Clinical Pharmacology BLA Review

Division of Clinical Evaluation and Pharmacology/Toxicology

Office of Tissues and Advanced Therapy

BLA	125736/0
Product	ABECMA (idecabtagene vicleucel, Ide-cel, bb2121) cell suspension for infusion
Sponsor	Celgene Corporation
Indication	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
Date Received	July 27, 2020
Reviewer	Xiaofei Wang, Ph.D. Clinical Pharmacology Reviewer, General Medicine Branch 2 Division of Clinical Evaluation and Pharmacology/Toxicology
RPM	Colleen Caldwell Juliane Carvalho
Through	Tejashri Purohit-Sheth, M.D., FACAAI, CQIA Director Division of Clinical Evaluation and Pharmacology/Toxicology

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1 EXECUTIVE SUMMARY

Celgene Corporation seeks approval of its BLA for ABECMA (idecabtagene vicleucel, Ide-cel, BB2121) 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. ABECMA is a genetically modified autologous T cell immunotherapy product consisting of T cells transduced with anti-B-cell maturation antigen (BCMA) chimeric antigen receptor (CAR) lentiviral vector (LVV). ABECMA is to be administered as a single intravenous infusion. The proposed target dose of ABECMA is 450 x 10^6 CAR-positive T cells with a range of (b) (4) x 10^6 CAR-positive T cells.

The clinical pharmacology section of this biologics license application (BLA) is supported by two clinical studies: one supportive Phase 1 clinical study (CRB-401) and a pivotal Phase 2 study in subjects with relapsed and/or refractory multiple myeloma (RRMM).

After infusion, ide-cel proliferated and underwent rapid multi-log expansion, with the maximum peak expansion occurring at a median of 11 days. The exposure of ide-cel increased in a dose-dependent manor. Exploratory dose/exposure-response relationship analysis indicates within the dose range of 140.8 to 518.4 x 10^6 CAR+ T cells: a higher dose of ide-cel was associated with higher overall response rate (ORR) and a higher cytokine release syndrome incidence rate. A higher cellular expansion of ide-cel was associated with higher ORR and complete response (CR) rates. Additional covariates such as sex (female), baseline soluble BCMA levels and usage of steroids in last prior medications were potentially positively associated higher ORR. A higher cellular expansion of ide-cel was also associated with incidence of any grade of CRS. Due to high inter-subject variability of ide-cel expansion, ide-cel expansion overlapped across doses. This may due to heterogenicity of ide-cel drug product composition with respect to different T cell subsets.

Anti-drug antibodies (ADAs) did not develop in the first month post-infusion of ide-cel. About 43.8% of the subjects were ADA-positive by Month 6 post-infusion. Ide-cel expansion occurs in the first month after infusion. The presence of ADA did not appear to have a clinically significant impact on pharmacokinetics, safety or efficacy.

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

2 INTRODUCTION

ABECMA is a B-cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy indicated 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.

Autologous T cells transduced ex vivo with the anti-BCMA02 CAR LVV express the anti-BCAM CAR on the T cell surface. The ABECMA 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 ABECMA 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 ABECMA results in CAR+ T cell proliferation, cytokine secretion, and subsequent cytolytic killing of BCMA-expressing cells.

The final product of ABECMA is formulated and cryopreserved in a solution containing Plasma-Lyte A ad CryoStor® CS10. ABECMA is provided as a single-dose of infusion in one or more bags containing a total of (b) (4) x 10^6 CAR+ T cells.

This application is supported by a supportive Phase 1 study and a pivotal Phase 2 study:

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

3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

General Cellular Kinetics/Pharmacokinetics

- Following infusion, ide-cel proliferated and underwent rapid multi-log expansion, with the maximum peak expansion occurring at a median of 11 days across the evaluated dose range of ide-cel: 150 to 540 x 10^6 CAR+ T cells. Persistence of (b) (4) was observed up to 1 year.
- Within the dose range evaluated, ide-cel exposure increased in a dose-dependent manor. However, due to high inter-subject variability in ide-cel PK profiles, ide-cel exposure overlapped across different dose levels. This may due to heterogenicity of ide-cel drug product composition with respect to different T cell subsets.
- Ide-cel expansion after the second dose was substantially lower than ide-cel expansion after the first dose in retreated subjects.
- Exploratory multivariate regression analysis indicates that ide-cel vector copy number was positively associated with ide-cel dose normalized $AUC_{0\text{-}28d}$ and Cmax. Subject's body weight and the percentage of CD3+CAR+CCR7+CD27- T cells subset in ide-cel final product were negatively associated with ide-cel dose normalized $AUC_{0\text{-}28d}$ and Cmax.

Pharmacodynamics

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

Dose/Exposure-Response Relationship

Ide-Cel Dose

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

Ide-Cel Exposure/Expansion

- A higher cellular expansion ($AUC_{0\text{-}28d}$, Cmax and expansion rate) of ide-cel was associated with both higher ORR and complete response (CR) rate. In addition to ide-cel expansion, covariates such as sex (female), baseline soluble BCMA levels and usage of steroids in last prior medications were potentially positively associated with a higher ORR.
- A higher cellular expansion of ide-cel was associated with any grade of CRS incidence. Additionally, potential association was indicated between pre-lymphodepletion TNFα level and any grade of CRS incidence.
- There was no apparent association between ide-cel exposure and incidence of any grade neurotoxicities (NT).
- A higher ide-cel cellular expansion of ide-cel appeared to be associated with greater reduction in post-infusion BCMA levels.
- A higher ide-cel cellular expansion of ide-cel was associated with higher likelihood of achieving minimal residual disease (MRD) negativity.

Immunogenicity

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

Replication-competent Lentivirus (RCL) Testing

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

4 LABELING COMMENTS

The clinical pharmacology reviewer has reviewed the package insert for BLA 125736 and finds it acceptable pending the following revisions shown below.

12. CLINICAL PHARMACOLOGY

Reviewer's Comments:

Per FDA Guidance for Industry – Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format (December 2016), *the CLINICAL PHARMACOLOGY section of the labeling must contain the following subsections:*

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

Please include pharmacodynamic subsection in your labeling.

12.1. Mechanism of Action

ABECMA is a chimeric antigen receptor (CAR)-positive T cell therapy targeting B-cell maturation antigen (BCMA), which is expressed on the surface of normal and malignant plasma cells. The CAR construct includes an anti-BCMA scFv-targeting domain for antigen specificity, a transmembrane domain, a CD3-zeta T cell activation domain, and a 4-1BB costimulatory domain. Antigen-specific activation of ABECMA results in CAR-positive T cell proliferation, cytokine secretion, and subsequent cytolytic killing of BCMA-expressing cells.

12.3. Pharmacokinetics

Reviewer's Comments:

Please update Table 5 based on clinical reviewer recommended therapeutic dose range: 300 x 10^6 – 460 x10^6 CAR+ T cells.

PK information in responding and responding subjects, subjects using tocilizumab and/or corticosteroids for CRS management was updated based on clinical reviewer's analysis.

Following ABECMA infusion, the CAR-positive cells proliferate and undergo rapid multi-log expansion followed by a bi-exponential decline. The median time of maximal expansion in peripheral blood (T_{max}) occurred 11 days after infusion.

ABECMA can persist in peripheral blood for up to 1 year post-infusion. A summary of T_{max}, $AUC_{0\text{-}28days,}$ and C_{max} by target dose level and across doses is provided in Table 5.

Table 5: Pharmacokinetic Parameters of ABECMA by Target Dose Level in Subjects with Relapsed/Refractory Multiple Myeloma in the KarMMa Study

Pharmacokinetic Parameter	Summary Statistic	[150 x 10^6] CAR-Positive T Cells	[300 x 10^6] CAR-Positive T Cells	[450 x 10^6] CAR-Positive T Cells	Total [150 to 450 × 10^6] CAR-Positive T Cells
T_{max} (days)	Median (Range)	14 (11-14) N = 4	11 (7-30) N = 69	11 (7-28) N = 54	11 (7-30) N = 127
C_{max} (copies/mcg)	Geometric mean (geometric CV%)	204,229 (169) N = 4	180,185 (210) N = 69	321,117 (126) N = 54	231,278 (178) N = 127
$AUC_{0\text{-}28days}$ (days*copies/mcg)	Geometric mean (geometric CV%)	1,942,929 (154) N = 4	2,138,414 (215) N = 68	4,277,327 (152) N = 53	2,860,340 (197) N = 125

$AUC_{0\text{-}28days}$ = area under the curve of the transgene level from time of dose to 28 days post-infusion; C_{max} = the maximum transgene level; T_{max} = time of maximum observed transgene level.

ABECMA transgene levels were positively associated with objective tumor response (partial response or better). The median C_{max} levels in responders (N =~~93~~ 73) were approximately 4.7-fold higher compared to the corresponding levels in non-responders (N =~~34~~ 28). Median $AUC_{0\text{-}28days}$ in responding subjects (N =~~93~~ 73) was approximately 5.5-fold higher than non-responders (N =~~32~~ 26).

Tocilizumab and Corticosteroid Use

Some patients required tocilizumab and/or corticosteroid for the management of CRS. ABECMA can continue to expand and persist following tocilizumab or steroid administration *[see Warnings and Precautions (5.1)]*.

Patients with CRS treated with tocilizumab had higher ABECMA cellular expansion levels, as measured by 1.4-fold and 1.6-fold higher median C_{max} (N = 66) and $AUC_{0\text{-}28days}$ (N = 65), respectively, compared to patients who did not receive tocilizumab (N = 60 for C_{max} and N = 59 for $AUC_{0\text{-}28days}$).

Patients with CRS treated with corticosteroids had higher ABECMA cellular expansion levels, as measured by 1.7-fold and 2.2-fold higher median C_{max} (N = 18) and $AUC_{0\text{-}28days}$ (N = 18), respectively, compared to patients who did not receive corticosteroids (N = 108 for C_{max} and N = 106 for $AUC_{0\text{-}28days}$).

Specific Populations

Geriatric

Age (range: 33 to 78 years) had no significant impact on expansion parameters *[see Use in Special Populations (8.5)]*.

Pediatric

The pharmacokinetics of ABECMA in patients less than 18 years of age have not been evaluated.

Patients with Hepatic/Renal Impairment

Hepatic and renal impairment studies of ABECMA were not conducted.

Patients with Other Intrinsic Factors

Gender, race, and ethnicity had no significant impact on ABECMA expansion parameters. Subjects with lower body weight had higher expansion. Due to high variability in pharmacokinetic cellular expansion, the overall effect of weight on the pharmacokinetics of ABECMA is considered not to be clinically relevant.

5 RECOMMENDATIONS

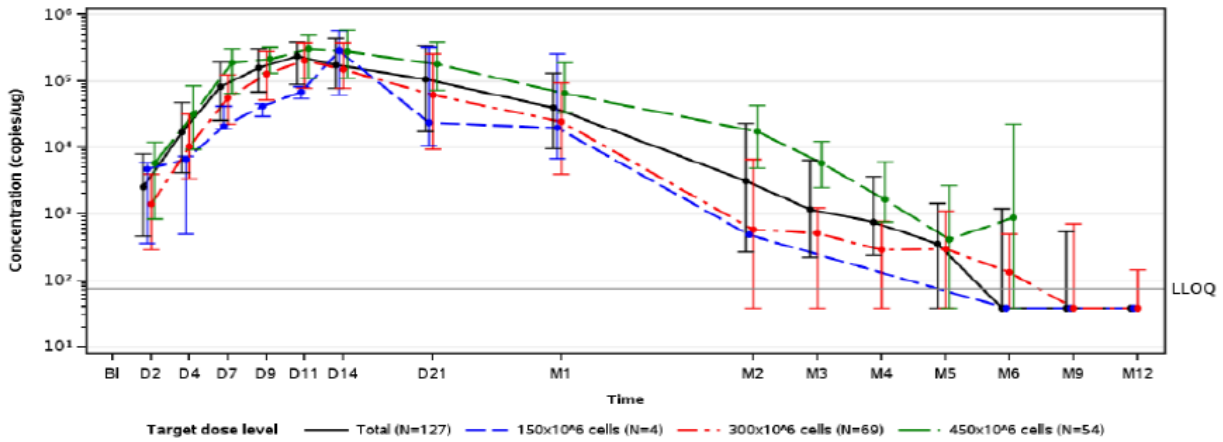
The clinical pharmacology information in this BLA is acceptable, provided that satisfactory agreement is reached between the sponsor and the FDA regarding the language in Section 12 of the package insert. Please refer to section 4 for detailed Labeling Recommendations.

6 COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

6.1 General Pharmacology and Cellular Kinetic/Pharmacokinetic Characteristics

As shown in Figure 1, following ide-cel infusion, the cells proliferated and underwent rapid multi-log expansion, with the maximum peak expansion occurring at a median of 11 days across the evaluated dose range of ide-cel: 150 to 540 x 10^6 CAR+ T cells.

Figure 1. Median (Q1, Q3) Transgene Levels of Ide-Cel by Dose Levels Following a Single Infusion (Study MM-001)



B = baseline; D = day; LLOQ = lower limit of quantification; M = month; PK = pharmacokinetic.
Solid grey horizontal line represents lower limit of quantification (75 copies/ug).
The plot shows median (Q1, Q3) time course profile.

Source: Applicant. Summary of Clinical Pharmacology: Figure 1.

Table 1 summarized the PK parameters of ide-cel in Study MM-001. With the increase of dose, exposure of ide-cel increased. PK results from Study CRB-401 also showed dose-depend increase of ide-cel exposure.

