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BLA Clinical Review and Evaluation

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	Supplemental BLA
Application Number(s)	125736/218
Priority or Standard	Standard
Submit Date(s)	February 15, 2023
Received Date(s)	February 15, 2023
PDUFA Goal Date	December 16, 2023
Division/Office	Office of Clinical Evaluation, Division of Clinical Evaluation, Hematology
Review Completion Date	April 4, 2024
Established Name	Idecabtagene vicleucel
(Proposed) Trade Name	ABECMA
Pharmacologic Class	B-cell maturation antigen directed, genetically modified T cell immunotherapy
Applicant	Celgene Corporation, a Bristol-Myers Squibb Company
Formulation(s)	ABECMA is supplied in one or more infusion bag(s) containing a frozen suspension of genetically modified autologous T cells in 5% DMSO.
Dosing Regimen	300-510x10e6 CAR positive T cells
Applicant Proposed Indication(s)/Population(s)	Treatment of adult patients with relapsed or refractory multiple myeloma who have received an immunomodulatory agent (IMiD), a proteasome inhibitor (PI), and an anti-CD38 monoclonal antibody.
Recommendation on Regulatory Action	Traditional Approval

Recommended Indication(s)/Population(s) (if applicable)	ABECMA is a B-cell maturation antigen directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory multiple myeloma after two or more prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.

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Reviewers of Multi-Disciplinary Review and Evaluation (If Applicable)

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Branch Chief (CHB)	Robert Sokolic
Division Director (DCEH)	Lola Fashoyin-Aje
OCE Director (or designate)	Marc Theoret
Director, Office of Clinical Evaluation	Lola Fashoyin-Aje

Abbreviations: OCE=Oncology Center of Excellence, CHB=Clinical Hematology Branch, DCEH=Division of Clinical Evaluation, Hematology

Additional Reviewers of Application

Statistical Reviewer	Xue (Mary) Lin, Ph.D.
Statistical Team Lead	Zhenzhen Xu, Ph.D.
Statistical Division Director	John Scott, Ph.D.

Glossary

AE	adverse event	ICH	International Council on Harmonisation
AESI	adverse event of special interest	IgG	immunoglobulin G
ALT	alanine aminotransaminase	IMiD	immunomodulatory drug
AMT	antimyeloma therapy	IMWG	International Myeloma Working Group
ANC	absolute neutrophil count	IND	Investigational New Drug
aPTT	activated partial thromboplastin time	IPD	Important Protocol Deviations
ASCT	autologous stem cell transplant	IRC	Independent Review Committee
AST	aspartate transaminase	IRT	Interactive Response Technologies
AUC	area under the concentration vs time curve	ITT	intent to treat
BLA	biologics license application	ISS	International Staging System
BMS	Bristol Myers Squibb	K-M	Kaplan-meier
BRA	Benefit-Risk assessment	LDC	Lymphodepleting chemotherapy
CAR	chimeric antigen receptor	LPLV	Last patient last visit
CFR	Code of Federal Regulations	LTFU	long term follow-up
CI	confidence interval	mAbs	Monoclonal Antibodies
Cmax	maximum (or peak) concentration	MAS	Macrophage activation syndrome
CrCl	creatinine clearance	MedDRA	Medical Dictionary for Regulatory Activities
CRF	case report form	MRD	Minimal residual disease
CRP	c-reactive protein	NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
CRS	cytokine release syndrome	NGS	Next generation sequencing
CSR	clinical study report	NT	Neurotoxicity
DBL	database lock	ORR	Overall response rate
ddPCR	droplet digital polymerase chain reaction	OS	Overall survival
dex	dexamethasone	PD	pharmacodynamics
DMC	data monitoring committee	PD	Progressive disease
DoR	duration of response	PFS	progression free survival
DPd	DARA + POM + dex	PFS2	Progression-free survival on next line of therapy
DSMB	data safety monitoring board	PI	Proteasome inhibitor
DVd	liposomal doxorubicin, vincristine, and low-dose dexamethasone	PK	pharmacokinetics
ECG	electrocardiogram	PR	Partial response
ECOG	eastern cooperative oncology group	PRO	patient reported outcome
E-R	Exposure-Response	QLQ	Quality of Life questionnaire
EFS	Event Free Survival	R/R	relapsed or refractory
EHA	European Hematology Association	SAE	Serious adverse event
ELO	Elotuzumab	SAP	Statistical analysis plan
EORTC	European Organization for Research and Treatment of Care	sCR	Stringent complete response
EPd	ELO + pomalidomide and low dose dex	SD	Stable disease; Standard deviation
EQ 5D	EuroQol 5-dimension	SPM	Second primary malignancies
ESMO	European Society for Medical Oncology	Tlast	Time of last measurable CAR T cell concentration
FDA	Food and Drug Administration	Tmax	time of maximum observed CAR T cell concentration
GCP	good clinical practice	TTP	Time to progression

HR	hazard ratio	TTR	Time to response
ICF	Informed Consent	VGPR	Very good partial response

Glossary (FDA)

