Study BB2121-CRB-401

	Male			Female		
Dose	**ORR**	**VGPR**	**CR**	**ORR**	**VGPR**	**CR**
50	1/2 (50%)	0/2 (0%)	0/2 (0%)	0/1 (0%)	0/1 (0%)	0/1 (0%)
150	7/17 (41%)	4/17 (24%)	3/17 (18%)	5/5 (100%)	5/5 (100%)	4/5 (80%)
300	25/38 (66%)	16/38 (42%)	11/38 (29%)	26/32 (81%)	20/32 (62.5%)	11/32 (34%)
450	40/57 (70%)	32/57 (56%)	18/57 (32%)	33/35 (94%)	22/35 (63%)	13/35 (37%)
800	1/1 (100%)	1/1 (100%)	1/1 (100%)	2/2 (100%)	2/2 (100%)	1/2 (50%)

Source: Adapted from Applicant's submission. In each cell, numerator indicates the responder number and denominator indicates overall N number in the pooled study. Number in parentheses indicates the response rate.

Table 18: Observed Efficacy Result of Efficacy Stratified by Gender and Dose in Pivotal Study BB2121-MM-001

	Male			Female		
Dose	**ORR**	**VGPR**	**CR**	**ORR**	**VGPR**	**CR**
150	2/4 (50%)	2/4 (50%)	1/4 (25%)	-	-	-
300	25/38 (66%)	16/38 (42%)	11/38 (29%)	26/32 (81%)	20/32 (63%)	11/32 (34%)
450	22/34 (65%)	15/34 (44%)	10/34 (29%)	19/20 (95%)	14/20 (70%)	8/20 (40%)

Source: Adapted from Applicant's submission. In each cell, numerator indicates the responder number and denominator indicates overall N number in the pooled study. Number in parentheses indicates the response rate.

Overall it seems female has a better response compared with male in each dose level. At dose level 450 million cells, female is predicted to have the overall response rate of 0.94. However, the model predicted ORR for male is 0.71 (95% CI: 0.60, 0.80) and it might be improved if a higher dose is tolerable in this cohort. It is still unknow whether gender is associated with other baseline factors or it's risk factor by itself.

6.3.3 Multivariate Regression Model for Exposure Response Relationship Analysis for Efficacy

Multivariable logistic regression model was conducted, and the following factors were tested.

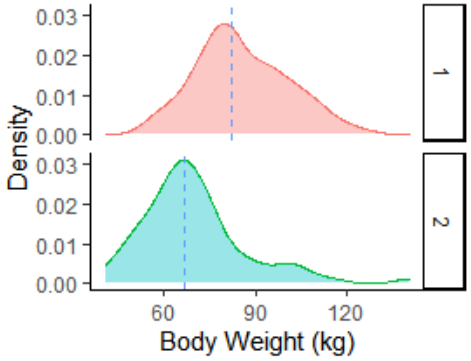
Parameter	Description
DOSEA	Actual administered dose
Log (exp_rate)	CD3 T cell Expansion Rate determined by (b) (4) . Defined as Cmax/Tmax in log scale
Log (cmax)	CD3 T Cell Cmax determined by (b) (4) in log scale
Log (AUC28D)	AUC first 28 day in log scale
Log (AUC 3M)	AUC first 3 months in log scale
CD4	Administered CD4 cell number (determined by (b) (4))
CD8	Administered CD8 cell number (determined by (b) (4))
CD4.CD8	Initial pre infusion CD4: CD8 Ratio
Age	age
Ethnicity	1: Hispanic or latino; 2: not Hispanic or latino; 99: not know
Weight	Baseline Body Weight (kg)
BSA	Baseline Body Surface Area
RACE	1: American Indian or alaska native 2: Asian 3: Black or African American 4: native havaiian or other pacific islander 5: white 99: unknown and others
SEX	1: male 2: female
BECOG	Baseline ECOG
PRBMP	Pre LD chemo bone marrow plasma cell (%)
PLSB	Post LD chemo soluble BCMA (ng/ML)

Among all these factors, age, ethnicity, and race do not appear to have no obvious impact on efficacy. PK parameters have positive correlations with ORR. Since the four PK parameters are highly correlated, expansion rate was selected as the most relevant parameter.

Effect of actual administered dose (DOSEA) on efficacy (ORR) could be better explained by CD3 T cell expansion rate determined by (b) (4) . Once log (exp_rate) was incorporated into the model, addition of DOSEA does not contribute to the prediction of ORR anymore. Pre LD chemo bone marrow plasma cell percentage (PRBMP) and post LD chemo soluble BCMA level(PLSB) had negative impact on overall efficacy endpoint measured as ORR (Table 19), VGPR (Table 20) and CR (Table 21).

Body weight or BSA showed an apparent negative correlation with efficacy (data not shown), however after incorporating sex (male or female), their impact did not further contribute to model prediction Figure 10.

Figure 9: Distribution of Baseline Body Weight Between Male (Upper) and Female (Lower)



Source: Reviewer's analysis.