Table 1. Summary of Exposure Parameters of Ide-Cel (Study MM-001)

Parameter	Statistic	Target Dose (x10^6 CAR+ T cells)		
		150	300	450
C_{max} (copies/µg)	N	4	69	54
	Arithmetic Mean (SD)	317,794 (284,926)	337,281 (368,619)	455,054 (340,203)
	Median (range)	287,407 (74,733 – 621,627)	206,398 (7,078 – 1,757,151)	356,472 (13,158 – 1,717,248)
	Geometric Mean (Geometric CV)	204,229 (169.3%)	180,185 (210.0%)	321,117 (126.1%)
$AUC_{0\text{-}28days}$ (days*copies/µg)	N	4	68	53
	Arithmetic Mean (SD)	3,262,626 (4,112,563)	4,184,630 (4,835,831)	6,546,833 (5,327,388)
	Median (Range)	1,382,564 (888,838 – 9,396,539)	2,337,323 (75,456 – 24,669,681)	4,611,110 (138,896 – 23,790,037)
	Geometric Mean (Geometric CV)	1,942,929 (153.9%)	2,138,414 (215.0%)	4,277,327 (151.6%)
$AUC_{0\text{-}3M}$ (days*copies/µg)	N	2	62	51
	Arithmetic Mean (SD)	10,535,484 (13,555,616)	6,045,163 (7,681,749)	9,791,689 (8,961,378)
	Median (Range)	10,535,484 (950,216 – 20,120,752)	3,066,558 (118,860 – 40,341,361)	6,182,578 (175,096 – 38,862,714)
	Geometric Mean (Geometric CV)	4,372,535 (1023%)	2,952,312 (212.9%)	5,955,266 (170.3%)

$AUC_{0\text{-}28days}$ = area under the curve of the transgene level from time of dose to 28 days postinfusion; $AUC_{0\text{-}3M}$ = area under the curve of the transgene level from time of dose to 3 months postinfusion; CAR = chimeric antigen receptor; C_{max} = maximum transgene level; CV = coefficient of variation; SD = standard deviation

Source: Applicant. Clinical Pharmacology Report.

In general, the exposure of ide-cel increased in a dose-dependent manor across the dose range evaluated. Univariate logistic regression analysis indicated that ide-cel actual dose was positively associated with ide-cel PK parameters (Table 2).

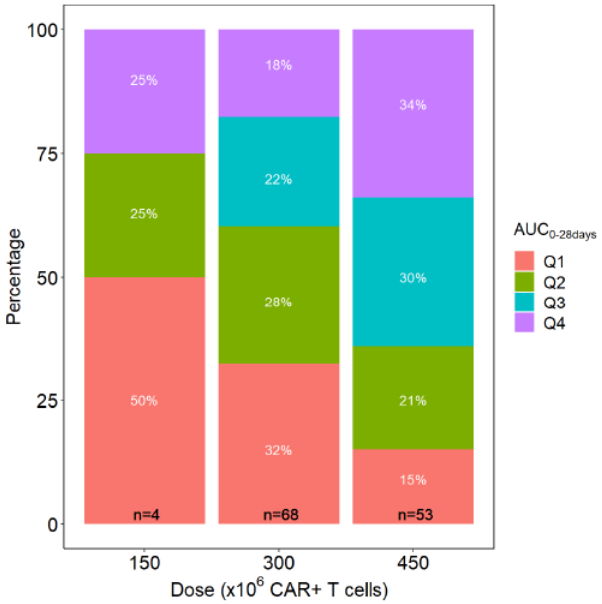
Table 2. Univariate Correlations between Ide-cel Dose and Pharmacokinetic Parameters

PK Parameter	Estimate	Standard Error	P value
$LnAUC_{0\text{-}28d}$	0.003935	0.001317	0.0034**
LnCmax	0.002936	0.001234	0.0189*
LnExprate	0.002967	0.001192	0.0141*

Quantile analysis also showed this similar dose-dependent increasing trend in exposure (Figure 2). However, due to high inter-subject variability, there were overlaps in exposures between the doses. Ide-cel is an autologous CAR T cell product. Heterogenicity of ide-cel product composition with

respect to T cell subsets may contribute to observed high inter-subject variability and overlap of ide-cel exposure across different dose levels. The distribution of dose normalized $AUC_{0\text{-}28d}$ was similar between three dose levels, with no appreciable trend remaining with dose.

Figure 2. Relative Contribution of the Quantiles of $AUC_{0\text{-}28d}$ in Each Dose Level of Ide-Cel (Study MM-001)



$AUC_{0\text{-}28days}$ = area under the curve of the transgene level from time of dose to 28 days postinfusion; CAR = chimeric antigen receptor
Note: Q1-Q4 are the first (Q1), second (Q2), third (Q3) and fourth (Q4) quartiles of the $AUC_{0\text{-}28days}$ distribution.

Source: Applicant. Summary of Clinical Pharmacology: Figure 4.

Idel-cel can persist in peripheral blood for up to one-year post-infusion. At 12 months after infusion, 36.4% of subjects in Study MM-001 had detectable transgene levels (Table 3).

Table 3. Persistence of Ide-cel Over Time (Study MM-001)

Visit	Total Number of Observations	Number of Observations with Detectable 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%)

BLQ= below limit of quantification; PK = pharmacokinetic.

Source: Applicant. Clinical Study Report: BB2121-MM-001.

6.1.1 Factors Impacting Cellular Kinetics/Pharmacokinetics of Ide-Cel

To explore factors impacting cellular kinetics/pharmacokinetics of ide-cel, the applicant conducted univariate analysis and assessed the following factors:

- 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 Group (ECOG) performance status, concomitant medications of tocilizumab or corticosteroids administered to manage CRS, bridging therapy;
- Baseline (pre-lymphodepletion chemotherapy)/Preinfusion variables, including serum soluble BCMA (sBCMA) levels, urine monoclonal protein (m-protein); serum m-protein; and
- Antidrug Antibody (ADA) status
- Product attributes:
  - Lot release attributes: T cell percentage (% CD3+ of CD45+), viable cell percentage (% viable), CAR T cell percentage (% CD3+CAR+), vector copy number (copies/CAR+ T cell), CD137 activation (% CD137+ cells), total number of ide-cel CAR T cell infused, and cell concentration (cells/mL); and
  - Characterization attributes: CD4/CD8 ratio, antigen specific cytokine secretion (IFNγ, TNF-α, IL-17a, GM-CSF, and IL-8), memory T cell composition (CCR7 x CD45RA, CD28 x CCD27, CCR7 x CD27), and live cell (annexin V-/ToPro3-).

Univariate analysis showed that the following baseline factors were significantly associated with ide-cel exposure (Cmax and AUC0-28d): body weight, body surface area, baseline soluble BCMA. Ide-cel exposures appeared to decrease with increasing body weight and body surface area and showed an increasing trend with baseline sBCMA (Table 4). Since BSA is highly correlated with body weight and the effects of BSA are considered secondary to the effects of body weight, further assessment of the clinical relevance of these effects focused on body weight. Other factors, such as age, race, ethnicity, sex, ADA status, and number of prior anti-MM therapies were not found to influence the cell expansion parameters.

Table 4. Univariate Correlations between Dose-Normalized $AUC_{0\text{-}28d}$ and Statistically Selected 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: Applicant. Clinical Pharmacology Report: Table 9.

Following product attributes showed potential association with ide-cel expansion (PK parameters) based on univariate analysis: ide-cel cell concentration, dose, memory T cell status (CD3+CAR+CCR7+CD27-), and vector copy number (VCN) (Table 5).

Table 5. Ide-cel Drug Product Attributes Correlated to Pharmacokinetics (Study MM-001)

Attribute	Clinical Endpoint	Relationship Classification	Effect Size	p-value	Q
% CD3+CAR+ CCR7+CD45RA-	$AUC_{0\text{-}28\ days}$	Potential Relationship	-0.365	5.1×10^{-5}	0.004
	C_{max}	Potential Relationship	-0.340	1.6×10^{-4}	0.007
Vector Copy Number	$AUC_{0\text{-}28\ days}$	Potential Relationship	0.254	0.005	0.049
	C_{max}	Potential Relationship	0.262	0.003	0.030
Dose	$AUC_{0\text{-}28\ days}$	Potential Relationship	0.240	0.007	0.065
	C_{max}	Potential Relationship	0.219	0.013	0.099

Source: Applicant. Elucidation of Structure and Other Characteristics – Clinical Correlative Analysis.

Based on applicant's univariate analysis, reviewer conducted multivariate logistic analysis to explore factors impacting ide-cel cellular kinetic/pharmacokinetic parameters (dose normalized $AUC_{0\text{-}28d}$ and dose normalized Cmax) besides dose. As shown in Table 6, ide-cel vector copy number was positively associated with ide-cel dose normalized $AUC_{0\text{-}28d}$ and Cmax. Subject's body weight and the percentage of CD3+CAR+CCR7+CD27- T cells subset in ide-cel final product were negatively associated with ide-cel dose normalized $AUC_{0\text{-}28d}$ and Cmax.

Table 6. Multivariable Analysis of Potential Impacting Factors for Ide-cel Pharmacokinetic Parameters (Study MM-001)

Covariates/Attributes	PK Parameter	Estimate	Standard Error	P value
Intercept	$LnAUC_{0\text{-}28d}$	1.006	0.9333	< 2e-16***
	LnCmax	7.4047	0.8731	1.28e-13***
Body Weight	$LnAUC_{0\text{-}28d}$	-0.0195	0.0083	0.0213*
	LnCmax	-0.0202	0.0078	0.0108*
Sex (Female)	$LnAUC_{0\text{-}28d}$	-0.1457	0.2596	0.5756
	LnCmax	-0.0966	0.2428	0.6916
Baseline Soluble BCMA	$LnAUC_{0\text{-}28d}$	0.00003	0.0003	0.9297
	LnCmax	0.0002	0.0003	0.4610
VCN	$LnAUC_{0\text{-}28d}$	0.1681	0.0658	0.0120*
	LnCmax	0.1718	0.0616	0.0062**
% CD3+CAR+CCR7+CD27-	$LnAUC_{0\text{-}28d}$	-0.0347	0.094	0.0002***
	LnCmax	-0.0285	0.0086	0.0012**
% CD3+CAR+CCR7+ CD45RA-	$LnAUC_{0\text{-}28d}$	0.0121	0.0082	0.1454
	LnCmax	0.0094	0.0077	0.2235

6.1.2 Cellular Kinetics/Pharmacokinetics of Ide-cel Retreatment

As of PK data cutoff date on April 19, 2019, 15 subjects received a second dose of ide-cel ranging from 300 – 450 x 10^6 CAR+ T cells. As shown in Table 7, Ide-cel expansion was substantially limited after the second dose, compared to ide-cel expansion after the first dose in retreated subjects.

Table 7. Summary of Ide-cel Pharmacokinetic Parameters in Subjects who Were Retreated with a Second Dose of Ide-cel (Study MM-001)

Pharmacokinetic Parameter	Initial Treatment Target Dose (CAR+ T cells) 300 to 450 x 10^6	Retreatment Target Dose (CAR+ T cells) 300 to 450 x 10^6
C_{max} (copies/µg)	208,020 (169) N =15	47,613 (351) N = 15
T_{max} (days)	11 (9-21) N =15	7 (2-9) N = 15
T_{last} (days)	143 (30-254) N =15	29 (7-63) N = 15
$AUC_{0\text{-}28days}$ (days*copies/µg)	2,394,290 (196) N =15	378,110 (421) N = 12
$AUC_{0\text{-}3M}$ (days*copies/µg)	3,140,886 (268) N =14	667,555 (399) N = 9
$AUC_{0\text{-}6M}$ (days*copies/µg)	4,075,241 (254) N =12	681,758 (367) N = 9
$AUC_{0\text{-}9M}$ (days*copies/µg)	4,083,610 (253) N =12	685,986 (383) N = 9

Source: Applicant. Clinical Study Report for MM-001: Table 45.

6.2 Pharmacodynamics of Ide-Cel

6.2.1 Immune-related Soluble Factors

A panel of 27 soluble immune-related factors (including markers of inflammation, CRP and ferritin) was measured to understand pharmacodynamic changes post ide-cel infusion. After infusion of ide-cel, most of T cell activation-related soluble factors were induced in a dose-dependent manor (Table 8). For majority of these soluble factors, peak levels were generally observed within 7 days post-infusion and the levels returned to baseline within first month after infusion.

Table 8. Baseline and Peak Levels (Cmax) of IL-2, IL-6, IFN-γ and TNF Up to Month 1 (Study MM-001)

Soluble Factor (units)	Endpoint	Ide-cel (CAR+ T cells) Target Dose			
		$150x10^6$ (N = 4) Median Q1, Q3	$300x10^6$ (N = 66) Median Q1, Q3	$450x10^6$ (N = 54) Median Q1, Q3	Total $150 to 450 x 10^6$ (N = 124) Median Q1, Q3
IL-2 (pg/mL)	Baseline	8.30 7.2, 9.1	8.35 5.4, 14.0	18.00 9.8, 34.0	11.00 6.6, 21.0
	C_{max}	17.50 13.5, 25.0	40.00 23.0, 23.0	57.00 37.0, 85.0	44.00 28.0, 71.5
IL-6 (pg/mL)	Baseline	7.85 7.0, 9.8	12.00 6.6, 20.0	13.00 8.2, 25.0	12.00 7.2, 22.0
	C_{max}	76.50 31.0, 5952.0	304.00 60.0, 4130.0	3840.00 216.0, 15950.0	821.00 75.0, 9645.0
INF-γ (pg/mL)	Baseline	26.5 21, 31	27.5 11, 55	78.0 40,162	40.5 19, 87
	C_{max}	67.0 57, 80	244.5 131, 647	1130.0 340, 9030	453.0 170, 1850
TNF (pg/mL)	Baseline	19.5 17, 28	19.0 14, 25	26.0 20, 33	22.0 17, 29
	C_{max}	46.5 31, 60	69.5 51, 90	114 62, 192	79.5 53, 131

C_{max} = maximum observed value measured up to M1; ide-cel = idecabtagene vicleucel; IL = interleukin; IFN-γ= interferon gamma; Q = quartile; TNF = tumor necrosis factor.
Note: Baseline = day of ide-cel infusion;

Source: Applicant. BB2121-MM-001-BM Biomarker Report: Table 4.