AE	adverse event
BT	bridging therapy
BCMA	B-cell maturation antigen
CAR	chimeric antigen receptor
CAR-T	chimeric antigen receptor T (cells)
CD	cluster of differentiation
CI	confidence interval
CR	complete response
CRS	cytokine release syndrome
DPd	daratumumab, pomalidomide, and dexamethasone
DVd	daratumumab, bortezomib, dexamethasone
EORTC	European Organization for Research and Treatment of Care
EPd	elotuzumab, pomalidomide, and dexamethasone
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
HLH	hemophagocytic lymphohistiocytosis
HR	hazard ratio
ide-cel	idecabtagene vicleucel
IgG	immunoglobulin G
IMiD	immunomodulatory agent
IMWG	International Myeloma Working Group
IPD	important protocol deviation
IRC	independent review committee
IRd	ixazomib, lenalidomide, and dexamethasone
ITT	intent-to-treat
LDC	lymphodepleting chemotherapy
Kd	carfilzomib and dexamethasone
MAS	macrophage activation syndrome
MM	multiple myeloma
MRD	minimal residual disease
NT	neurotoxicity
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PI	proteasome inhibitor

PMR	post marketing requirement
PRO	patient-reported outcome
REMS	Risk Evaluation and Mitigation Strategies
RRMM	relapsed refractory multiple myeloma
SAE	serious adverse event
SAP	statistical analysis plan
sBLA	supplemental Biologics License Application
sCR	stringent complete response
TEAE	treatment-emergent adverse event

1 Executive Summary

1.1 Product Introduction

Idecabtagene vicleucel (ABECMA; hereafter referred to as ide-cel) 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 cluster of differentiation (CD) 3-zeta T cell activation domain, and a 4-1BB costimulatory domain. Antigen-specific activation of ide-cel results in CAR-positive T cell proliferation, cytokine secretion, and subsequent cytolytic killing of BCMA-expressing cells.

Current Indication: Ide-cel is currently approved for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) after four or more prior lines of therapy, including a proteasome inhibitor (PI), an immunomodulatory agent, and an anti-CD38 monoclonal antibody (traditional approval, March 26, 2021).

The recommended dose range is 300 to 460x10e6 CAR+ T cells as a single administration.

On February 15, 2023, the Applicant submitted a supplemental Biologics License Application (sBLA) for Abecma.

Proposed Indication: This Applicant is seeking an indication for the treatment of adult patients with RRMM who have received an immunomodulatory agent, a PI, and an anti-CD38 monoclonal antibody.

Proposed Dose: The Applicant has requested an extension of the upper end of the dose range from 460 to 510 x 10e6 CAR+ T cells. The proposed dose range is 300 to 510 x 10e6 CAR+ T cells.

1.2 Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of the effectiveness of ide-cel for the proposed indication is based on one adequate and well controlled study, KarMMa-3. KarMMa-3 is a Phase 3, randomized (2:1), open-label, multicenter study that compares ide-cel to the standard of care (SOC) in adults with relapsed refractory multiple myeloma after 2 to up to 4 prior lines of therapy who had received a PI, an immunomodulatory agent (IMiD), and daratumumab, and who were refractory to the last line of therapy. KarMMa-3 enrolled 386 subjects who were randomized to receive ide-cel or one of the five SOC regimens: (daratumumab, pomalidomide, and dexamethasone [DPd]; daratumumab, bortezomib, and dexamethasone [DVd]; elotuzumab, pomalidomide, and

dexamethasone [EPd]; ixazomib, lenalidomide, and dexamethasone [IRd]; or carfilzomib and dexamethasone [Kd]). Patients received ide-cel as a single infusion at a dose of 150 to 450 million (+20%) CAR+ T cells following lymphodepleting therapy with fludarabine and cyclophosphamide. Upon independent review committee (IRC)-confirmed disease progression, at investigator discretion, and if eligibility criteria were met, patients from the SOC arm could cross over to the ide-cel arm.

The primary efficacy outcome measure for KarMMa-3 was progression-free survival (PFS) as determined by a blinded IRC using the International Myeloma Working Group (IMWG) 2016 criteria. Key secondary efficacy outcome measures in hierarchical testing order were : overall response rate (ORR) and overall survival (OS). Patient-reported outcomes were evaluated as an exploratory endpoint.

KarMMa-3 met its primary endpoint (data cutoff April 18, 2022) and demonstrated a statistically significant and clinically meaningful improvement in PFS the ide-cel arm compared to the SOC arm (hazard ratio [HR] of 0.495 [95% confidence interval (CI): 0.379, 0.647] based on a stratified log-rank test; p-value <0.0001). The median PFS was 13.3 months in the ide-cel arm (95% CI: 11.8, 16.1) and was 4.4 months (95% CI: 3.4, 5.9) in the SOC arm.

The IRC-assessed best ORR was statistically significant; 71% (95% CI:66, 77) in the ide-cel arm compared to 42% (95% CI:33, 50) in the SOC arm. Similarly, the overall complete response rate (stringent CR +CR rate) was higher at 39% (95% CI:33, 45) in the ide-cel cel arm compared to 5% (95% CI: 1.5, 9.1) in the SOC arm. At the time of the primary analysis of PFS, overall survival (OS) was immature (information fraction of 49%) for efficacy purpose. The FDA considered ide-cel effect on OS as part of the safety assessment. Results from the second interim OS analysis (74% IF) done at the time of the final PFS analysis with more mature OS data and an additional one year of follow-up were consistent with the first interim OS analysis with persistent OS detriment for approximately 15 months after randomization.

Sixty-nine subjects (31%) in the ide-cel treated population received a dose of >460 to 510 x10e6 CAR+ T cells which is the dose expansion requested in the sBLA. The median PFS and ORR per IRC assessment in this dose range was similar to that of the approved ide-cel dose range of 300to 460 x10e6 CAR+ T cells and to the overall ide-cel arm.