The final model prediction parameters of covariates impact on efficacy measured as ORR (Table 19), VGPR (Table 20) and CR (Table 21) were shown below:

Table 19: Estimated Parameters in Multivariable Logistic Regression for ER Relationship for Efficacy (ORR)

	Sub-Population	Estimate	Std. Error	P value
Intercept		-9	2.51	0.000342 ***
PRBMP		-0.0083	0.0095	0.382
PLSB		-0.0018	0.00092	0.05 *
Log (Exp_Rate)	Male	1.1	0.27	5.92×10^{-5} ***
	Female	1.26	0.29	1.21×10^{-5} ***

Source: FDA's analysis

Table 20: Estimated Parameters in Multivariable Logistic Regression for ER Relationship for Efficacy (VGPR and Above)

	Sub-Population	Estimate	Std. Error	P value
Intercept		-7.9	2.4	0.001 **
PRBMP		-0.0055	0.0079	0.49
PLSB		-0.0017	0.0009	0.067
Log (Exp_Rate)	Male	0.89	0.25	0.00045 ***
	Female	0.95	0.25	0.00014 ***

Source: FDA's analysis

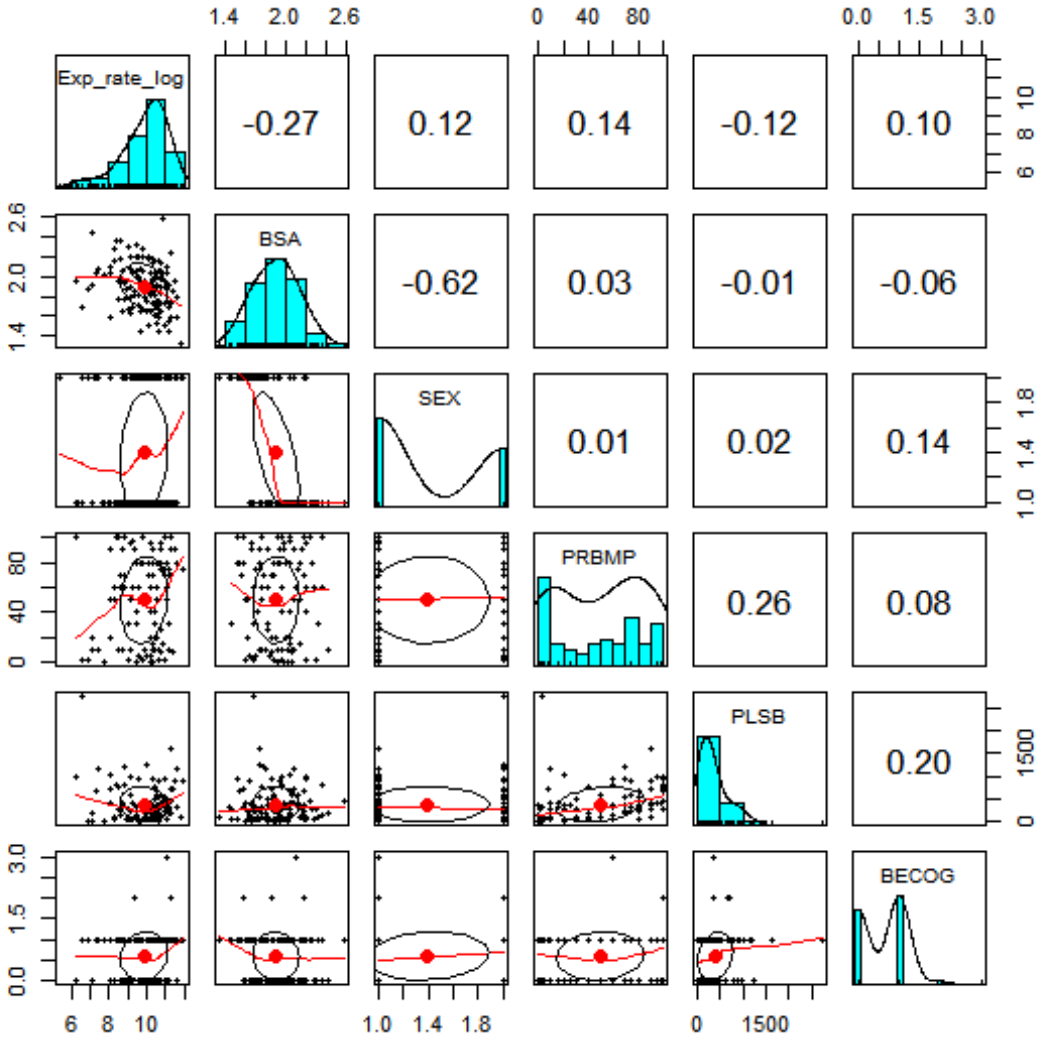
Table 21: Estimated Parameters in Multivariable Logistic Regression for ER Relationship for Efficacy (CR)

	Sub-Population	Estimate	Std. Error	P value
Intercept		-5.79	2.54	0.0227 *
PRBMP		-0.0028	0.0079	0.726
PLSB		-0.0029	0.0012	0.0192 *
Log (Exp_Rate)	Male	0.62	0.266	0.0199 *
	Female	0.64	0.258	0.0132 *

Source: FDA's analysis

The distribution and correlation of these parameters are shown below in Figure 10:

Figure 10: Distribution and Correlation of Logistic Regression Parameters



Source: Reviewer's Analysis.