Immune-related Soluble Factors and Tumor Characteristics

The relationship between immune-related soluble factors and tumor characteristics was evaluated. After ide-cel infusion, the Cmax of IL-18 was elevated in subjects with ≥ 50% tumor burden. Subjects with high baseline levels of soluble BCMA (sBCMA) (≥ 75th percentile), showed increased baseline levels of several pro-inflammatory factors, including Ang-, ferritin, IL-, CRP, and MIP1α and decreased levels of Ang-1, IL-4 and IFN-γ, compared with subjects with lower sBCMA levels (< 75th percentile). Elevated pre-infusion sBCMA levels were associated with CRS requiring corticosteroids compared to CRS not requiring steroids.

Immune-related Soluble Factors and Efficacy Response

There was no association between pre-infusion immune-related soluble factors levels and response. Peak concentrations of CRP, IFN-γ, IL-10 and IL-6 were higher in responders compared to non-responders ($p<0.05$).

Immune-related Soluble Factors and Safety Response

Cytokine Release Syndrome

Within the first day after infusion, seven immune-related soluble factors (GM-CSF, IFN-γ, IL-10, IL-13, IL-2, IL-6, and IL-8) were rapidly induced to significantly higher levels in subjects with any grade of CRS compared with subjects with no CRS (Table 9). All above soluble factors except IL-15, remained at significantly higher levels through peak concentrations. The following additional soluble factors were significantly elevated at the time of peak concentration in

subjects with Grade ≥ 1 CRS: CRP, granzyme B, IL-18, IL-2Rα, IL-5, MIP-1β, TNF, and TNFSF6 (FasL).

Table 9. Early Post-infusion Fold Change (Day 1/Baseline) of Soluble Factors by Cytokine Release Syndrome (CRS) (Study MM-001)

Soluble Factor (units)	Grade 0 CRS (N = 20) Median Q1, Q3	Grade ≥ 1 CRS (N = 104) Median Q1, Q3	p-value[a]	Grade 0 CRS (N = 20) Median Q1, Q3	Grade 1 + 2 CRS (N = 97) Median Q1, Q3	Grade ≥ 3 CRS (N = 7) Median Q1, Q3	p-value[a]
GM-CSF (pg/mL)	8.45 5.7, 13.5	23.00 13.0, 53.0	0.0010	8.45 5.7, 13.5	21.00 13.0, 48.0	54.00 21.0, 197.0	0.0011
IFN-γ (pg/mL)	70.5 45, 133	288.0 129, 578	< 0.0001	70.5 45, 133	245.0 127, 563	911.0 340, 1080	< 0.0001
IL-10 (pg/mL)	92.0 46, 260	242.0 126, 482	0.0172	92.0 46, 260	234.0 121, 479	465.0 338, 725	0.0148
IL-13 (pg/mL)	4.85 3.0, 10.8	15.50 8.9, 32.0	0.0021	4.85 3.0, 10.8	16.00 9.3, 35.0	15.00 3.0, 30.0	0.0103
IL-2 (pg/mL)	15.00 9.7, 33.0	41.00 25.0, 75.5	0.0001	15.00 9.7, 33.0	40.00 25.0, 70.0	68.00 47.0, 116.0	0.0003
IL-6 (pg/mL)	26.50 18.5, 39.5	114.50 47.0, 381.0	< 0.0001	26.50 18.5, 39.5	102.00 46.0, 312.0	184.00 55.0, 2385.0	0.0001
IL-8 (pg/mL)	14.00 11.5, 18.5	29.00 15.0, 52.0	0.0144	14.00 11.5, 18.5	25.00 15.0, 48.0	154.00 29.0, 879.0	0.0136

CRS = cytokine release syndrome; GM-CSF = granulocyte macrophage colony stimulating factor, ide-cel = idecabtagene vicleucel; IFN-γ = interferon gamma, IL = interleukin; Q = quartile.

[a] p-values are based on the Mann-Whitney-Wilcoxon test for comparing dichotomous groups or Kruskal-Wallis test for comparing three or more groups, with multiplicity adjusted p-value using the Holm step-down Bonferroni method across different cytokine biomarkers

Note: D1 = Day 1 post ide-cel infusion

Source: Applicant. BB2121-MM-001-BM Biomarker Report: Table 7.

Neurotoxicity

As shown in Table 10, nine immune-related soluble factors (GM-CSF, IFN-γ, IL-10, IL-2, IL-5, IL-6, IL-8, and IL-13) were rapidly induced to significantly higher levels within the first day post infusion in subjects with any grade of neurotoxicity (NT) compared with subjects with no NT. Substantial higher values of Cmax of ferritin, granzyme B, IFN-γ, IL-10, IL-15, IL-18, IL-2, IL-2Rα, IL-5, IL-6, IL-8, MIP-1β, and TNF were associated with any grade of neurotoxicity.

Table 10. Early Post-infusion Fold Change (Day 1/Baseline) of Soluble Factors by Neurotoxicity (NT) (Study MM-001)

Soluble Factor (units)	Grade 0 iiNT (N = 102) Median Q1, Q3	Grade ≥ 1 iiNT (N = 22) Median Q1, Q3	p-value[a]	Grade 0 iiNT (N = 102) Median Q1, Q3	Grade 1 iiNT (N = 11) Median Q1, Q3	Grade ≥ 2 iiNT (N = 11) Median Q1, Q3	p-value[a]
GM-CSF (pg/mL)	18.00 8.7, 35.0	22 59.00 29.0, 197.0	0.0001	18.00 8.7, 35.0	55.00 35.0, 140.0	83.00 18.0, 209.0	0.0006
IFN-γ (pg/mL)	162.0 89, 451	22 549.5 245, 3435	0.0008	162.0 89, 451	536.0 173, 3435	563.0 337, 3665	0.0040
IL-10 (pg/mL)	204.0 91, 383	22 488.5 260, 853	0.0020	204.0 91, 383	465.0 245, 735	554.0 260, 1265	0.0087
IL-15 (pg/mL)	64.00 42.0, 108.0	22 128.50 79.0, 165.0	0.0036	64.00 42.0, 108.0	93.00 70.0, 165.0	139.00 82.0, 308.0	0.0154
IL-2 (pg/mL)	32.00 19.0, 51.0	22 99.00 42.0, 188.0	0.0001	32.00 19.0, 51.0	85.00 45.0, 209.0	113.00 29.0, 188.0	0.0006
IL-6 (pg/mL)	60.00 35.0, 197.0	22 268.00 124.0, 3830.0	0.0026	60.00 35.0, 197.0	292.00 124.0, 8150.0	244.00 92.0, 611.0	0.0128
IL-8 (pg/mL)	19.00 12.0, 38.0	22 71.50 34.0, 183.0	0.0001	19.00 12.0, 38.0	88.00 30.0, 211.0	47.00 36.0, 183.0	0.0007
IL-5 (pg/mL)	32.00 15.0, 56.0	22 69.50 38.0, 114.0	0.0129	32.00 15.0, 56.0	72.00 38.0, 108.0	58.00 31.0, 218.0	0.0586[b]
IL-13 (pg/mL)	12.50 3.0, 22.0	27.50 14.0, 55.0	0.0293	12.50 3.0, 22.0	24.00 15.0, 32.0	41.00 12.0, 63.0	0.1172[b]

D1 = Day 1 post ide-cel infusion; GM-CSF = granulocyte macrophage colony stimulating factor, ide-cel = idecabtagene vicleucel; iiNT = investigator identified neurotoxicity; IFN-γ = interferon gamma, IL- = interleukin; Q = quartile.

[a] p-values are based on the Mann-Whitney-Wilcoxon test for comparing dichotomous groups or Kruskal-Wallis test for comparing three or more groups, with multiplicity adjusted p-value using the Holm step-down Bonferroni method across different cytokine biomarkers.

[b] p value > 0.05 is non-significant.

Data cutoff date: 16 Oct 2019

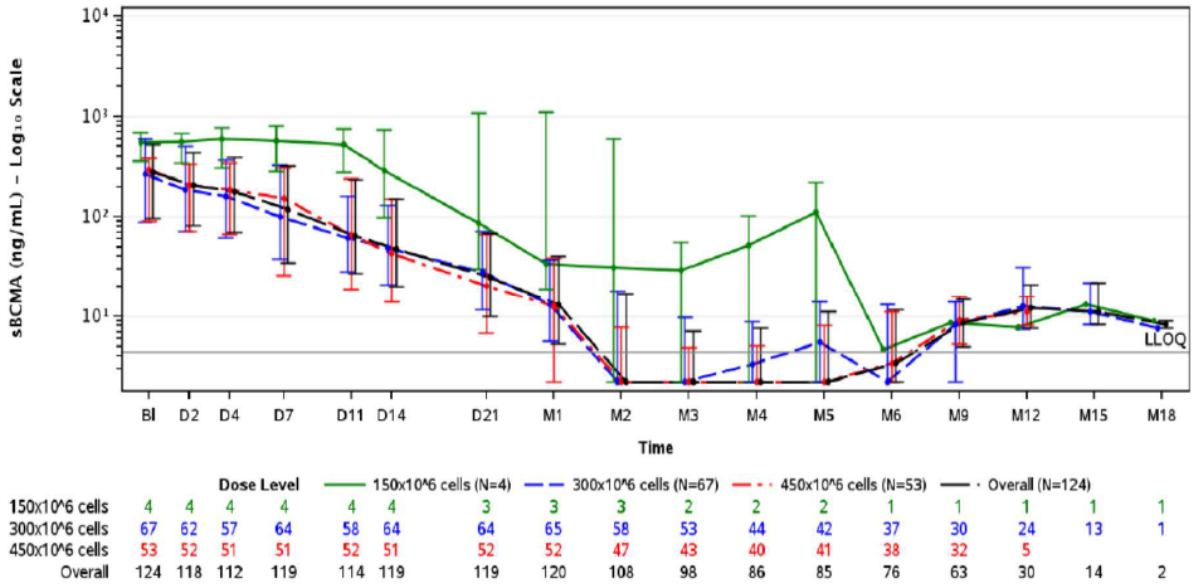
Source: Applicant. BB2121-MM-001-BM Biomarker Report.

6.2.2 Tumor-associated Soluble Factor – Soluble BCMA (sBCMA)

Soluble BCMA is a peripherally accessible biomarker of myeloma disease burden that correlates with the total number of normal and malignant plasma cells. As a marker of plasma cell abundance, serum sBCMA may provide a composite biomarker of disease burden for patients.

As shown in Figure 3, following ide-cel infusion, median serum sBCMA levels decreased from baseline of 276.0 ng/mL to below LLOQ (4.4 ng/mL) at Month 2. The magnitude and kinetics of sBCMA level changes from baseline to nadir were comparable for both 300 x 10^6 and 450 x 10^6 CAR+ T cells.

Figure 3. Median sBCMA Concentration (Quantile) Versus Time Course (Study MM-001)



Bl = Baseline (day of ide-cel infusion), D = Day; ide-cel = idecabtagene vicleucel; log10 = logarithm 10; M = Month; sBCMA = soluble BCMA;
Note: For biomarker-based assays where LLOQ values are available, all concentrations below the LLOQ were imputed to LLOQ/2. sBCMA LLOQ is 4.4, resulting in an imputed value of 2.2.
Data cutoff date: 16 Oct 2019

Source: Applicant. BB2121-MM-001-BM Biomarker Report: Figure 15.

Soluble BCMA and Efficacy Response

The relationship between sBCMA concentration and efficacy was assessed. Non-responders had higher median sBCMA concentrations at screening and baseline, compared to responders. After infusion of ide-cel, the median concentrations of sBCMA at nadir were below lower limit of quantification (LLOQ) (4.4 ng/mL) in responders and 243.0 ng/mL in non-responders. The percent of subjects with elimination to levels below LLOQ at nadir was 81.4% in responders compared to 13.51% in non-responders (Table 11).

Table 11. Serum sBCMA Concentration by Responders Versus Non-responders (Study MM-001, Ide-cel-treated Population)

Time Point	Responders	Non-Responders	p-value
Screening			
N	88	38	0.0287*
Median (ng/mL)	213.0	317.5	
Q1, Q3	74.0, 408.5	139.5, 635.3	
<LLOQ n (%)	0 (0)	0 (0)	

Time Point	Responders	Non-Responders	p-value
Baseline			
N	86	37	0.0108*
Median (ng/mL)	254.5	422.0	
Q1, Q3	86.75, 384.75	165.0, 781.5	
<LLOQ n (%)	0 (0)	0 (0)	
Nadir			
N	86	37	< 0.00001***
Median (ng/mL)	2.2	243.0	
Q1, Q3	2.2, 2.2	20.0, 485.0	
<LLOQ n (%)	70 (81.40%)	5 (13.51%)	

Soluble BCMA and Safety Response

Cytokine Release Syndrome

Serum sBCMA pre and post-infusion levels were investigated for association with CRS. As shown in Table 12, higher pre-infusion sBCMA levels at screening tended to be associated with any grade of CRS. After infusion of ide-cel, subjects with any grade CRS achieved lower median concentration at nadir and had a greater percentage of subjects with complete elimination of sBCMA than without CRS. There was no association observed for sBCMA levels between subjects with severe CRS (CRS grade ≥ 3) compared to subjects without severe CRS (CRS grade <3).