The primary evidence of the safety of ide-cel for the proposed indication derives from KarMMa-3. KarMMa and KarMMa-2 provides supportive evidence of safety. The primary analysis of safety was conducted in patients enrolled in KarMMa-3 who received conformal ide-cel in the investigational arm (n=222) and patients who received SOC therapy (n=126). All patients in the ide-cell arm and 98% of patients in the SOC arm experienced at least one treatment-emergent adverse event (TEAE). The most common (≥5%) Grade 3 to 4 TEAEs in the ide-cel arm were

febrile neutropenia (51%), infection (16%), fever (9%), hypertension (7%), hypoxia (6%), and renal failure (5%). The rate of serious adverse events (SAEs) was higher in the SOC arm (ide-cel arm: 43%; SOC arm: 56%). The rate of death from AEs was similar between the two arms: (ide-cel arm: 9%;SOC arm: 8%). The rate of Grade 3 to 4 hematological toxicity was higher in the ide-cel arm (neutropenia: 96%, thrombocytopenia: 59%, anemia: 52%) compared to the SOC arm (neutropenia: 72%, thrombocytopenia: 46%, anemia: 45%).

There was a numerically higher rate of Grade 3 cytokine release syndrome (CRS), Grade 3 to 4 neurotoxicity (NT) and Grade 3 to 4 thrombocytopenia at the extended dose range of >460 to 510x10e6 CAR+ T cells compared to the 300 to 460x10e6 CAR+ dose range. However, the extension of the dose range has been assessed to be acceptable for approval given the variability in manufacturing of a biological product and data to support efficacy.

A higher proportion of patients randomized to the ide-cel arm compared to the SOC arm experienced death in the first 9 months post randomization (n=45/254; 18% versus n=15/132; 11%). Early deaths occurred in 8% (20/254) and 0% prior to ide-cel infusion and SOC treatment, respectively, and 10% (25/254) and 11% (15/132) after ide-cel infusion and SOC arm treatment respectively.

The increased proportion of early deaths up to 9 months was observed in the ide-cel arm due to disease progression prior to ide-cel treatment. There was also a higher rate of fatal adverse reactions within 90 days of treatment start in the ide-cel arm compared to the SOC arm, but the difference was smaller in magnitude (2.7% versus 1.6%). The higher early mortality observed with ide-cel was not associated with any specific disease characteristics or poor prognostic factors.

FDA convened a meeting of the Oncologic Drugs Advisory Committee (ODAC) to discuss the risk-benefit of ide-cel for the proposed indication given the increased risk of early deaths in the ide-cel arm. The FDA ODAC voted 8 to 3 in favor of ide-cel for the proposed indication.

Cytokine release syndrome (CRS) and NT associated with ide-cel therapy are serious, life-threatening, and can be fatal. Treatment algorithms to mitigate these AEs, as implemented in the study, permit the benefits of treatment to outweigh these risks. Increased risk of secondary malignancies due to insertional mutagenesis is a known risk. A post marketing requirement (PMR), long-term follow-up registry study will be required to follow recipients of the commercial product for short-term and long-term toxicity up to 15 years.

In conclusion, KarMMa-3 provides substantial evidence of effectiveness of ide-cel for patients with RRMM after two to four prior lines of therapy, including a PI, an IMiD and anti-CD38 monoclonal antibody and refractory to last line of therapy. KarMMa-3 demonstrated clinical benefit through clinically meaningful improvements in PFS, ORR, sCR rate, and the potential for

durable duration of response in the proposed patient population with a single administration without the need for continuous therapy. The most common serious risks of ide-cel have been characterized and are mitigated through product labeling and a Risk Evaluation and Mitigation Strategies (REMS). The observed higher rate of early death observed in KarMMa-3 does not have a clear etiology but may represent an inherent risk of the CAR-T treatment and its administration. KarMMa-3 was not designed to evaluate the cause of these early deaths nor evaluate how this risk can be mitigated. Treatment with ide-cel may require careful consideration of individual patient characteristics, disease characteristics, and the therapeutic context, among other factors. The risk of increased early mortality with ide-cel will be included under Warning and Precautions section of the USPI.

The review team recommends traditional approval of ide-cel for the treatment of adult patients with RRMM who have received at least two prior lines of therapy, including a PI, an IMiD, and an anti-CD 38 monoclonal antibody. The indication that is granted is different than the Applicant's proposed indication and reflects the patient population enrolled on the KarMMa 3 trial. The review team recommends approval of the proposed dose range of 300 to 510 x 10e6 CAR+ T cells.

The recommendation for approval is based on demonstration of substantial evidence of effectiveness and favorable benefit-risk of ide-cel in the indicated population based on data from the Phase 3 KarMMa-3 study. Safety data from single-arm studies, KarMMa and KarMMa-2.1 provide supportive evidence for safety.

Table 1. FDA – Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment:

The benefit-risk assessment for ide-cel for the indicated population is primarily based on the results of KarMMa-3, a Phase 3, randomized (2:1), open-label, multicenter study. A total of 386 patients with relapsed and refractory MM after two to four prior lines of therapy including a PI , an IMiD, and anti-CD38 monoclonal antibody and refractory to the last line of therapy were enrolled. The primary efficacy endpoint is progression free survival (PFS), as determined by a blinded (IRC) using the international myeloma working group (IMWG) 2016 criteria. Key secondary efficacy outcome measures in hierarchical testing order are overall response rate (ORR) and overall survival (OS).