6.3.4 The Impact of CD4:CD8 Ratio on Efficacy Endpoint (VGPR)

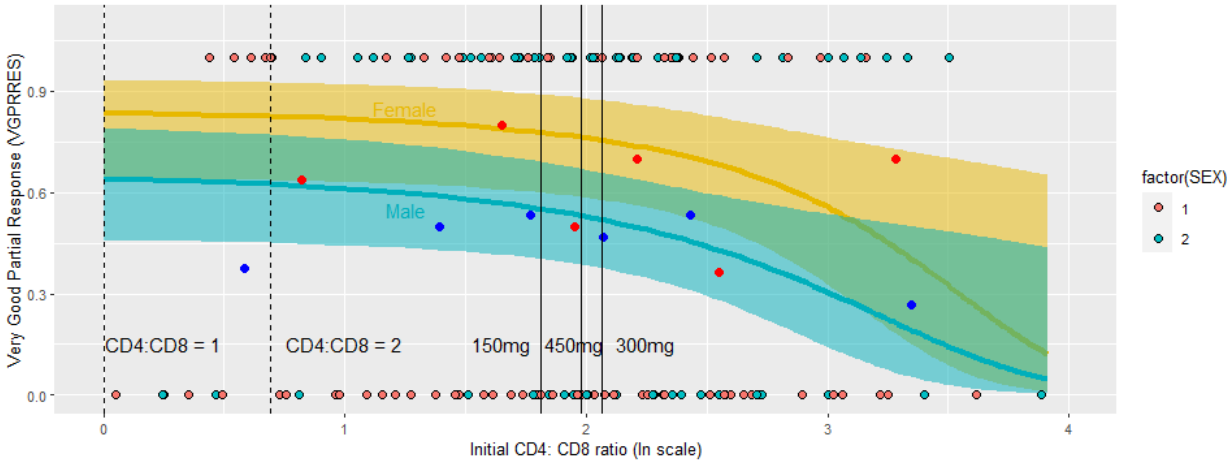
The impact of administered CD4:CD8 cell ratio was shown in Figure 11. The median levels of CD4:CD8 ratio are 6, 8 and 7 for the dose levels of 150, 300 and 450 million cells respectively in study BB2121-MM-001. Initial CD4: CD8 seems to have a negative impact on VGPR adjusted by PRBMP, PLSB and sex. The final parameter was listed in Table 22.

Table 22: Estimated Parameters in Multivariable Logistic Regression for ER Relationship for Efficacy (VGPR and Above)

	Estimate	Std. Error	P value
Intercept	1.077	0.518	0.0378*
CD4.CD8 ratio	-0.073	0.033	0.0257*
Gender female	1.048	0.487	0.0315*
PRBMP	-4.66×10^{-5}	7.02×10^{-3}	0.9947
PLSB	-1.52×10^{-3}	7.25×10^{-4}	0.0358*

Source: FDA's analysis

Figure 11: Relationship of Initial CD4: CD8 Ratio on Efficacy Endpoint (VGPR)



Source: Reviewer's Analysis

6.3.5 Multivariate Regression Model for Exposure Response Relationship Analysis for Safety

Dose Response for Cytokine Release Syndrome (CRS) and Neurotoxicity (NT):

We have conducted dose-response analysis for safety event for Ide-Cel with all grade CRS event, grade 3 and above CRS event and grade 2 and above neurotoxicity event. The relationships between administered cell number and safety events were evaluated for subjects in 62 patients in study BB2121-crb-401 and 128 patients in study BB2121-MM-001 (pooled studies) and pivotal study BB2121-MM-001 alone for sensitivity analysis.

There is a positive relationship between administered dose and all grade CRS events (Figure 12), and a shallow positive relationship with grade 3 and above CRS event (Figure 13). Unlike the impact on ORR, there is no different safety effect between male and female cohort in terms of CRS event or GR3+ CRS events rate.

There is no positive relationship between administered dose and GR2+ neurotoxicity in pooled datasets or pivotal trial alone (Figure 14). However, gender seems to be a significant covariate. Female patients had higher risk to develop grade 2 and above neurotoxicity event (p=0.034).

Model predicted safety events rate are shown in Table 24 and Table 25. Generally, there is no difference between model developed based on pooled studies or on the pivotal study BB2121-MM-001 alone.

Observed Safety event rate in pooled study is shown in Table 26, and observed safety event rate in the pivotal study is shown in Table 27.