Table 12. Serum sBCMA Concentration by Cytokine Release Syndrome (Study MM-001)

Time Point	CRS Grade 0	CRS Grade ≥ 1	p-value
Screening			
N	18	108	0.0488*
Median (ng/mL)	333.5	215.5	
Q1, Q3	158.0, 723.5	82.75, 413.72	
<LLOQ n (%)	0 (0)	0 (0)	
Baseline			
N	18	105	0.1497
Median (ng/mL)	405.0	273.0	
Q1, Q3	98.75, 833.25	99.0, 458.5	
<LLOQ n (%)	0 (0)	0 (0)	
Nadir			
N	18	105	< 0.00001***
Median (ng/mL)	291.5	2.2	
Q1, Q3	4.98, 728.25	2.2, 11.0	
<LLOQ n (%)	4 (22.22%)	71 (67.62%)	

Higher pre-infusion sBCMA levels were observed in subjects with CRS requiring corticosteroids treatment compared to subjects with CRS not requiring corticosteroids treatment (Table 13). No

association was observed for sBCMA levels between subjects with CRS requiring tocilizumab treatment compared to subjects with CRS not requiring tocilizumab.

Table 13. Serum sBCMA Concentration by Use of Corticosteroids in Cytokine Release Syndrome Management (Study MM-001)

Time Point	With Corticosteroids	Without Corticosteroids	p-value
Screening			
N	19	89	0.6818
Median (ng/mL)	355.0	169.0	
Q1, Q3	251.0, 610.0	75.0, 384.5	
<LLOQ n (%)	0 (0)	0 (0)	
Baseline			
N	19	86	0.0155*
Median (ng/mL)	356.0	238.0	
Q1, Q3	300.0, 696.0	81.5, 395.25	
<LLOQ n (%)	0 (0)	0 (0)	
Nadir			
N	19	86	0.0164*
Median (ng/mL)	2.2	2.2	
Q1, Q3	2.2, 17.0	2.2, 6.55	
<LLOQ n (%)	(21.05%)	(68.27%)	

Neurotoxicity

Serum sBCMA pre- and post-infusion levels were investigated for association with neurtoxicities (NTs). There was no association of sBCMA levels pre or post infusion with any grade NT.

6.3 Exposure-Response Relationships

Exploratory exposure-response analysis was performed to evaluate the relationship between ide-cel dose/exposure and clinical response (safety and efficacy) endpoints. Exposure-response (E-R) relationship analysis was generally conducted based on Study MM-001. Per clinical reviewer, 18 subjects at the dose level of 150 x 10^6 CAR+ T cells from Study CRB-401 was included in efficacy assessment, therefore, these subjects were included in E-R analysis for efficacy endpoints.

6.3.1 Exposure-Response Relationship: Efficacy

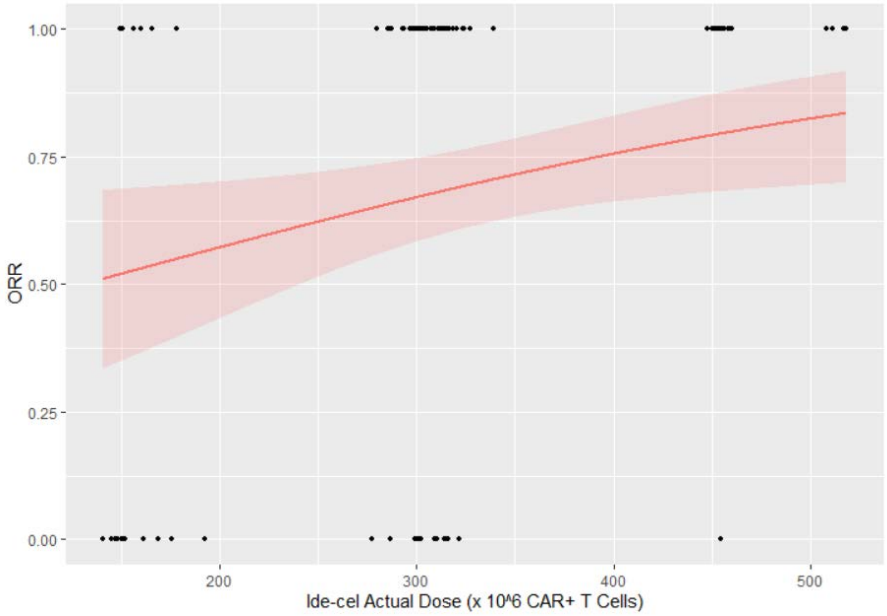
Dose-Response Relationship: Efficacy

Overall response rate is defined as percentage of subjects with partial response or better responses (including complete response, very good partial response and partial response). As shown in Table 14, the overall response rate (ORR) of ide-cel increased with the increase of dose across doses ranging from 150 to 450 x 10^6 CAR+ T cells. Univariate logistic regression analysis indicated positive association between ide-cel actual dose (140.80 to 518.45 x 10^6 CAR+ T cells) and ORR: odds ratio: 1.0040, 95% confidence interval (CI): 1.0006 - 1.0075 (p=0.0239) (Figure 4). The 95% CI of ORR was above 50% for dose levels of 300 and 450 x 10^6 CAR+ T cells.

Table 14. Ide-cel Dose and Overall Response Rate (ORR) (Efficacy Analysis Set)

Dose Level (x 10^6 CAR+ T cells)	Overall Response Rate (ORR) [(%), (Responders/Total Subjects)]	95% CI of ORR (%)
150	54.55 (12/22)	32.21 – 75.61
300	64.29 (45/70)	51.93 – 75.39
450	79.25 (42/53)	65.89 – 89.16

Figure 4. Ide-cel Dose-Response Relationship for Efficacy (Overall Response Rate, ORR) (Efficacy Analysis Set)



To explore other confounding factors impacting ORR, logistic regression analysis was conducted for covariates, including subject demographic characteristics, baseline conditions and ide-cel product characteristics. Univariate logistic analysis suggested potential associations between some covariates (sex, age, baseline sBCMA, VCN, and percentage of CD3+CAR+CCR7+CD27-

T cells) and ORR. Multivariate analysis was then performed and no covariate was identified as a significant impacting factor except percentage of CD3+CAR+CCR7+CD27- T cells subset of ide-cel final product. The percentage of CD3+CAR+CCR7+CD27- T cells was negatively associated with ORR probability (p=0.0191) (Table 15).

Table 15. Multivariate Logistic Regression Analysis for Dose and Ide-cel Efficacy Responses (Efficacy Analysis Set)

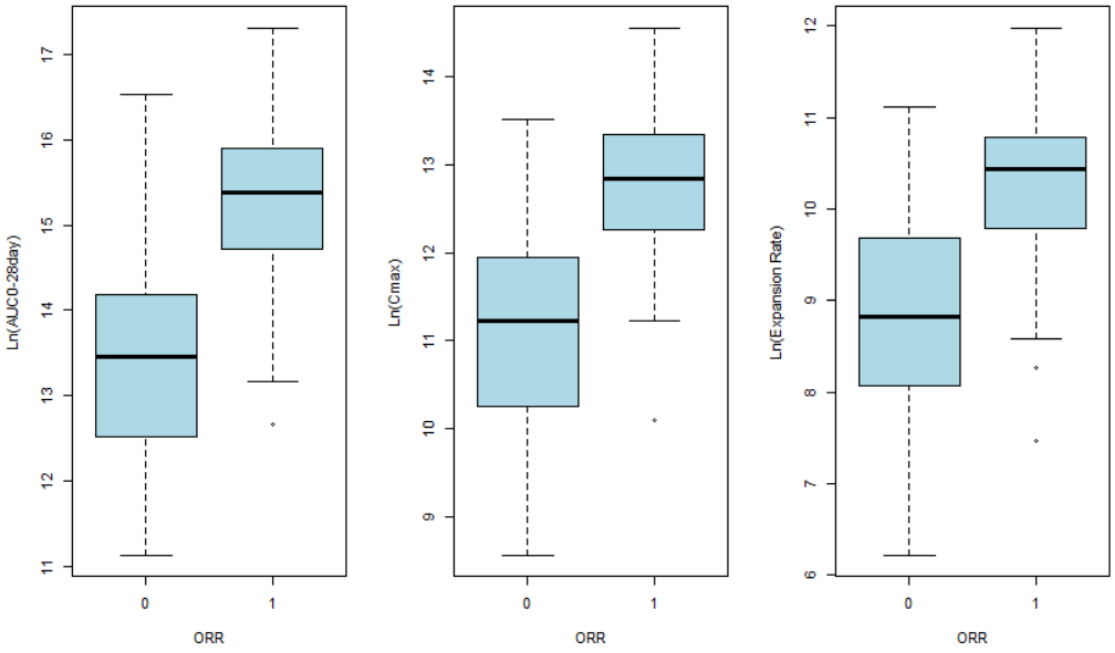
Covariates/Attributes	Estimate	Standard Error	P value
Intercept	0.5082	2.5096	0.8395
Actual Dose	0.0031	0.0029	0.2979
Age (< 65 years)	-0.8029	0.5346	0.1331
Body Weight	0.0044	0.0177	0.8195
Sex (Female)	0.6446	0.5783	0.2650
Baseline (pre-Lymphodepletion) Soluble BCMA	-0.001	0.0007	0.1157
Vector Copy Number (VCN)	0.2874	0.1641	0.0798
% CD3+CAR+CCR7+CD27-	-0.0368	0.0157	0.0191*

No apparent association between dose and complete response (CR) rate was observed.

Exposure-Response Relationship: Efficacy

As shown in Figure 5 and Table 16, responding subjects had substantial higher ide-cel expansion ($AUC_{0\text{-}28d}$, Cmax and expansion rate) compared to non-responding subjects.

Figure 5. Correlations between Ide-cel PK Parameters and Overall Responding Rate (ORR)



0: Non-responders (n=46); 1: Responders (n=99)

Table 16. Ide-cel Exposure and Efficacy Responses – Descriptive Statistics (Efficacy Analysis Set)

a. Overall Response Rate (ORR)

Parameters (Unit)	Unit	Responding Subjects N=99	Non-Responding Subjects N=46	P value*
Cmax [median, (min, max)]	copies/µg DNA	375224.0 (24391.0, 2095336.0)	72397.0 (0.0, 744913.0)	< 0.00001***
Tmax [median, (min, max)]	day	11.0 (7.0, 28.0)	9.0 (0.0, 30.0)	--
$AUC_{0\text{-}28d}$ [median, (min, max)]	days*copies/µg DNA	4769184.0 (317700.6, 32799004.0)	699719.8 (68807.3, 15064645.0)	< 0.00001***
Expansion Rate [median, (min, max)]	copies/µg DNA/day	34047.5 (1742.2, 159741.0)	6579.2 (0.0, 67719.4)	< 0.00001***

*Wilcoxon rank sum test

b. Complete Response (CR)

Parameters (Unit)	Unit	CR Subjects N=39	Non-CR Subjects N=106	P value*
Cmax [median, (min, max)]	copies/µg DNA	383056.0 (105843.0, 1757151.0)	195462.5 (0.0, 2095336.0)	0.0002***
Tmax [median, (min, max)]	day	11.0 (7.0, 28.0)	11.0 (0.0, 30.0)	--
$AUC_{0\text{-}28d}$ [median, (min, max)]	days*copies/µg DNA	4769184.0 (1234681.3, 24669681.0)	1998645.1 (68807.3, 32799004.0)	0.0002***
Expansion Rate [median, (min, max)]	copies/µg DNA/day	34047.5 (9622.1, 159741.0)	18023.4 (0.0, 132217.2)	0.0032**

*Wilcoxon rank sum test

Univariate logistic regression analysis also suggested positive associations between ide-cel PK parameters and efficacy endpoints: ORR and CR rate (Table 17).

Table 17. Univariate Correlations between Ide-cel Expansion and Efficacy Responses (Efficacy Analysis Set)

a. Overall Response Rate (ORR)

	Odds Ratio	95% CI	P value
LnAUC0-28d	4.98	3.03 – 9.25	1.32e-08***
LnCmax	5.53	3.21 – 10.83	2.78e-08***
LnExpansionRate	4.09	2.59 – 7.09	3.62e-08***

b. Complete Response Rate (CR)

	Odds Ratio	95% CI	P value
LnAUC0-28d	1.94	1.38 – 2.89	0.0004***
LnCmax	2.10	1.42 – 3.32	0.0005***
LnExpansionRate	1.90	1.30 – 2.96	0.0021**

To explore other confounding factors impacting ORR, multivariate logistic regression analysis was conducted. In addition to ide-cel PK parameters, among subject baseline conditions and ide-cel product characteristics assessed, sex (female), baseline soluble BCMA levels and usage of steroids in last prior medications were positively associated ORR probability (Table 18).