KarMMa-3 demonstrated a statistically significant and clinically meaningful improvement in PFS for ide-cel compared to standard of care (SOC) ((HR) was 0.495 [95% confidence interval (CI): 0.379, 0.647]; p-value <0.0001). Median PFS was 13.3 months in the ide-cel arm (95% CI: 11.8, 16.1) and was 4.4 months (95% CI: 3.4, 5.9) in the SOC arm. The IRC-assessed ORR rate was statistically significant; 71% (95% CI: 66, 77) in the ide-cel arm compared to 42% (95% CI: 33, 50) in the SOC arm. At the time of the primary analysis of PFS, OS was immature (information fraction of 49%); FDA considered ide-cel's effects on OS as part of the safety assessment.

The rate of adverse reactions of ide-cel was similar to prior studies, including the rate of the serious risks such as CRS, NT,HLH/macrophage activation syndrome (MAS), prolonged cytopenia, and infections. However, in KarMMa-3, a signal of increased early deaths was observed in patients randomized to ide-cel compared to patients randomized to SOC arm. Specifically, a higher proportion of patient randomized to ide-cel compared to SOC experienced death in with first 9 months following randomization (n=45/254;18% vs. n=15/132;11%). The higher early mortality with ide-cel was observed across multiple prognostic subgroups and was observed even in the absence of individual poor prognostic factors. In the safety analysis population, there was also a higher rate of fatal adverse reaction that occurred within 90 days from starting treatment with ide-cel arm compared to the SOC arm (2.7% versus 1.6%). The increased risk of early deaths and the benefit risk of ide-cel for the indicated population was discussed at an oncologic drug advisory committee meeting. The ODAC voted 8-3 that the benefit-risk was favorable.

Overall, the benefit of treatment with ide-cel outweigh its risks in the indicated population of patients with RRMM after two or more prior lines of therapy, including an IMiD, a PI, and an anti-CD38 monoclonal antibody The risks can be mitigated through product labeling and REMS.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Multiple myeloma (MM) is the second most common hematological malignancy. Therapy for patients with relapsed or refractory MM (RRMM) has improved considerably over the years with approval of multiple new therapies with improvement in response rate and PFS. However, MM remains incurable, with a 5-year survival rate of 60%.	RRMM is a serious and life-threatening condition.
Current Treatment Options	Drugs and combinations within the three main classes of IMID, PI, and anti-CD38 antibodies can be used in triple class exposed patients if they are not refractory to these agents. Two BCMA-directed CAR T cell therapies, cilta-cel and ide-cel, are approved in patients who have received four or more prior lines of therapy and who are triple class exposed. Several bispecific T-cell engagers have been approved in this population. Other options include selinexor-based regimens, high dose therapy followed by autologous transplant, and chemotherapy combinations. The selection of the regimen is based on exposure to prior regimens and tolerability considerations.	Despite the availability of multiple therapies, RRMM remains an incurable disease. Patient who are triple class exposed and have received at least two prior lines of therapy remains an unmet medical need.
Benefit	KarMMa -3 is a Phase 3, randomized, open-label controlled study that compared ide-cel to SOC arm with five anti-myeloma regimens (DPd, DVd, IRd, Kd, or EPd) in RRMM who have received 2 to 4 prior lines of therapy including a PI, an IMiD, and daratumumab. The primary endpoint point was PFS as assessed by an IRC. At a median follow up of 15.9 months, the median PFS in the ide-cel arm was 13.3 months compared to 4.4 months in the SOC arm, HR of 0.49 (95% CI: 0.379, 0.647 stratified p<0.0001). ORR was significantly improved with ide-cel arm compared to the SOC arm: 71% (95% CI: 66%, 77%; p<0.0001) compared to 42% (95% CI: 33%, 50%). . Similarly, the overall complete response rate (sCR +CR rate) was higher at 39% (95% CI:33, 45) in the ide-cel cel arm compared to 5% (95% CI: 1.5, 9.1) in the SOC arm.	• This study demonstrated improvement in PFS and ORR with ide-cel compared to the SOC arm in a triple class exposed relapsed and refractory multiple myeloma population. • The statistically significant improvement in PFS compared to the control arm represents clinical benefit in the proposed patient population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	The first interim OS analysis done at the time of the primary PFS analysis suggested a higher rate of deaths in the ide-cel arm compared to the SOC arm for up to 15 months (data cutoff April 18, 2022). Results from the second interim OS analysis done at the time of the final PFS analysis with more mature OS data and an additional one year of follow-up. These results were consistent with the first interim OS analysis with persistent OS detriment for approximately 15 months after randomization. An increased rate of early deaths was observed in the ide-cel arm compared to the SOC arm in the first 9 months post randomization; 18% versus 11%. This includes a higher rate of death from disease progression, any adverse events, and unknown causes. FDA convened a meeting of the Oncologic Drugs Advisory Committee (ODAC) to discuss whether the results of KarMMa-03 are sufficient to support a positive risk-benefit of ide-cel for the proposed indication and if the risk of early death associated with ide-cel treatment is acceptable in the context of the PFS benefit. The voting question for the ODAC was "is the risk-benefit assessment for ide-cel for the proposed indication favorable?" The ODAC voted 8 to 3 in favor of the risk-benefit assessment for ide-cel for the proposed indication. The most substantial risks with ide-cel arm are CRS, neurologic toxicity, prolonged cytopenia, HLH/MAS, life-threatening infections and hypogammaglobulinemia. CRS and NT were mitigated in the trial by careful site selection, training of investigators, and protocol-specified treatment guidelines.	Risk of early mortality associated with ide-cel observed in KarMMa-3 is added to the Warning and Precautions section of the USPI. The label for ide-cel has boxed warnings for CRS, neurologic toxicities, HLH/MAS, prolonged cytopenia with bleeding, and infection. Hypogammaglobulinemia is included under Warning and Precaution. T cell neoplasms have been reported with approved anti-CD19 and anti-BCMA CAR T therapies triggering a chimeric antigen receptor-T cell (CAR-T cell) therapy class safety labeling change to include this risk in Boxed Warning for Abecma's USPI.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	There are theoretical risks for secondary malignancy based on the potential for replication competent lentivirus due to the potential for insertional mutagenesis. No patients with T cell lymphoma were observed in the study. However, T cell neoplasms have been reported with approved anti-CD19 and anti-BCMA CAR T therapies triggering a CAR-T cell therapy class safety labeling change to include this risk in Boxed Warning.	