Dose response for Grade 5 AE:

We have also explored the dose-safety relationship for the grade 5 adverse event. The relationships between administered cell number and Gr5 AE were evaluated for subjects in128 patients in study BB2121-MM-001. Safety dataset updated in Dec. 28th 2020 (3rd adae.xpt dataset for study BB2121-MM-001) was used for Gr5 AE analysis.

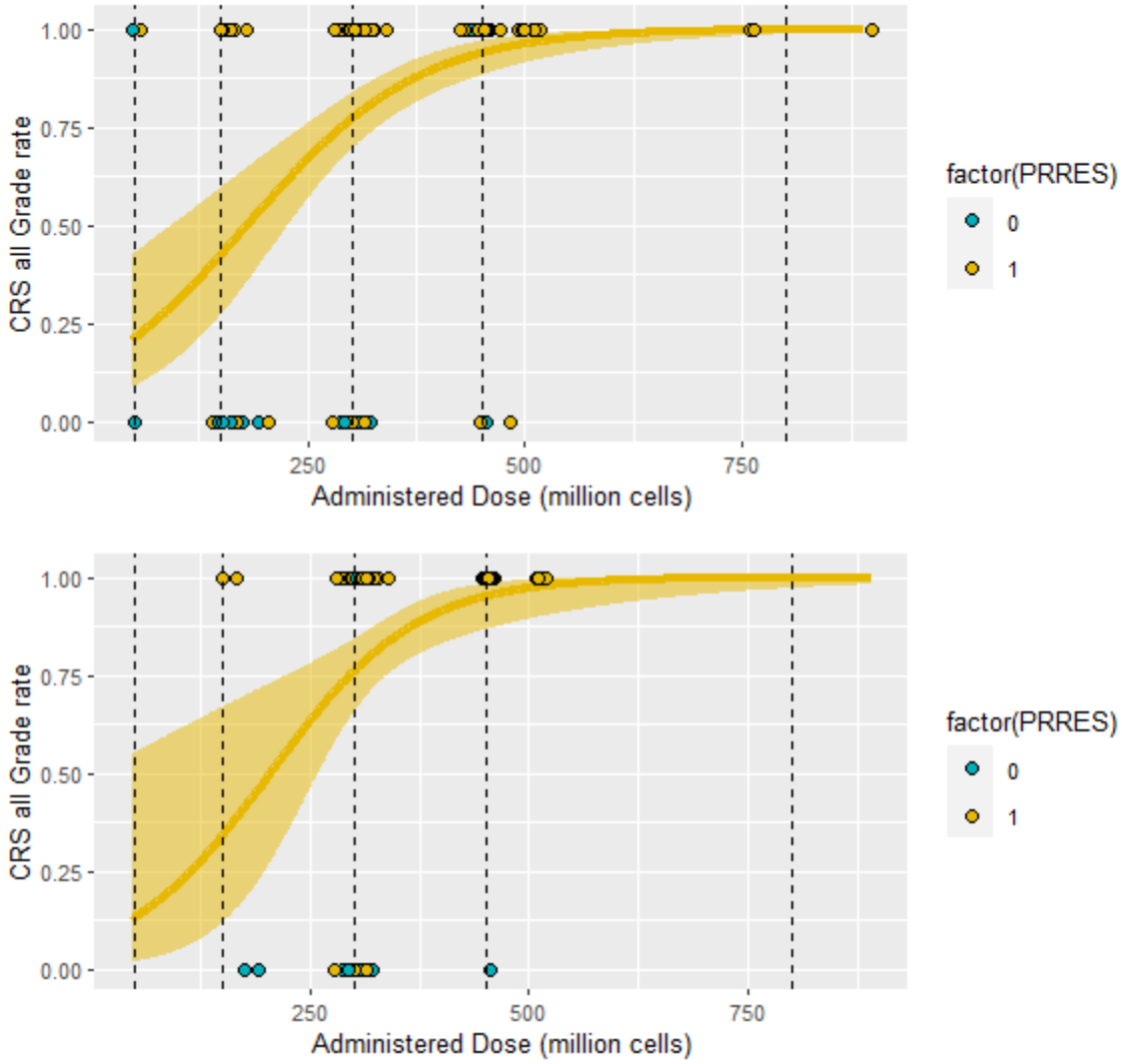
Observed dose-GR5 AE with first safety cut-off data was submitted by applicant in Table 3. An updated dose- grade 5 AE with third safety update was conducted and present in Table 27. There is a consistent trend of negative relationship of GR5 AE with initial planned dose. Consistent with planned dose-Gr5 AE relationship, actual administered dose has a negative relationship with actual administered initial dose (Figure 15).

Clearly, the GR5 AE is associated with inadequate effectiveness in those patients. The concordance between ORR and GR5 AE is shown below (Table 23). Model predicted Grade 5 AE rate is shown in Table 25.