Table 18. Multivariate Logistic Regression Analysis for Ide-cel PK Parameters and Efficacy Responses (Efficacy Analysis Set)

Covariates/Attributes	Estimate	Standard Error	P value
Intercept	-32.2469	8.1648	0.00008 ***
Ln(AUC0-28d)	1.9720	0.4326	0.00005 ***
Age (< 65 years)	-0.9697	0.7103	0.1722
Body Weight	0.0295	0.0265	0.2653
Sex (Female)	1.7178	0.8743	0.0494*
Baseline (pre-Lymphodepletion) Soluble BCMA	-0.0026	0.0013	0.0397*
Last Prior Medication: Steroids (Yes)	2.2574	1.0997	0.0401*
Vector Copy Number (VCN)	0.1374	0.2083	0.5093
% CD3+CAR+CCR7+CD27-	0.0025	0.0212	0.9075

The applicant evaluated E-R relationship of ide-cel efficacy endpoints. Because ide-cel PK parameters, $AUC_{0\text{-}28d}$, Cmax and expansion rate were closely correlated, $AUC_{0\text{-}28d}$ was selected as primary exposure parameter and used in analysis. As shown in Figure 6, graphical evaluation suggested potential E-R relationship between ide-cel exposure and ORR. The applicant attempted logistic regression analysis with both linear and sigmoid Emax models. Based on fitting results, sigmoid Emax model was selected. The applicant's approach is reasonable. Figure 6 shows the observed and model-predicted ORR E-R relationship using Ln(AUC0-28d) as exposure metric using sigmoid Emax model with clinical reviewer's efficacy analysis results. It was noticed that the 95% prediction CI was substantially wide (data not shown). This may due to small sample size, high inter-subject variability and lack of additional idel-cel PK information (such as functionality data). Additional information may be needed to improve the model prediction performance.

Figure 6. Exposure-Response Relationship between Ide-cel Exposure (Quantiles of Ln(AUC_{0-28d})) and Overall Response Rate (ORR%) (Efficacy Analysis Set)

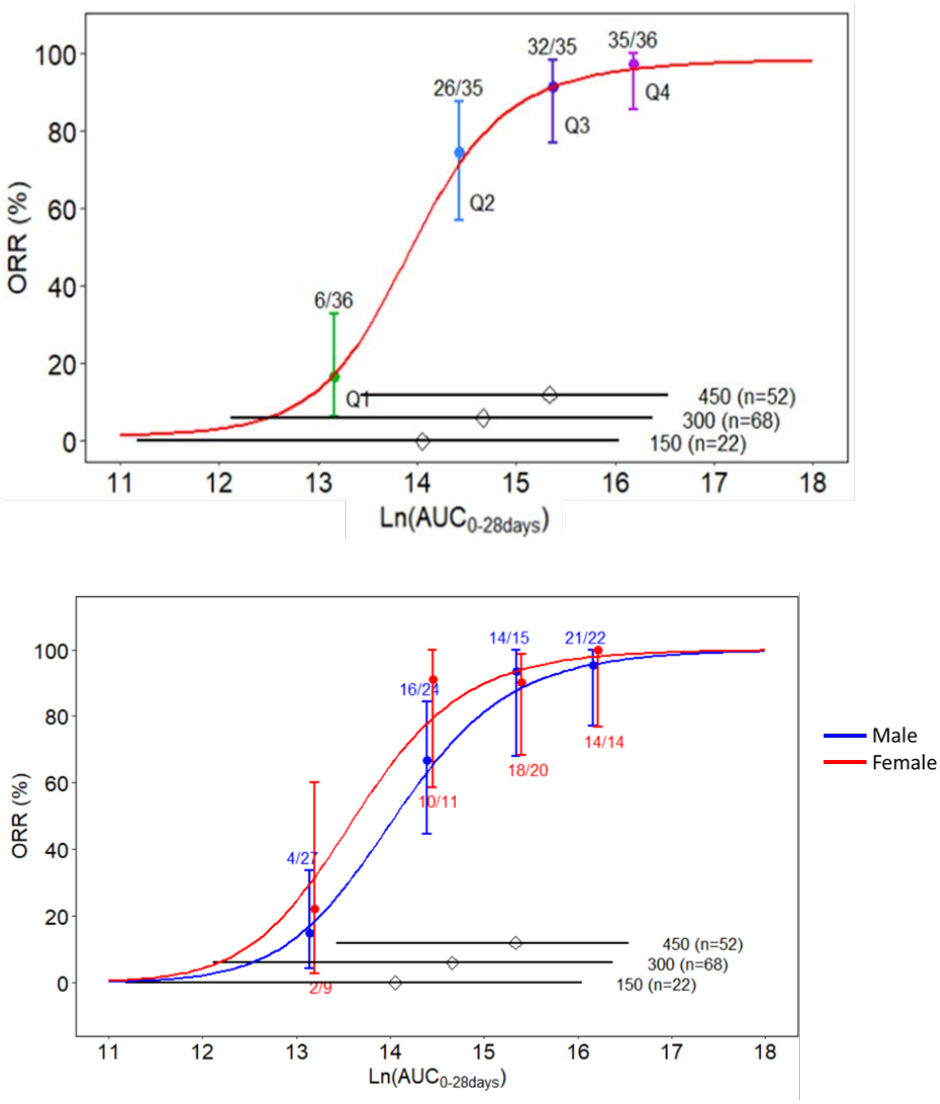
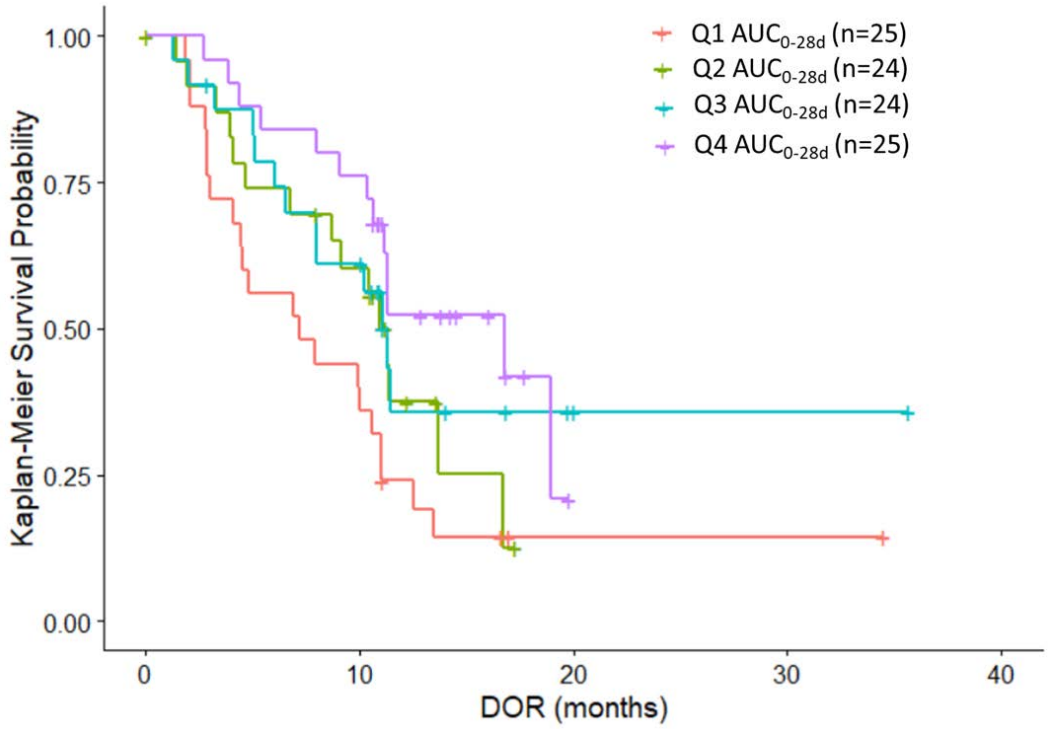
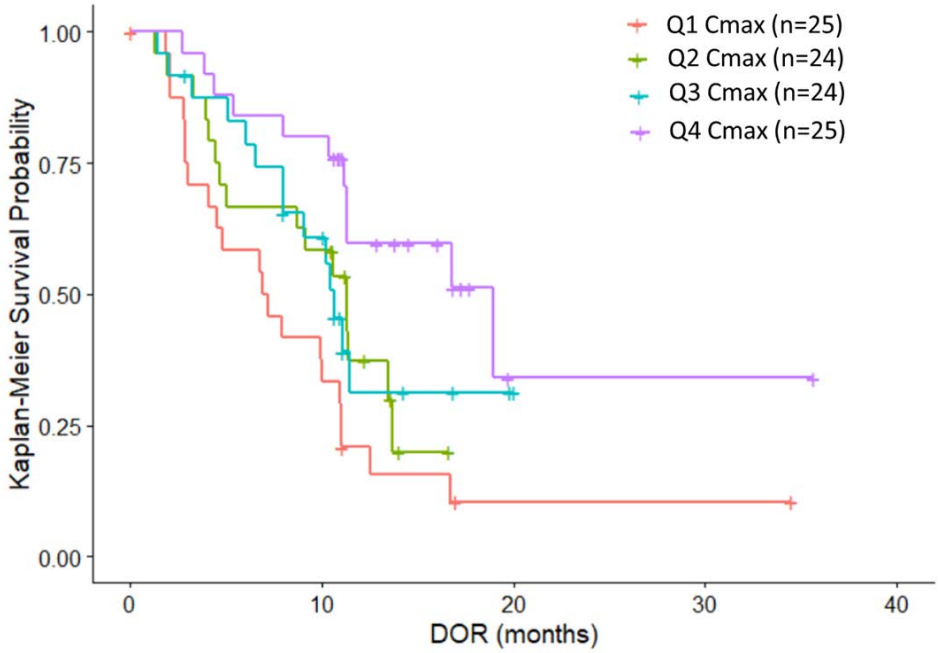


Figure 7 shows Kaplan-Meier curves of duration of response (DOR) by quantile analysis of ide-cel exposure (Cmax and AUC_{0-28d}). Subjects with the highest quantile of ide-cel exposure tend to have longer DOR.

Figure 7. Kaplan-Meier Curve of Duration of Response (DOR) by Ide-cel Exposure Quantile Groups (Efficacy Analysis Set)





6.3.2 Exposure-Response Relationship: Safety

6.3.2.1 Cytokine Release Syndrome (CRS)

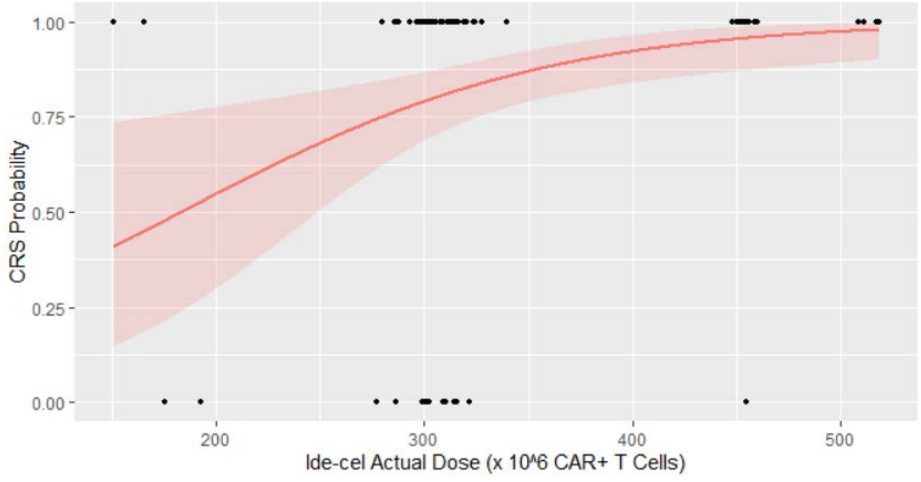
Dose-Response Relationship: Cytokine Release Syndrome (CRS)

As shown in Table 19, the incidence of cytokine release syndrome (CRS) after infusion of ide-cel increased with the increase of ide-cel dose across doses ranging from 150 to 450 x 10^6 CAR+ T cells (actual dose range: 140.80 to 518.45 x 10^6 CAR+ T cells). Univariate logistic regression analysis indicated positive association between ide-cel actual dose and incidence of any grade CRS: odds ratio: 1.0114, 95% confidence interval (CI): 1.0044 - 1.0203 (p=0.00362) (Figure 8). With respect of severe CRS (≥ Grade 3), there was no difference between dose levels of 300 x 10^6 and 450 x 10^6 CAR+ T cells.