1.3 Patient Experience Data

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

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☒	Patient-reported outcome	8.1.2
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

2 Therapeutic Context

2.1 Analysis of Condition

The Applicant's Position:

MM is a plasma cell neoplasm that, despite recent advances in treatment, remains largely incurable. In the US, MM accounts for approximately 19% of hematologic malignancies, primarily occurring in older individuals (median age at onset of 69 years), and is very rare in individuals younger than 40 years.[1,2] In the US, 34,470 new cases of MM and 12,640 deaths due to MM were estimated in 2022.[3] African Americans are disproportionately affected by MM,[3] with higher incidence rates than for Whites reported overall (males: 15.9 vs. 7.5 cases per 100,000; females: 11.7 vs 4.5 cases per 100,000), a trend that also extends to mortality (males: 7.6 vs 4.0 deaths per 100,000; females: 5.6 vs. 2.4 MM deaths per 100,000.[4] Worldwide, 176,404 new cases of MM were reported in 2020, corresponding to an age standardized incidence of 1.78 per 100,000 persons with highest incidences in Australia and New Zealand, northern America, and northern Europe, and lowest incidences in western Africa, Melanesia, and southeastern Asia.[5] The mortality of MM in 2020 was 1.14 per 100,000 persons globally.[5]

The course of MM is characterized by a period of disease control after initial therapy followed by progression.[6,7] Tumors typically recur more aggressively with each relapse and with each subsequent line of therapy, leading to successive declines in rate (ORR), depth (CR), and duration of response (DoR), and ultimately, refractory MM, which is associated with shortened survival times.[8,9,10]

The increase in survival has been driven by the availability of newer therapies and novel combination approaches, as well as by improved supportive therapies.[11] However, even with optimal frontline therapy, most patients with MM progress or relapse, and need further treatment. The increasing use of triplet and quadruplet combination regimens in earlier lines of therapy, many of which include an anti-CD38 monoclonal antibody, limit therapeutic options in the myeloma patients who become triple class exposed in the early line relapse setting, and underscores the need for drugs with a novel mechanism of action.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

2.2 Analysis of Current Treatment Options

The Applicant's Position:

No clear standard of care exists in RRMM patients who become TCE earlier in the course of their disease.[11] Treatment options in frontline consist mostly of triplet and quadruplet combination regimens, including IMiDs and PIs, with or without DARA (NCCN[11] and EHA-ESMO[12] guidelines).

Therapeutic options after the first or second relapse are largely driven by the type, response, and tolerability of prior therapies received, and are comprised of regimens including next generation IMiDs or PIs, anti-CD38 mAbs, anti-SLAMF7 mAbs, HDAC inhibitors, nuclear export inhibitors, and alkylating chemotherapies.[11,12] In recent years, the expanded availability and use of DARA-based regimens in frontline and early line relapse patients has contributed to OS improvement in MM; however, this has also led to the emergence of a new subset of patients who are TCE (ie, IMiDs, PIs, and anti-CD38 monoclonal antibodies) earlier in their disease course.[13,14,15,16,17]

Exposure to these 3 classes of standard therapies profoundly impacts the disease course and biology, and leads to limited treatment options with poor clinical outcomes.[8,18,19,20,21,22] Notably, in a prospective observational study in TCE RRMM patients who received a median of 4 prior regimens, survival outcomes were similarly poor regardless of the number of prior therapies received, which further underscores that it is the content of prior regimens rather than the number of prior regimens received that most strongly impact clinical outcomes from subsequent therapies.[23] Despite several therapies having been recently approved for TCE RRMM patients, they are for patients with at least 4 prior lines of therapy, under the premise that the number of prior lines of therapy accurately pinpoints patients with an unfavorable prognosis based on existing treatments. However, in a fast-paced drug development environment and with assimilation of new agents in earlier disease settings, such a premise may likely result in a therapeutic vacuum for TCE patients in early line relapse.[24]

A clear unmet need exists for safe and effective treatments with novel modes of action for RRMM patients who became TCE earlier during the course of their disease. Conventional therapies in the early relapse setting have been evaluated and approved in populations that are not exposed to more than 2 classes of therapies in the early relapse setting. Given the increasing use of anti-CD38 mAb containing regimens in frontline and early line relapse, therapeutic options in TCE patients in this disease setting consist largely of between or within class switch regimens and treatment guidelines are non-specific. Real world data from TCE later line relapse patients indicates that disease control with conventional therapies is poor, with short mPFS of approximately 4 months and OS of about 1 year.[23,25] Therefore, the clinical profile of these conventional therapies for early line relapse TCE patients would be expected to be similarly poor.