Table 23: Concordance between ORR and GR5 AE

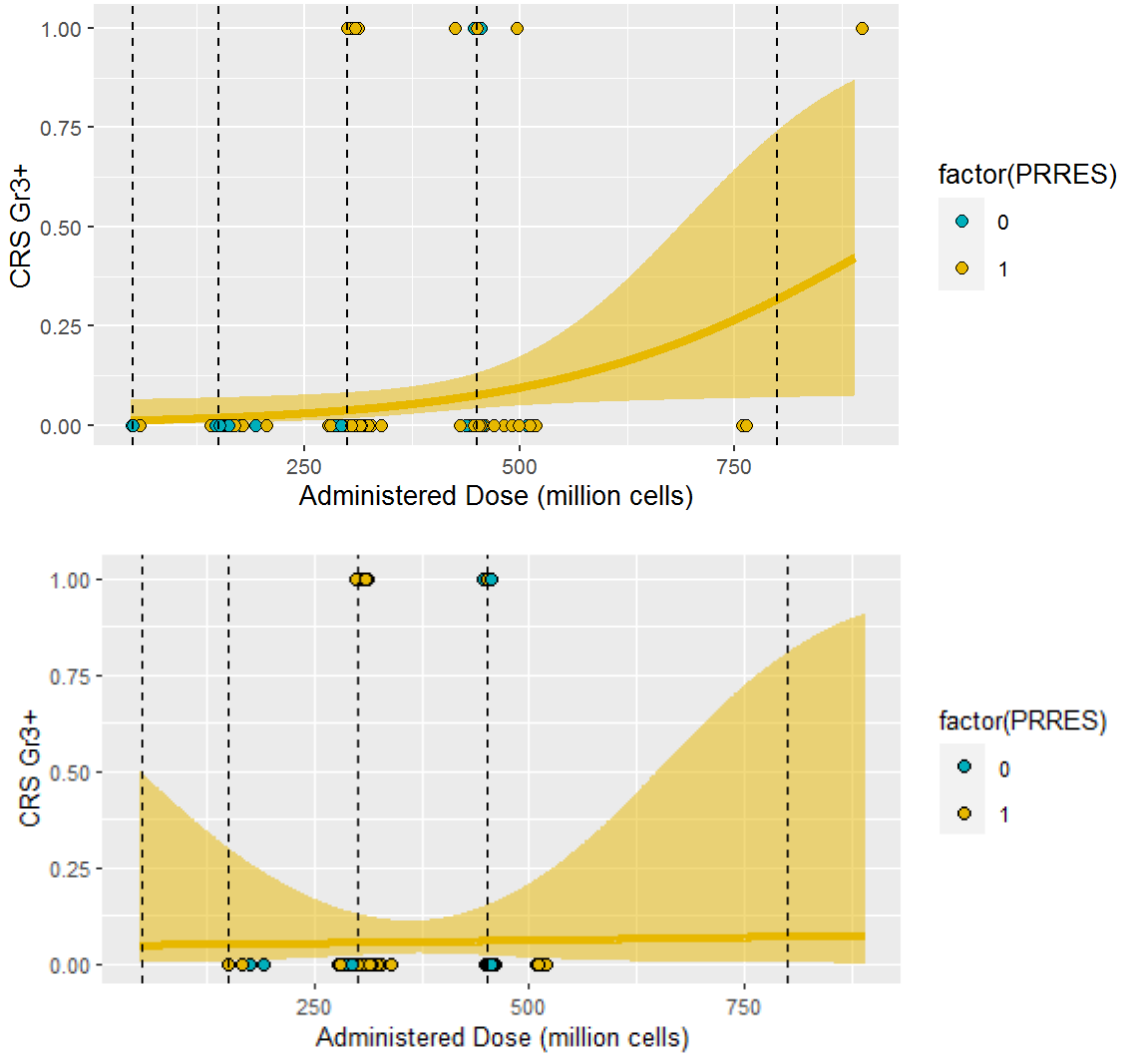
	Non-responder	Responder
Non Gr5 AE	16	82
Gr5 AE	18	12

Figure 12: Relationship of All Grade CRS Event with Actual Administered Dose in Pooled Studies (Upper) and Pivotal Study BB2121-MM-001 Alone (Lower)