Table 19. Ide-cel Dose and Cytokine Release Syndrome (CRS) (Study MM-001)

Dose Level (x 10^6 CAR+ T cells)	Incidence Rate of Any Grade CRS, (%)	95% CI of CRS (%)	Incidence Rate of Severe CRS (≥Grade 3), (%)	95% CI of Severe CRS (≥ Grade 3) (%)
150	50.00 (2/4)	6.76 – 93.24	0.00 (0/4)	0.00 – 60.24
300	78.57 (55/70)	67.13 – 87.48	10.00 (7/70)	4.12 – 19.52
450	96.23 (51/53)	87.02 – 99.54	9.43 (5/53)	3.13 – 20.66

Figure 8. Ide-cel Dose-Response Relationship for Cytokine Release Syndrome (CRS) (Study MM-001)

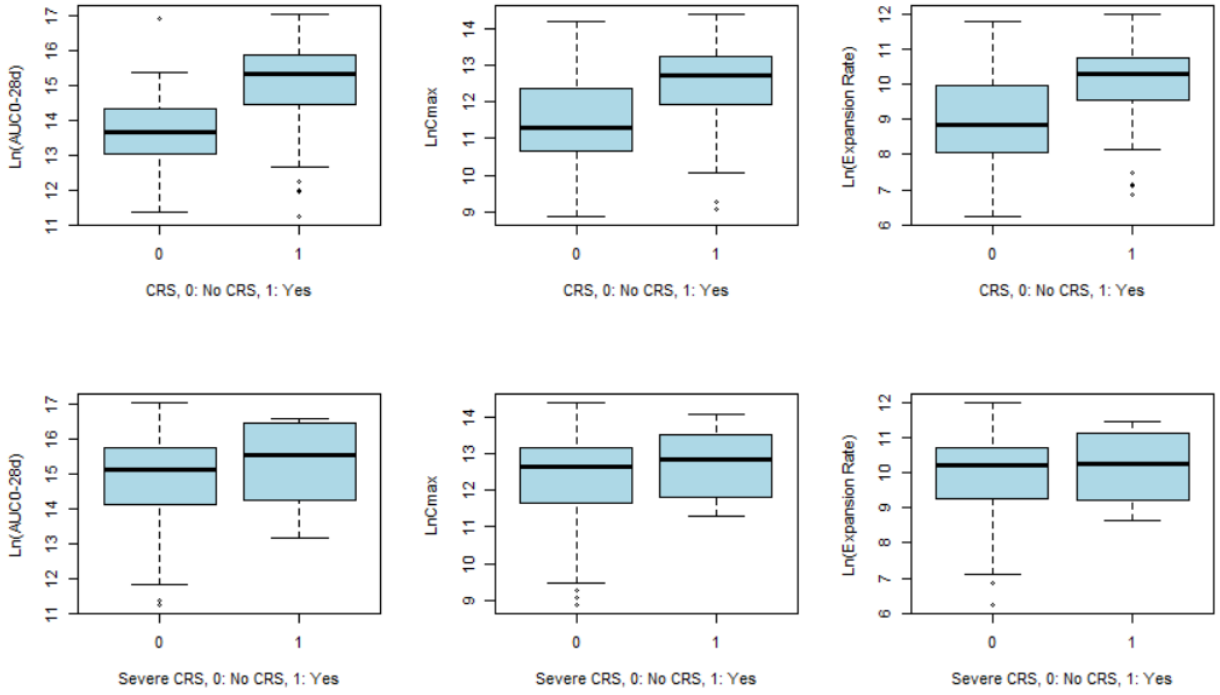


In addition to ide-cel dose, other covariates including subject's demographic and baseline covariates and product characteristics were evaluated using logistic regression to explore potential covariate(s) attributing CRS. No potential association was suggested for other covariates.

Exposure-Response Relationship: Cytokine Release Syndrome (CRS)

In general, subjects with any grade cytokine release syndrome (CRS) (n=108) had 4.22-fold, 5.31-fold, and 4.3-fold higher median Cmax, $AUC_{0\text{-}28d}$, and expansion rate of ide-cel, respectively, compared to subjects without any grade CRS (n=19) (Figure 9). Subjects with severe CRS (≥ Grade 3) (n=12) had 1.31-fold, 1.55-fold, and 1.25-fold higher median Cmax, $AUC_{0\text{-}28d}$, and expansion rate of ide-cel, respectively, compared to subjects had Grade 2, Grade 1, or no CRS (n=115). Univariate logistic regression analysis indicated that ide-cel PK parameters (AUC0-28d, Cmax and expansion rate) were positively associated with CRS rate, but not severe CRS rate.

Figure 9. Correlation Between Ide-cel Pharmacokinetic Parameters and Cytokine Release Syndrome (CRS) (Study MM-001)



Medications such as tocilizumab or corticosteroids were used to manage cytokine release syndrome (CRS). In Study MM-001, 66(52.0%) subjects received at least 1 dose of tocilizumab and 19 (15.0%) subjects received at least 1 dose of corticosteroids, 1 (0.8%) subject received siltuximab and 2 (1.6%) subjects received anakinra for management of CRS. Subjects with CRS treated with tocilizumab had higher ide-cel cellular expansion levels, as measured by 1.36-fold, 1.62-fold, and 1.74-fold higher median Cmax, AUC0-28d, and expansion rate, respectively, compared to subjects without CRS or subjects with CRS not receiving tocilizumab. Subjects with CRS treated with corticosteroids had higher ide-cel cellular expansion levels, as measured by 1.67-fold, 2.20-fold and 1.95-fold higher median Cmax, AUC0-28d, and expansion rate, respectively, compared to subjects without CRS or subjects with CRS not receiving corticosteroids (Table 20).

Table 20. Ide-cel Pharmacokinetic Parameters and Use of Tocilizumab and Corticosteroids in CRS Management

a. Tocilizumab

	Yes (N=66)	No (N=61)
$AUC_{0\text{-}28d}$ (day*copies/µg DNA)		
Median	4,452,614	2,749,749
Min, Max	204,436, 24,465,245	75,456, 21,807,583
Cmax (copies/µg DNA)		
Median	328,438	241,387
Min, Max	23,788, 1,757,151	7,078, 1,454,389
Tmax (day)		
Median	11	11
Min, Max	7, 28	7. 30
Expansion Rate (copies/µg DNA/day)		
Median	30,300	17,397
Min, Max	3,398, 159,741	506, 132,217

b. Corticosteroids

	Yes (N=18)	No (N=109)
$AUC_{0\text{-}28d}$ (day*copies/µg DNA)		
Median	6,786,554	3,083,119
Min, Max	204,436, 23,790,037	75,456, 24,669,681
Cmax (copies/µg DNA)		
Median	461,994	277,336
Min, Max	23,788, 1,717,248	7,078, 1,757,151
Tmax (day)		
Median	11	11
Min, Max	7, 21	7. 30
Expansion Rate (copies/µg DNA/day)		
Median	24,124	46,993
Min, Max	3,398, 110,257	506, 159,741

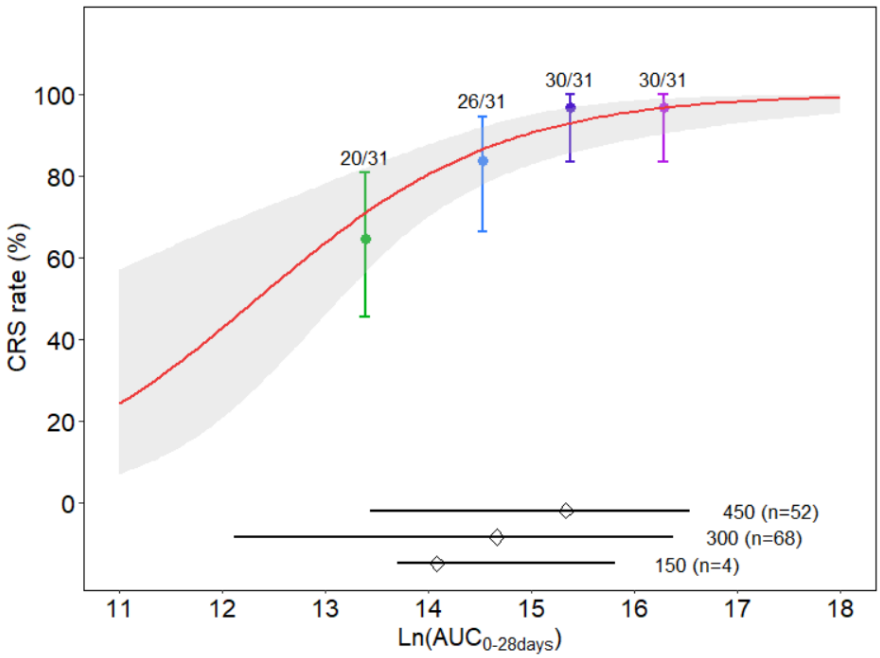
The observations are in line with the fact that higher ide-cel expansion levels are associated to more severe adverse events that require management with medications such as tocilizumab and/or corticosteroids.

Additional covariates including subject's demographic and baseline covariates and product characteristics were evaluated using logistic regression to explore potential covariate(s) attributing CRS. Potential positive association was suggested between pre-lymphodepletion TNFα level and CRS (p=0.01910*).

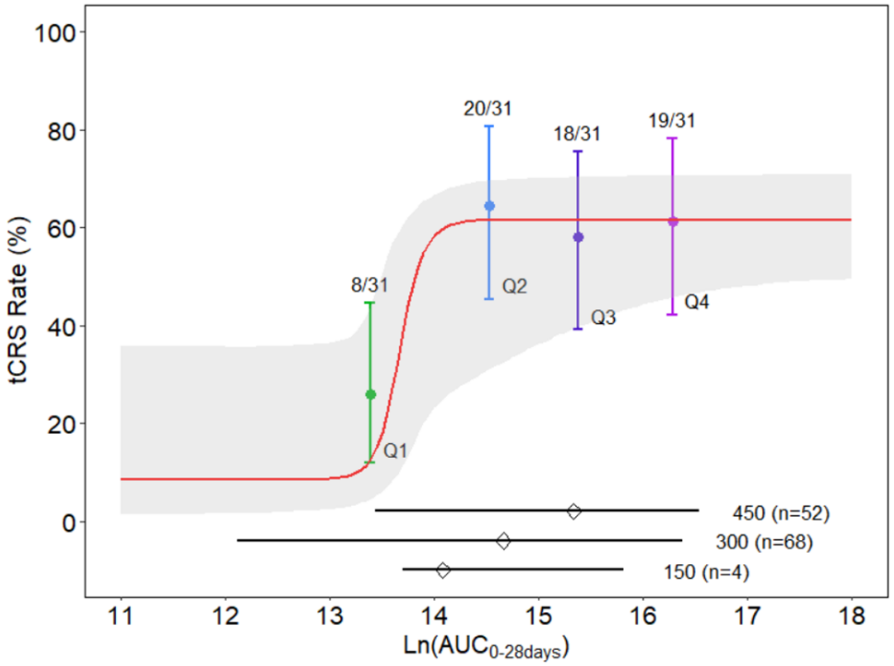
The applicant also evaluated linear and sigmoidal Emax models to characterize the E-R relationship for CRS-related endpoints. The applicant's analysis suggested that the relationship for tCRS could be best described by an Emax model and the relationships for CRS and sCRS by a linear model. The applicant's approach appears reasonable. Figure 10 shows E-R relationship using $AUC_{0\text{-}28d}$ as primary exposure metrics based clinical reviewer's safety analysis results. Higher ide-cel exposure was associated with lower rates of CRS, tCRS and sCRS.

Figure 10. Observed and Model-Predicted CRS Related Safety Events by Ide-Cel Exposure (Ln($AUC_{0\text{-}28d}$) Quantile Analysis) (Study MM-001)

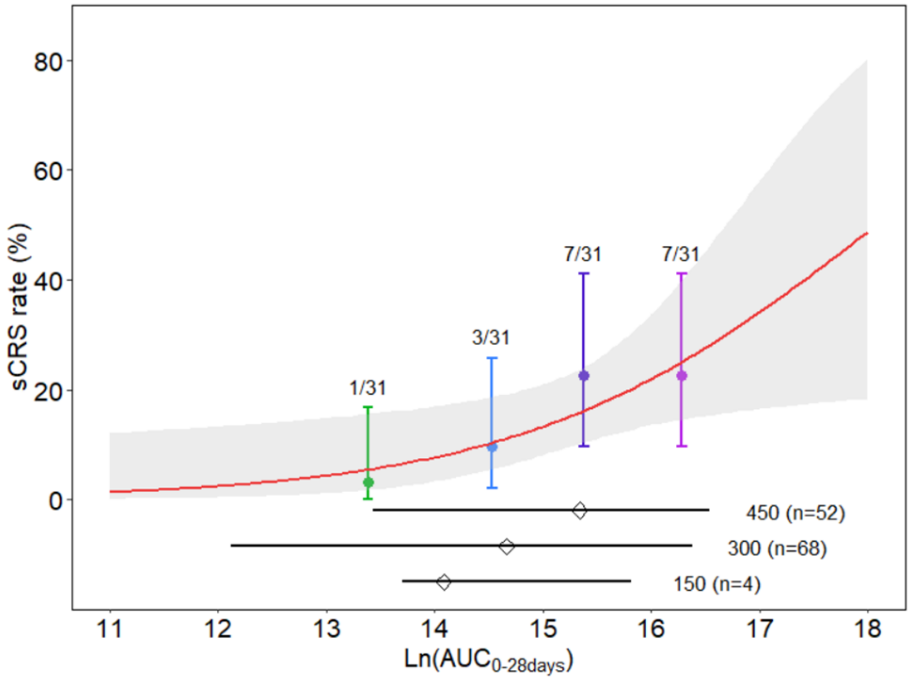
a. CRS



b. tCRS (Tocilizumab-treated CRS)



c. sCRS (Corticosteroids-treated CRS)



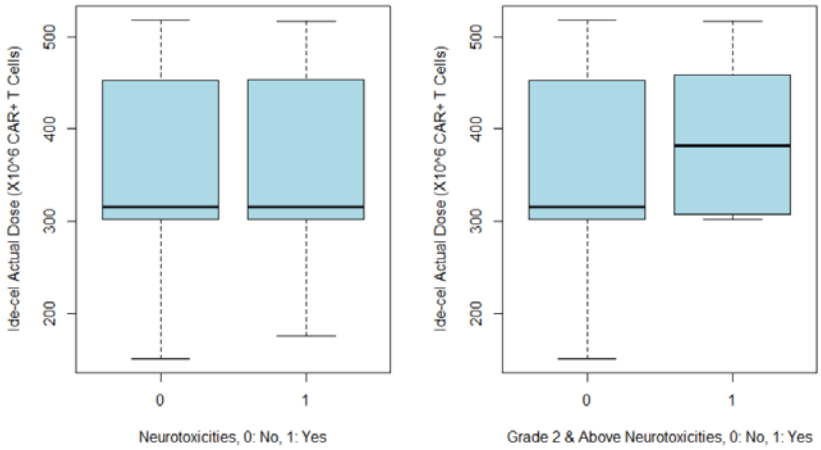
Expansion of ide-cel continued in subjects who received tocilizumab and corticosteroids after infusion of ide-cel.