A treatment option with a novel mechanism of action, that is capable of achieving deep and durable responses with a manageable safety profile, and that could offer the opportunity for prolonged disease control and treatment-free intervals for TCE RRMM patients is warranted given the current RRMM therapeutic landscape. Pivotal, Phase 3, MM-003, demonstrated the benefit of ide-cel compared with the standard regimens that are commonly utilized in current clinical practice for this patient population with unmet medical need.

The FDA's Assessment:

FDA agrees that patients who are exposed to the three major classes of myeloma therapy have an unmet medical need (Gandhi at al. 2019). While most patients in the United States with relapsed disease will have been exposed to an IMiD, a PI, corticosteroids, and an anti-CD38

monoclonal antibody (triple-class exposed), retreatment with previously used agents or agents in the same class of drug can be effective, provided that the patient is not refractory to that agent or was not exposed to that agent in the last line of therapy. The choice of treatment regimen is generally guided by both efficacy and tolerability considerations.

Selinexor, a selective inhibitor of nuclear export, in combination with bortezomib and dexamethasone, is another treatment option for triple-class-exposed patients with MM. Autologous HSCT is considered in eligible patients who have not received HSCT or had a prolonged response to initial HSCT. In addition, several alkylator-based chemotherapy regimens such as bortezomib-thalidomide-dexamethasone-cisplatin-doxorubicin-cyclophosphamide-etoposide (VTd-PACE), cyclophosphamide, and bendamustine-containing regimens are off-label treatment options for the triple-class-exposed population.

Two BCMA directed CAR T cell therapies, cilta-cel (USPI 2022) and ide-cel (USPI 2021) , are approved in patients who have received four or more prior lines of therapy and who are triple class exposed. In addition, several bispecific T-cell engagers have been approved in this population.

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Not applicable.

The FDA's Assessment:On March 26, 2021, FDA granted traditional approval to ide-cel for the treatment of RRMM after four or more prior lines of therapy including an IMiD, a PI, and an anti-CD38 monoclonal antibody. The approval was based on ORR, sCR, and duration of response observed in a single arm trial (KarMMa) which enrolled patients with RRMM with a median of six prior lines of therapy including an IMiD, a PI, and an anti-CD38 monoclonal antibody. The recommended regimen is a single dose of ide-cel, with a dose range of 300 to 460 x10e6CAR+ T cells administered by IV infusion and preceded by fludarabine and cyclophosphamide conditioning for lymphodepletion.

3.2 Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Table 2. Applicant - Regulatory Milestones and Prior Meetings/Alignment With FDA

Date	Regulatory Milestone
30-Sep-2015	IND 016664 submission to FDA (submitted by bluebird bio)
11-May-2016	Orphan drug designation granted for the treatment of MM; Designation #(b) (4)
12-Jul-2017	IND 016664 Change in Sponsor from bluebird bio to Celgene Corporation
14-Nov-2017	Breakthrough Therapy Designation granted for the treatment of patients with BCMA-expressing MM refractory to or relapsed after at (b) (4) prior therapies including a PI, an IMiD, and DARA
01-Mar-2018	Type B Breakthrough Therapy Designation Initial Comprehensive Multidisciplinary Meeting held to discuss the development program for ide-cel, including Study BB2121-MM-003 design; CRMTS #11071
19-Jul-2018	Study BB2121-MM-003 Original Protocol submitted to IND 016664, SN 130
19-Dec-2018	Study BB2121-MM-003 Protocol Amendment 1 submitted to IND 016664, SN 169
10-Jan-2020	Study BB2121-MM-003 Protocol Amendment 2 submitted to IND 016664, SN 264
27-Jul-2020	Original BLA 125736 submitted to support the safety and efficacy of ide-cel in relapsed/refractory multiple myeloma
26-Aug-2020	Study BB2121-MM-003 Protocol Amendment 3 submitted to IND 016664, SN 323
26-Mar-2021	Approval of Original BLA 125736 (Abecma for the treatment of adult patients with RRMM after four or more prior lines of therapy, including an IMiD, a PI, and an anti-CD38 monoclonal antibody)
12-Oct-2021	Written Responses received for the Type B Format and Content Meeting to support a supplemental BLA submission based on the results of Study BB2121-MM-003, CRMTS #13613
12-Nov-2021	Study BB2121-MM-003 Protocol Amendment 4 submitted to IND 016664, SN 406
01-Dec-2022	Type B Pre-sBLA meeting held to discuss a supplemental BLA submission based on the results of Study BB2121-MM-003, CRMTS #14352

The FDA's Assessment:

In addition to the Applicant's summary of the pre-submission and submission regulatory, the following additional key pre- and post-submission interactions are provided below:

Table 3. FDA – Regulatory History

Date	Purpose and/or Key Comments Provided
August 21, 2020	Protocol amendment to update CRS, neurotoxicity, and infection management guidelines to mitigate the risk of treatment-related mortality of 2.7% (9/326) observed with ide-cel across the clinical development program. Four out of the nine deaths which prompted revisions in the treatment guidelines had occurred in KarMMa 3.