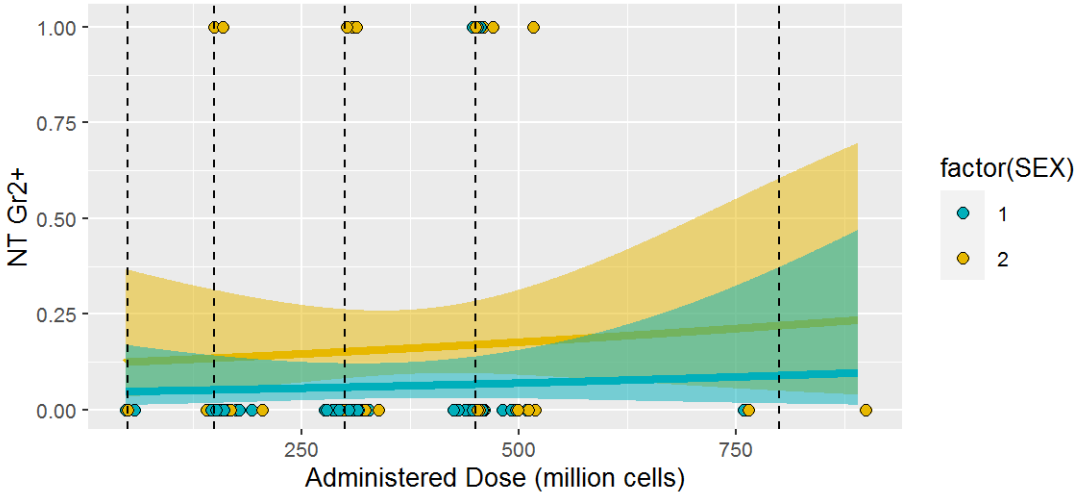
Source: Reviewer's independent Analysis based on a pooled study of study BB2121-MM-001 and study BB2121-CRB-401 (Upper) and pivotal study BB2121-MM-001 alone (Lower). X axis is administered actual dose of CAR+ Cells (million cells). Y axis is all grade CRS event. Dashed lines are tested dose levels (50, 150, 300, 450, 800 million cells). Solid yellow line is the logistic regression of the predicted CRS. The area is the 95% CI. Dots at y=1 represent an observed CRS event at the patient' s actually administered dose. Dots at y=0 represent an observed non-CRS event at the patient' s actually administered dose. Blue color represents a responder and yellow color represent a non-responder.

Figure 13: Relationship of Grade 3 and Above CRS Event with Actual Administered Dose in Pooled Studies (Upper) and Pivotal Study BB2121-MM-001 Alone (Lower)



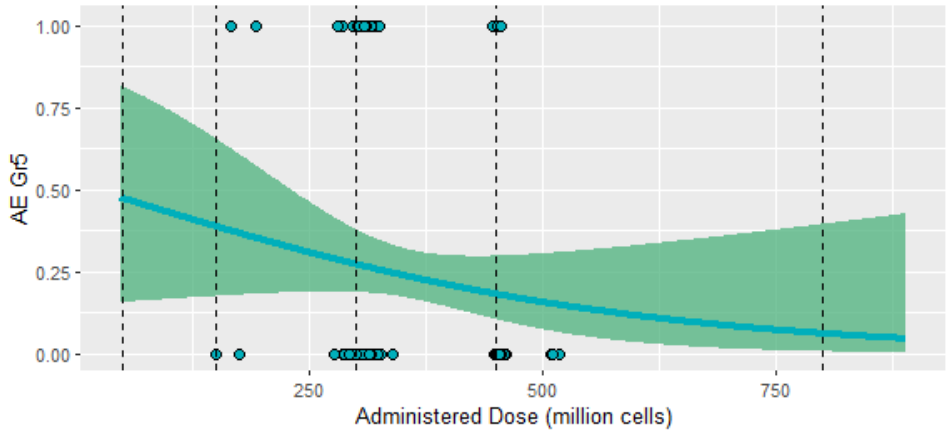
Source: Reviewer's independent Analysis based on a pooled study of study BB2121-MM-001 and study BB2121-CRB-401(Upper) and pivotal study BB2121-MM-001 alone (Lower). X axis is administered actual dose of CAR+ Cells (million cells). Y axis is all grade CRS event. Dashed lines are tested dose levels (50, 150, 300, 450, 800 million cells). Solid yellow line is the logistic regression of the predicted CRS. The area is the 95% CI. Dots at y=1 represent an observed CRS event at the patient' s actually administered dose. Dots at y=0 represent an observed non-CRS event at the patient' s actually administered dose. Blue color represents a responder and yellow color represent a non-responder.

Figure 14: Relationship of Grade 2 and Above Neurotoxicity Event with Actual Administered Dose in Pooled Studies (Upper) and Pivotal Study BB2121-MM-001 Alone (Lower)



Source: Reviewer's independent Analysis based on a pooled study of study BB2121-MM-001 and study BB2121-CRB-401(Upper) .X axis is administered actual dose of CAR+ Cells (million cells). Y axis is grade 2 and above neurotoxicity event. Dashed lines are tested dose levels (50, 150, 300, 450, 800 million cells). Solid yellow line is the logistic regression of the predicted GR2+ NT. The area is the 95% CI. Dots at y=1 represent an observed GR2+ NT event at the patient' s actually administered dose. Dots at y=0 represent an observed non-GR2+ NT event at the patient' s actually administered dose. Blue color represents male and yellow color represent female.

Figure 15: Relationship of Grade 5 Adverse Event with Actual Administered Dose in Pivotal Study BB2121-MM-001



Source: Reviewer's independent Analysis based on pivotal study BB2121-MM-001 alone. X axis is administered actual dose of CAR+ Cells (million cells). Y axis is grade 5 AE. Dashed lines are tested dose levels (50, 150, 300, 450, 800 million cells). Solid blue line is the logistic regression of the predicted GR5 AE. The area is the 95% CI. Dots at y=1 represent an observed GR2+ NT event at the patient' s actually administered dose. Dots at y=0 represent an observed non-GR2+ NT event at the patient' s actually administered dose. Blue color represents male and yellow color represent female. Grade 5 AE data updated 3 on December 28th 2020 in study BB2121-MM-001.