6.3.2.2 Neurotoxicity

Dose-Response Relationship: Neurotoxicities (NT)

As shown in Figure 11, there's no apparent associations between ide-cel dose and incidence of any grade neurotoxicities. However, the median ide-cel dose for subjects had grade 2 (n=16) and above neurotoxicities was slightly higher (1.2-fold) than the median dose given to subjects with Grade 1 or no neurotoxicities (n=111). However, the difference was not significant (p=0.4122).

Figure 11. Ide-cel Dose and Neurotoxicities (Study MM-001)



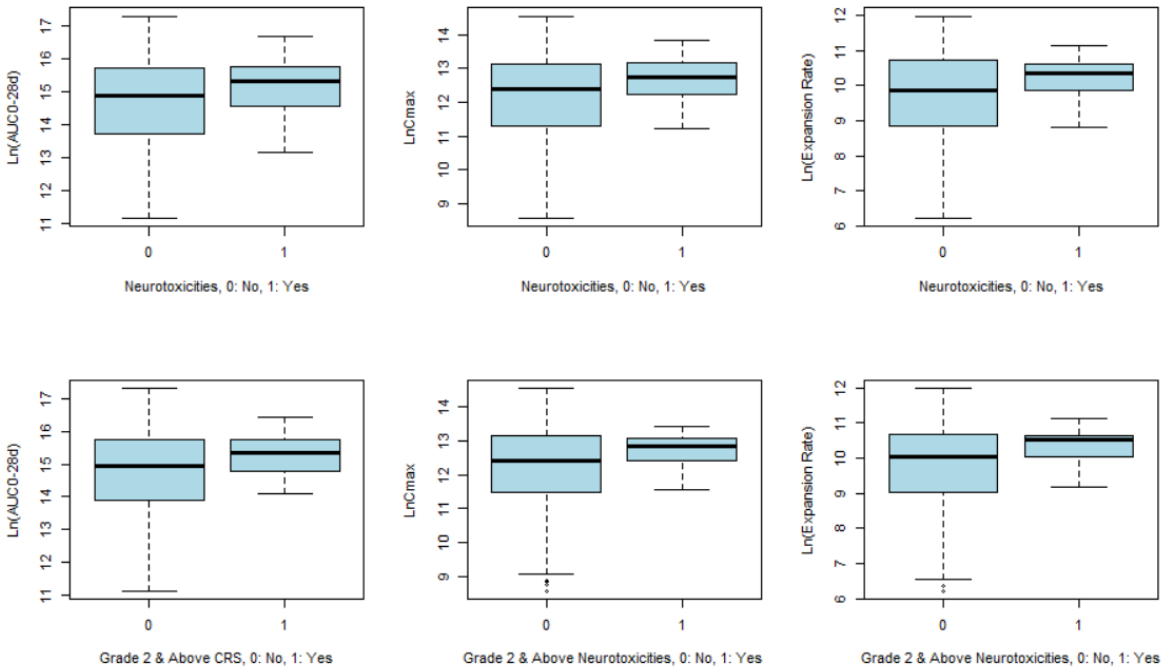
Multivariate logistic regression analysis was performed to explore potential covariates attributing incidence of neurotoxicities. Among subject demographic and baseline covariates and final product characteristics evaluated, subject age appeared to be associated with incidence of NT: subjects less than 65 years of age (NT rate: 20.7%, 17/82) were less likely to have NT compared to subject of 65 years or older (NT rate: 42.2%, 19/45). Based on univariate logistic analysis, with the age increases by 1 year, the probability of NT increases 1.06% (the odds ratio for age: 1.06, 95% CI: 1.01 – 1.11).

No evident correlations were observed between other covariates (including sex, tumor burden, product vector copy number) and the incidence of neurotoxicities.

Exposure-Response Relationship: Neurotoxicities (NT)

Subjects with any grade neurotoxicities (NTs) (n=36) had 1.14-fold, 1.40-fold, and 1.51-fold higher median Cmax, $AUC_{0\text{-}28d}$, and expansion rate of ide-cel, respectively, compared to subjects without any grade NT (n=91) (Figure 12). Subjects with Grade 2 or higher NT (n=16) had 1.36-fold, 1.39-fold, and 1.52-fold higher median Cmax, $AUC_{0\text{-}28d}$, and expansion rate of ide-cel, respectively, compared to subjects had Grade 1, or no NT (n=111). Above observed differences were not statistically significant based on results of Wilcoxon rank sum test ($p > 0.05$). There were no observed correlations between subject demographic and baseline characteristics (such as sex and tumor burden) and incidence of neurotoxicities.

Figure 12. Ide-cel Pharmacokinetic Parameters and Neurotoxicities (Study MM-001)



Based on above analysis, there were no significant associations between ide-cel dose/exposure and incidence of neurotoxicities (NTs).

Reviewer's Comments:

The E-R analysis for ide-cel clinical safety and efficacy results indicated that within the dose range of 150 to 540 x 10^6 CAR-positive T cells:

- The overall response rate (ORR) of ide-cel increased with increased dose. The 95% CI of ORR was above 50% for dose levels of 300 and 450 x 10^6 CAR+ T cells.
- A higher ide-cel dose and exposure was associated higher rate of any grade CRS, but not severe (≥ Grade 3) CRS.
- There were no significant associations between ide-cel dose/exposure and incidence of neurotoxicities (NTs).

Per clinical review of the safety and efficacy of ABECMA, the clinical reviewer recommends the following dose range for ABECMA: 300 to 460 x 10^6 CAR-positive T cells. The dose of (b) (4) x 10^6 CAR-positive T cells was not recommended because of inadequate efficacy (lower bound of 95% CI of ORR was less than 50%). Due to very limited sample size (5 subjects in Study MM-001), doses higher than 460 x 10^6 CAR-positive T cells were not recommended. Considering the limited sample size, high inter-subject variability in PK parameters and lack of association between ide-cel dose and complete response (CR) rate, clinical reviewer's dose recommendation is reasonable. Additional data are needed for doses higher than 460 x 10^6 CAR-positive T cells.

6.3.3 Exposure-Response Relationship: PD Biomarkers

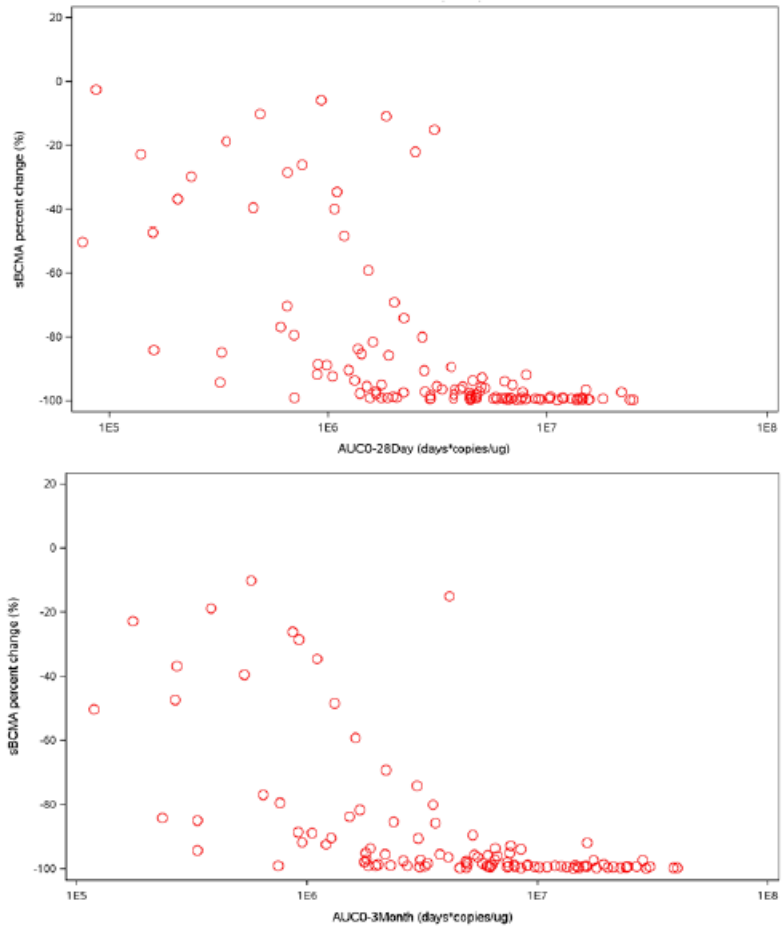
Tumor BCMA and Cellular Expansion

The relationship between baseline tumor BCMA levels (as measured by immunohistochemistry assay) and cellular expansion (i.e. $AUC_{0\text{-}28d}$ and $AUC_{0\text{-}3M}$) was examined. No apparent trends between $AUC_{0\text{-}28d}$ and $AUC_{0\text{-}3M}$ versus baseline tumor BCMA was observed).

Soluble BCMA (sBCMA) and Cellular Expansion

A higher cellular expansion appeared to be associated with greater reduction in post-infusion BCMA levels (Figure 13). At the median level of cellular expansion (Cmax of 316,202 copies/µg, AUC_{28d} exposure of 3,734,134 copies*days/µg and $AUC_{0\text{-}3M}$ exposure of 7,925,440 copies*days/µg), the reduction of post-infusion sBCMA appeared to reach reductions of 90-100% from baseline.

Figure 13. Correlation of Soluble BCMA Maximal Reduction from Baseline and Ide-Cel Exposure (Study MM-001)

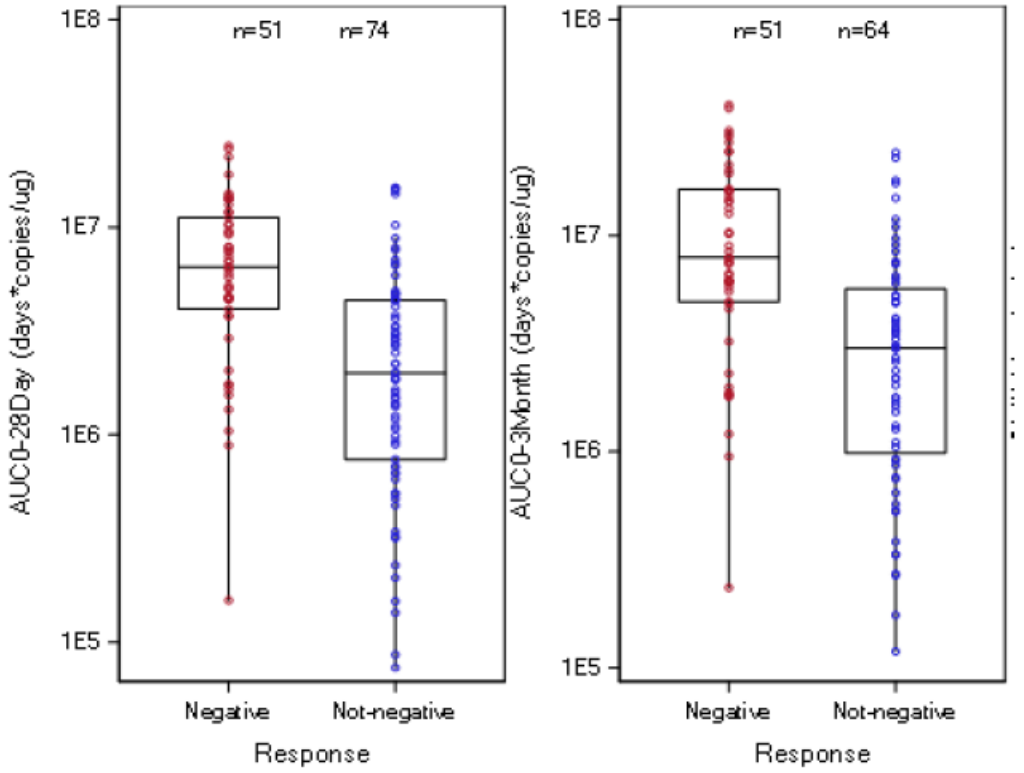


Source: Applicant. BB2121-MM-001 Clinical Study Report: Figure 34.

Minimal Residual Disease (MRD) and Cellular Expansion

Minimal residual disease (MRD) was assessed by next-generation sequencing (NGS). Cellular exposures were higher in subjects who were MRD negative at any timepoint within 3 months prior to achieving at least complete response (CR) until the time of PD or death (Figure 14). The median $AUC_{0\text{-}28d}$ was approximately 2.3-fold higher in subjects who were MRD negative compared to subjects who were MRD positive (did not achieve MRD negative at a sensitivity of 10^{-5} at all post-infusion visits, including subjects without any MRD assessment). The median $AUC_{0\text{-}3M}$ was approximately 2.1-fold higher in subjects who were MRD negative compared to subjects who were MRD positive. These observations indicate greater cellular expansion was associated with higher likelihood of achieving MRD negativity.

Figure 14. Correlation of Post-infusion Minimal Residual Disease Status at Sensitivity of 10^{-5} and Ide-Cel Exposure (Study MM-001)



Source: Applicant. BB2121-MM-001 Clinical Study Report.

6.4 Immunogenicity

In both Studies MM-001 and CRB-401, serum samples were analyzed for the presence of anti-ide-cel antibodies (anti-drug antibody [ADA]) using a validated (b) (4) immunoassay.