Date	Purpose and/or Key Comments Provided
October 12, 2021	FDA advised that : • The second interim PFS analysis for superiority should be performed at approximately 80% information fraction (IF) rather than the Sponsor's proposed analysis at 67% IF. • The study should continue until the final PFS and OS analyses are complete, even after the primary efficacy endpoint is met, to evaluate that the long-term efficacy and safety of the investigational regimen. • Sponsor should propose statistical analyses to address the effect of crossover on OS. • Sponsor should perform OS analyses at the interim and final PFS analyses regardless of the outcomes of PFS and ORR analyses, since OS is an indicator of safety and efficacy.
November 29, 2022	FDA stated that PFS benefit alone is insufficient to assess the risk and benefit of ide-cel in the proposed population and that OS data will be required for a regulatory submission.
December 22, 2022	At pre-BLA meeting, Applicant stated their plan to submit an OS report with the planned sBLA. KarMMa-3 study team to remain blinded to OS data per the SAP.
January 4, 2023	Sponsor informed FDA that it planned to perform a post hoc interim OS analysis based on October 3, 2022, data cutoff, which aligned with 90-day safety update.
January 12, 2023	FDA advised that a post hoc interim OS analysis cannot be used to support efficacy labeling claims and the OS analysis should be submitted at the time of the submission.
January 13, 2023	Applicant submitted an addendum to the SAP which outlined the plan to spend an administrative alpha of 0.001 for the additional post hoc interim OS analysis.
February 15, 2023	The Applicant submitted an efficacy supplement which included the results of both the first and the unplanned (post hoc) interim OS analyses.
April 13, 2023	A filing notification was sent informing the Applicant of a standard review. The filing letter identified the early potential OS detriment observed in the ide-cel arm compared to the standard of care arm in KarMMa-3 as a potential review issue.
August 18, 2023	The Applicant submitted the results of the second prespecified interim OS analysis performed at the time of the final PFS analysis with a data cutoff date of April 28, 2023.
September 27, 2023	FDA notified that the timeline for the final OS analysis is projected for November 2024.
October 13, 2023	Teleconference with Applicant to discuss the updated OS analysis.
October 30, 2023	Teleconference meeting held to discuss the results of the following Applicant exploratory analyses: • Early mortality in the ide-cel arm in subjects with respect to high-risk features • OS analyses with and without any high-risk features • OS analyses with and without 17 p deletion

Date	Purpose and/or Key Comments Provided
November 17, 2023	Teleconference meeting held to inform the Applicant of FDA's plan to convene an oncology drug advisory committee meeting to discuss the benefit-risk of ide-cel for the indicated population given the potential OS detriment with ide-cel.
March 15, 2024	An oncologic drug advisory committee convened to discuss the following questions: • Whether the results of KarMMa 3 are sufficient to support a positive risk-benefit assessment of ide-cel for the proposed indication. • Is the risk of early death associated with ide-cel treatment acceptable in the context of PFS benefit?

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

4.1 Office of Compliance and Biologics Quality (OCBQ)

Not Applicable for this supplement.

4.2 Product Quality

Three subjects (USUBJID: (b) (6)) received non-conforming lots in the ide-cel arm. These three subjects were excluded from the safety analysis. Given the ITT nature of the efficacy analysis, these three subjects were included in the efficacy analysis. Two subjects in the SOC arm (USUBJID: (b) (6) and (b) (6)) received non-conformal ide-cel after cross-over. These two subjects were included in the safety and efficacy analysis for the SOC arm. These two subjects were excluded from the safety analysis of the ide-cel subgroup in the SOC arm. The product reviewer has recommended approval for this supplement.

4.3 Devices and Companion Diagnostic Issues

Not Applicable for this supplement.

5 Summary of Nonclinical Pharmacology/Toxicology Findings

The Applicant's Position:

Not applicable.

FDA assessment

No new nonclinical data were submitted or are in need of review in the current submission.

6 Clinical Pharmacology

The Applicant's Position:

Clinical Pharmacology analyses to characterize the cellular kinetics (interchangeably referred to as PK) of ide-cel, the relationship between ide-cel dose and cellular expansion, and to assess the impact of covariates on cellular expansion, efficacy, and safety in RRMM subjects were based on data from MM-003 as well as pooled data from MM-003 and MM-002, Cohort 1. PK parameters

were not pooled between MM-001 and MM-003 because different primary PK assays were used in these two studies. PK data from MM-003 and MM-002, Cohort 1 were pooled because the same PK assay (ie, ddPCR in whole blood) was used in both studies. Additionally, biomarker analyses using data from MM-003 were conducted.

Overall, the findings of PK characterization, E-R analyses, and dose response regression analyses based on the data from MM-003 and the pooled data (MM-003 and MM-002 [Cohort 1]) were consistent with previous analyses of ide-cel data. Results of the analyses showed a flat dose-exposure relationship from 300 to 540 × 10^6 CAR T cells and apparent positive relationships between exposure and efficacy responses. Dose-response analyses further demonstrated consistent and balanced efficacy through the dose range of 300 to 540 × 10^6 CAR T cells with manageable safety. The established E-R and dose-response relationships for efficacy and safety, as well as additional support based on efficacy and safety analyses by 10 × 10^6 CAR T cells dose increments indicates a positive benefit-risk assessment across the exposure range associated with the doses between 300 × 10^6 and 510 × 10^6 CAR+ T cells in TCE RRMM patients.