Table 24: Model Predicted Safety Event at Different Dose Levels (Based on Pooled data)

Dose	CRS (%)	Gr3+ CRS (%)
50	0.21 (0.09, 0.43)	0.01 (0.0017, 0.066)
150	0.43 (0.27, 0.60)	0.018 (0.004, 0.069)
300	0.77 (0.69, 0.84)	0.04 (0.016, 0.082)
450	0.94 (0.88, 0.97)	0.07 (0.04, 0.13)
460	0.94 (0.89, 0.97)	0.08 (0.04, 0.14)
520	0.97 (0.93, 0.99)	0.10 (0.05, 0.19)
700	0.99 (0.97, 0.9989)	0.22 (0.06, 0.53)
800	0.998 (0.987, 0.9997)	0.32 (0.07, 0.74)

Source: Reviewer's Independent Analysis.

Table 25: Model Predicted Safety Event at Different Dose Levels (Based on Pivotal Trial BB2121-MM-001)

Dose	CRS (%)	Gr3+ CRS (%)	Gr5 AE
50	0.13 (0.02, 055)	0.05 (0.0024, 0.497)	0.47 (0.16, 0.81)
150	0.34 (0.12, 0.67)	0.049 (0.006, 0.30)	0.39 (0.17, 0.66)
300	0.76 (0.65, 0.84)	0.05 (0.02, 0.13)	0.27 (0.19, 0.38)
450	0.95 (0.87, 0.98)	0.057 (0.02, 0.15)	0.18 (0.10, 0.30)
460	0.96 (0.87, 0.99)	0.057 (0.019, 0.16)	0.18 (0.10, 0.30)
520	0.98 (0.91, 0.997)	0.06 (0.01, 0.27)	0.15 (0.06, 0.31)
700	0.9975 (0.956, 0.9998)	0.06 (0.003, 0.62)	0.08 (0.01, 0.36)
800	0.999 (0.97, 0.99998)	0.069 (0.001, 0.81)	0.06 (0.006, 0.39)

Source: Reviewer's Independent Analysis.

Table 26: Observed Safety Signal Stratified by Gender and Dose in Pooled Study BB2121-MM-001 and Study BB2121-CRB-401

	Male			Female		
Dose	**CRS**	**Gr3+ CRS**	**Gr2+ NT**	**CRS**	**Gr3+ CRS**	**Gr2+ NT**
50	2/2 (100%)	0/2	0/2	0/1 (0%)	0/1	0/1
150	6/17 (35%)	0/17	0/17	3/5 (60%)	0/5	2/5 (40%)
300	29/38 (76%)	1/38 (2.6%)	0/38	24/32 (75%)	3/32 (9.4%)	6/32 (18.75%)
450	54/57 (95%)	4/57 (7%)	7/57 (12%)	33/35 (94%)	2/35 (5.7%)	4/35 (11.4%)
800	1/1 (100%)	0/1	0/1	2/2 (100%)	1/2 (50%)	0/2

Source: Adapted from Applicant's submission. In each cell, numerator indicates the responder number and denominator indicates overall N number in the pooled study. Number in parentheses indicates the response rate.

Table 27: Observed Safety Signal Stratified by Gender and Dose in Pooled Study BB2121-MM-001 Alone

Dose	**CRS**	**Gr3+ CRS**	**Gr2+ NT**		**Gr5 AE***
			Male	Female	
150	2/4 (50%)	0/4	0/4	-	2/4 (50%)
300	53/70 (76%)	4/70 (6%)	0/38	6/32 (19%)	18/70 (26%)
450	52/54 (96%)	3/54 (6%)	4/34 (12%)	2/20 (10%)	10/54 (18.5%)

Source: Adapted from Applicant's submission. In each cell, numerator indicates the responder number and denominator indicates overall N number in the pooled study. Number in parentheses indicates the response rate. Grade 5 AE data updated 3 on December 28th 2020.

Exposure Response for Cytokine Release Syndrome (CRS) and Neurotoxicity (NT):

There seems to be increased rate of CRS with increased dose (Table 26) or exposure (Table 28). Sex is not a significant predictive marker with CRS and GR2+ neurotoxicity. CD3 expansion rate is a positive predictive marker for CRS and GR2+ NT (Table 28 and Table 29).