In Study MM-001, there were 5 of 128 (3.9%) subjects who had pre-existing ADA before infusion of ide-cel. In Study CRB-401, there were 3 of 62 (4.8%) subjects who had pre-existing ADA before infusion of ide-cel. The available data suggest that the impact of pre-existing ADA on cellular expansion appears to be limited.

In Study MM-001, ADAs did not develop in the first month post-infusion of ide-cel. By Month 3 and Month 6 after infusion, approximately 20.6% (21 of 102 subjects) and 43.8% (35 of 80 subjects) of the subjects, respectively were ADA-positive. A total of 65 subjects had at least one sample with detectable ADA post-infusion. The PK parameters (AUC0-28d and Cmax) values in these ADA-positive subjects were comparable to the overall PK values of observed in all study subjects.

In Study CRB-401, approximately 5.2% (3 of 58 subjects), 39.6% (19 of 48 subjects), and 64.9% (24 of 37 subjects) subjects were ADA-positive by Month 1, Month 3 and Month 6 post-infusion, respectively. A total of 37 subjects had at least 1 sample with detectable ADA post-infusion. The PK values in subjects with positive ADA post-infusion were comparable to PK values in the overall study subjects.

Majority study subjects did not develop ADA in the first month post-infusion, and ide-cel expansion occurs in the first month after infusion. Therefore, ADA development is not expected to impact cellular expansion kinetics of ide-cel.

6.5 Replication-Competent Lentivirus (RCL) Testing

Ide-cel comprises lentiviral vector transduced T cells, the presence of replication-competent lentivirus (RCL) in blood of the treated subject were monitored. As of the data cutoff date on October 16, 2019, all blood samples were reported as negative for RCL testing.

6.6 Clinical Pharmacology Evaluation Conclusions

General Cellular Kinetics/Pharmacokinetics

- Following infusion, ide-cel proliferated and underwent rapid multi-log expansion, with the maximum peak expansion occurring at a median of 11 days across the evaluated dose range of ide-cel: 150 to 540 x 10^6 CAR+ T cells. Persistence of (b) (4) was observed up to 1 year.

- Within the dose range evaluated, ide-cel exposure increased in a dose-dependent manor. However, due to high inter-subject variability in ide-cel PK profiles, ide-cel exposure overlapped across different dose levels. This may due to heterogenicity of ide-cel drug product composition with respect to different T cell subsets.
- Ide-cel expansion after the second dose was substantially lower than ide-cel expansion after the first dose in retreated subjects.
- Exploratory multivariate regression analysis indicates that ide-cel vector copy number was positively associated with ide-cel dose normalized $AUC_{0\text{-}28d}$ and Cmax. Subject's body weight and the percentage of CD3+CAR+CCR7+CD27- T cells subset in ide-cel final product were negatively associated with ide-cel dose normalized $AUC_{0\text{-}28d}$ and Cmax.

Pharmacodynamics

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

Dose/Exposure-Response Relationship

Ide-Cel Dose

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

Ide-Cel Exposure/Expansion

- A higher cellular expansion ($AUC_{0\text{-}28d}$, Cmax and expansion rate) of ide-cel was associated with both higher ORR and complete response (CR) rate. In addition to ide-cel expansion, covariates such as sex (female), baseline soluble BCMA levels and usage of steroids in last prior medications were potentially positively associated with a higher ORR.
- A higher cellular expansion of ide-cel was associated with any grade of CRS incidence. Additionally, potential association was indicated between pre-lymphodepletion TNFα level and any grade of CRS incidence.
- There was no apparent association between ide-cel exposure and incidence of any grade neurotoxicities (NT).
- A higher ide-cel cellular expansion of ide-cel appeared to be associated with greater reduction in post-infusion BCMA levels.
- A higher ide-cel cellular expansion of ide-cel was associated with higher likelihood of achieving minimal residual disease (MRD) negativity.

Immunogenicity

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

Replication-competent Lentivirus (RCL) Testing

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

7 APPENDIX - INDIVIDUAL STUDY

7.1 Study #1 – Study BB2121-MM-001

7.1.1 Study Design

Study Title: A Phase 2, multicenter study to determine the efficacy and safety of bb2121 in subjects with relapsed and refractory multiple myeloma (Study No. BB2121-MM-001, MM-001)

Objectives

Primary Objectives

- To evaluate the efficacy, as defined as overall response rate (ORR), of ide-cel in subjects with relapsed and refractory multiple myeloma (RRMM)

Secondary Objectives

- To assess the safety of ide-cel in subjects with RRMM;
- To assess additional efficacy outcomes including complete response (CR) rate, time to response (TTR), duration of response (DoR), progression-free survival (PFS), time to progression (TTP), and overall survival (OS);
- To characterize the expansion of CAR+ T cells in the peripheral blood (cellular kinetics/pharmacokinetics);
- To evaluate the development of an anti-CAR antibody (hereafter referred to as antidrug antibody [ADA] response;
- To evaluate the proportion of subjects who attained minimal residual disease (MRD)-negative status by next-generation sequencing (NGS);
- To describe changes in health-related quality of life (HRQoL) using the European Organization for Research and Treatment of Cancer – Quality of Life C30 questionaire (EORTC-QLQ-C30), the European Quality of Life-5 Dimensions health state classifier to 5 Levels (EQ-5D-5L0, and the European Organization for Research and Treatment of Cancer – Quality of Life Multiple Myeloma Module (EORTC-QLQ-MY20).

Study Design

This is an ongoing, open-label, single-arm, multicenter, Phase 2 study to determine the efficacy, safety, and cellular kinetics/pharmacokinetics of ABECMA in subjects with RRMM. ABECMA was infused to each subject at the target doses of 150, 300, and 450 x 10^6 CAR+ T cells. The PK data cutoff date for this submission is April 19, 2019 and clinical primary analysis cutoff date is October 16, 2019.

Eligible enrolled subjects underwent leukapheresis to enable ide-cel product generation. The treatment cycle included lymphodepleting chemotherapy with one 3-day cycle of fludarabine (30

mg/m^2 IV infusion) and cyclophosphamide (300 mg/m^2 IV infusion) starting 5 days prior to the target ide-cel infusion date. Ide-cel was administered intravenously at a dose range of 150 to 540 x 10^6 CAR+ T cells with 3 target dose levels: 150 (n=4), 300 (n=70) and 450 (n=54) x 10^6 CAR+ T cells. A total of 127 subjects had evaluable PK profiles.

For pharmacokinetic analysis, blood samples were collected at evaluation, pre-dose, and at 2, 4, 7, 9, 11, 14, 21 days, 1, 2, 3, 4, 5, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, and 36 months post-dose. The pharmacokinetic samples were evaluated using a validated (b) (4) assay.

7.1.2 Results

Please refer to section 6 for Study MM-001 clinical pharmacology assessment results.

7.2 Study #2 – Study CRB-401

7.2.1 Study Design

Study Title: A phase 1 study of BB2121 in BCMA-expressing multiple myeloma (Study No. CRB-401)

Objectives

Primary Objectives

There were 2 parts (Part A and Part B) to this study, each with their own primary objective. The primary objective of Part A of the study (dose escalation) was to determine the maximum tolerated dose (MTD) of idecabtagene vicleucel (bb2121, ide-cel) in subjects with multiple myeloma (MM) whose tumors expressed B-cell maturation antigen (BCMA) and to select a recommended Phase 2 dose (RP2D) for future studies. The primary objective of the Part B of the study (dose expansion) was to confirm the safety of the doses chosen in Part A).

Secondary Objectives

- To provide preliminary efficacy data on the antitumor effects of treatment with ide-cel in subjects with MM whose tumors expressed BCMA.

Study Design

This was a first-in-human, 2-part, nonrandomized, open-label, multicenter Phase 1 study in subjects with relapsed or refractory multiple myeloma.

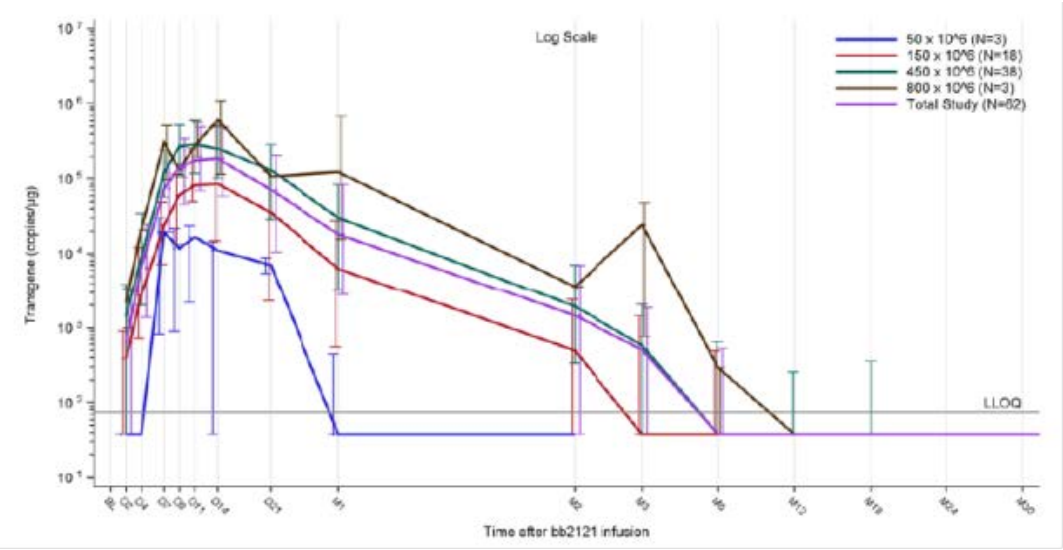
A total of 67 subjects ((24 subjects in Part A and 43 subjects in Part B) underwent leukapheresis and 62 subjects (21 subjects in Part A and 41 subjects in Part B) received ide-cel infusion after lymphodepletion. There were 4 dose levels were evaluated in Pat A (dose escalation): 50, 150, 450, and 800 x 10^6 CAR+ T cells. Based on safety and efficacy information from Part A, two dose levels were assessed in Part B (dose expansion): 150 and 450 x 10^6 CAR+ T cells. A total of 62 subjects had evaluable PK profiles. The PK data cutoff date for this submission is April 23, 2019 and clinical data cutoff date is July 22, 2019.

For pharmacokinetic analysis, blood samples were collected at evaluation, pre-dose, and at 2, 4, 7, 9, 11, 14, 21 days, 1, 2, 3, 4, 5, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, and 36 months post-dose. The pharmacokinetic samples were evaluated using a validated (b) (4) assay.

7.2.2 Results

Figure 15 shows Idel-cel PK profiles at different dose levels. Table 21 lists the summary of ide-cel PK parameters. Following ide-cel infusion, the cells proliferated and underwent rapid multi-log expansion, with the maximum peak expansion occurring at a median of 7-11 days across the dose levels evaluated. With the increase of dose, exposure of ide-cel increased.

Figure 15. Ide-cel Transgene Levels Versus Time (Study CRB-401)



Source: Applicant. Clinical Study Report CRB-401.

Table 21. Summary of Ide-cel Pharmacokinetic Parameters (Study CRB-401)

Pharmacokinetic Parameter	Parts A and B Combined by Ide-cel (CAR+ T Cells) Target Dose				RP2D (N = 56)[a]	Total Study (N = 62)[a]
	50×10^6 (N = 3)[a]	150×10^6 (N = 18)[a]	450×10^6 (N = 38)[a]	800×10^6 (N = 3)[a]		
C_{max}, copies/µg	10,907 (245)	107,335 (489)	306,727 (133)	389,278 (114)	218,866 (242)	194,650 (295)
T_{max}, days	7 (7, 10)	11 (4, 22)	11 (7, 20)	11 (10, 14)	11 (4, 22)	11 (4, 22)
T_{last}, days	21 (10, 30)	29.5 (14, 344)	91 (14, 555)	175 (90, 178)	84 (14, 555)	84 (10, 555)
$AUC_{0\text{-}28days}$, days*copies/µg	82,184 (722)	1,141,448 (509)	3,483,374 (155)	5,166,140 (184)	2,433,626 (271)	2,142,260 (366)
$AUC_{0\text{-}3M}$, days*copies/µg	288,445 [n = 1]	1,960,965 (468) [n = 16]	4,264,100 (171) [n = 36]	7,205,195 (262)	3,357,570 (252) [n =52]	3,347,769 (262) [n = 56]
$AUC_{0\text{-}6M}$, days*copies/µg	288,445 [n = 1]	2,614,645 (432) [n = 13]	4,433,749 (179) [n = 35]	7,432,030 (272)	3,842,848 (232) [n = 48]	3,797,980 (245) [n = 52]
$AUC_{0\text{-}9M}$, days*copies/µg	288,445 [n = 1]	2,628,137 (433) [n = 13]	4,465,385 (179) [n = 35]	7,461,621 (270)	3,868,211 (233) [n = 48]	3,821,989 (246) [n = 52]

Source: Applicant. Clinical Study Report CRB-401.

Idel-cel can persist in peripheral blood for up to one-year post-infusion. More than 40% and 20% of ide-cel treated subjects had measurable ide-cel levels at 6 months and 12 months post-infusion (Table 22).

Table 22. Persistence of Ide-cel Over Time (Study CRB-401)

Pharmacokinetic Timepoint	Total Number of Observations	Number of Observations with Detectable Values (%)	Number of Observations BLQ (%)
1 month	54	48 (88.9%)	6 (11.1%)
3 months	50	31 (62.0%)	19 (38.0%)
6 months	36	15 (41.7%)	21 (58.3%)
12 months	18	4 (22.2%)	14 (77.8%)

Source: Applicant. Clinical Study Report CRB-401.