Table 28: Estimated Parameters in Multivariable Logistic Regression for ER Relationship for Safety (CRS)

	Estimate	Std. Error	P value
Intercept	-6.59	2.57	0.01*
Log (Exp_Rate)	0.905	0.28	0.00127**
Factor (Sex): Female	0.046	0.76	0.9523
PRBMP	0.0129	0.01	0.264
PLSB	-0.0018	0.001	0.085

Source: FDA's analysis

Table 29: Estimated Parameters in Multivariable Logistic Regression for ER Relationship for Safety (GR2+ Neurotoxicity)

	Estimate	Std. Error	P value
Intercept	-10.8	4.86	0.026*
Log (Exp_Rate)	0.81	0.46	0.0783
Factor (Sex): Female	0.82	0.83	0.32
PRBMP	-0.02	0.014	0.15
PLSB	0.0012	9.2×10^{-4}	0.21

Source: FDA's analysis

6.3.6 Exploratory Analysis for Dose Range

Applicant's proposal to target 450 million CAR+ T cells is acceptable, however the actual administered dose range is relatively wide. The actual dosing range in patients who received 450 million cells targeted dose was 205-520 million cells for the pooled studies (BB2121-CRB-401 and BB2121-MM-001) and 340-520 million cells for the pivotal study BB2121-MM-001 (Figure 16). In pivotal study BB2121-MM-001, majority of patients (~90%) received initial dose below 460 million cells. Given the dose-response relationship, the dose range is recommended to be above 300 x 10^6 CAR+ T cells. Due to concern of the limited patient's number (n=5 in pivotal trial) at dose level above 460 million cells, exploratory analyses on efficacy (ORR and CR rate) and safety (CRS and neurotoxicity rate) was conducted.

Overall, lowering the upper bound of dose range from 540 to 460 million cells is predicted to be associated with a decreased CRS rate (~3%) as well as a decreased ORR (~3%). No obvious CR rate or GR2+ neurotoxicity rate was predicted to change in the 460-540 million cells level.

Efficacy:

ORR:

Observed ORR rate was higher in patients with an actual dose above 460 million cells compared to that in patients with a lower actual dose in both pooled study and pivotal study as shown below. Logistic regression also predicted ~3% ORR increase for patients with the actual dose of 520 million cells compared to that for patients with the actual dose of 460 million cells.

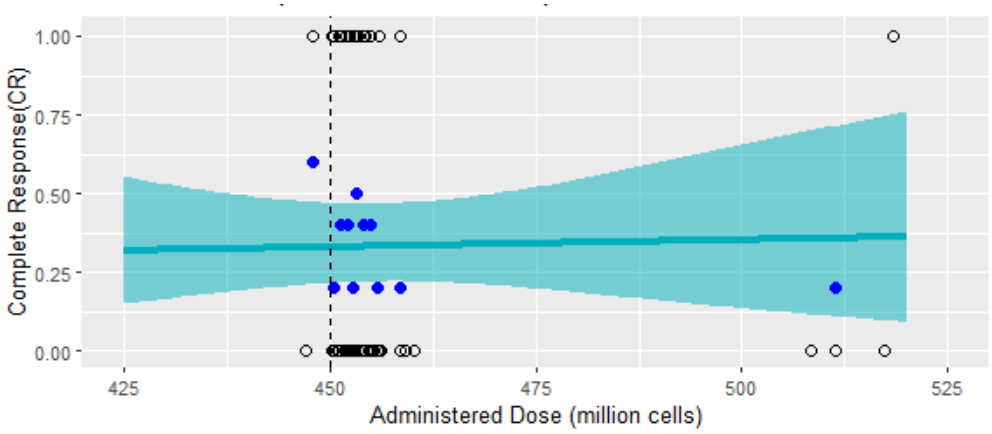
Table 30: Observative ORR in subpopulations with different initial dose

	>=460mg	**<460mg**	**>=460mg**	**<460mg**
	Pooled studies		**B2121-MM-001**	
N	10	82	5	49
ORR	9 (90%)	64 (78%)	4 (80%)	37 (75%)

CR:

An exploratory analysis of actual dose and complete response rate based on 54 patients with the targeted dose of 450 million cells in the pivotal study B2121-MM-001 was conducted. Consistent with the overall dose-CR rate relationship (Table 16, Figure 8), the relationship is flat. When we divided the patients (n=54) into 11 subgroups ranked based on their actual dose levels, no strong evidence suggesting that patients dosing between 460-520 mg (20% CR: 1/5, the most right blue dot in the following figure) has significant lower efficacy than the other groups (there are four groups (blue dots in the middle) having dosing around 450 mg also had 20% CR). (Figure 16).

Figure 16: Dose response for CR Rate in Pivotal Study B2121-MM-001 Patients who Had Planned Dose of 450 Million Cells



Source: Reviewer's Analysis. X axis is administered actual dose of CAR+ Cells (million cells). Y axis is CR rate. Dashed line is 450 million cells. Solid blue line is the logistic regression of the predicted CR rate. The area is the 95% CI. Blue dots represent the median actual dose level and CR rate in 5 patients in individual subgroups.

Safety:

There is a positive trend between actual dose vs. all grade CRS and Grade 3+ CRS as discussed previously. Cutting the upper end of the dose range from 520 to 460 million cells is predicted to reduce CRS rate from 97% to 94% and grade 3+ CRS from 11% to 8%. There is no obvious positive dose-GR2+ NT trend in the pooled studies or the pivotal study alone.