6.1 Cellular Product Characteristics Utilized in Evaluating Cellular Kinetics

Correlative relationships between cellular product characteristics and post-infusion cellular kinetics were evaluated via exploratory correlative analyses. Specifically, product characteristics including release attributes (T cell percentage, CAR T cell percentage, vector copy number, cell viability, and CD137 activation), and extended characterization attributes (T cell differentiation, T cell exhaustion/senescence, and BCMA-specific inflammatory/immunomodulatory cytokine secretion) were evaluated against Cmax, Tmax, AUC0-28 days, and Tlast within a univariate statistical model to assess the degree or extent of correlation between a given product attribute and a given PK endpoint.

The practical meaning of statistically defined ($Q < 0.1$; $p < 0.05$) relationships between product characteristics and PK parameters was established based on the magnitude of effect size or correlation coefficient, with strong relationships defined as having correlation coefficients $\geq|0.3|$, while potential relationships were defined as having correlation coefficients $\geq|0.1|$. No strong, practically significant relationships were identified between cellular product characteristics and PK endpoints; however, several potential relationships were identified for Cmax, Tmax, AUC0-28D, and Tlast for release and characterization attributes. These relationships include transduction state (CAR T cell percentage and vector copy number), effector T cell composition (CD3+CAR+CCR7-/CD45RA+ or CD3+CAR+CD28-/CD27-), and antigen-specific *in vitro* interferon gamma (IFNγ) where increasing attribute values all directly correlated with increasing Cmax, AUC0-28D. Conversely, increased proportions of senescent cells (CD3+CAR+CD57+) were associated with lower Cmax and will increased antigen-specific in vitro secretin of IL-5 was associated with delayed Tmax.

6.2 Characterization of Dose and Covariate Effects on Cellular Kinetics (PK)

PK characterization analyses conducted based on MM-003 and pooled data (MM-003 and MM-002, Cohort 1) showed that:

- The dose-exposure relationship, as characterized by the regression modeling analyses, suggested a statistically non-significant positive relationship between actual dose and exposure represented by AUC0-28D. Further analyses suggested similar exposures between the dose categories of 300 to 460 × 10^6 and > 460 to 540 × 10^6 CAR+ T cells and considerable inter-subject PK variability across all doses (> ~200% Geometric CV).

- Multivariable regression analyses identified several significant covariates for exposure represented by AUC0-28D in the ide-cel arm:

  - Baseline IL-15 and presence of baseline EMP were identified as significant covariates for exposure with positive and negative effects, respectively, and the magnitude of these effects was considered relatively modest (ie, up to 60% change for baseline IL-15 and ~40% decrease in AUC0-28 for presence of baseline EMP) relative to the overall exposure variability.

  - The post-infusion ADA status was found to be a significant covariate for exposure using the MM-003 data, but was statistically non-significant using the pooled data. This positive covariate effect should be interpreted with caution, since it was potentially associated with higher likelihood of observing positive ADA status in responders who had both better cell expansion and longer follow-up period than non-responders.

  - The effect of body weight was estimated to be a significant covariate with modest effect on exposure (ie, up to 40% change in AUC0-28D) in MM-003 while non-significant in the pooled data.

Vector platform type (sLVV or aLVV) was evaluated as a covariate in analyses of cellular expansion kinetics to support comparability assessment of the vector type, in addition to the manufacturing and clinical data. The covariate effect of the LVV type on exposure was estimated to be significant and modest using the MM-003 data (ie, < ~35% decrease in AUC0-28D in subjects dosed with ide-cel manufactured with sLVV vs aLVV), and did not translate into clinically meaningful differences in efficacy and safety outcomes.

6.3 Relationship between Pharmacodynamic Biomarkers and Clinical Outcomes

Biomarker analyses support select exploratory objectives of MM-003, which evaluated PD biomarkers and their relationships (univariate analyses) with baseline disease characteristics, safety events, and efficacy outcomes. Biomarker assessments included measurement of

cytokines, chemokines and other immune-related soluble factors including CRP and ferritin in the peripheral blood, detection and quantitation of tumor-associated BCMA antigen, both on tumor cells in the bone marrow and circulating in the peripheral blood (soluble BCMA), and determination of MRD negative status. Results of BCMA antigen assessments were also used to infer the frequency of suspected antigen escape after treatment with ide-cel. Key results are summarized below.

Immune-related soluble factors

- Immune-related soluble factors characteristic of T cell activation and proliferation were induced after ide-cel infusion; peak elevation was generally observed within 1 week and levels subsequently returned to baseline. Pre-infusion and Cmax concentrations did not differ across dose subgroups. Pre-infusion and Cmax concentrations were also similar across number of prior regimens subgroups with the exception that pre-infusion levels of CRP were higher in subjects who had received 3 or 4 prior regimens vs 2.
- Pre-infusion concentrations of a subset of cytokines, potentially indicative of basal inflammation, were associated with high tumor burden or high-risk tumor features, and suboptimal depth of clinical response.
- Higher peak concentrations of IL-15, a T cell homeostatic cytokine, were observed in subjects who achieved CR/sCR vs < CR.
- On the day of infusion, Ang-2 concentrations were positively associated with CRS grade; no other pre-infusion soluble factor levels were associated with incidence or grade of CRS. Substantially overlapping Ang-2 concentration ranges were observed across CRS grades and the prognostic value may be limited.
- Day of infusion Ang-2 and IL-8 were higher in subjects with Grade 2+ vs Grades 0-1 iiNT; no other pre-infusion soluble factor levels were associated with iiNT incidence or grade. Substantially overlapping concentration ranges were observed for both factors across iiNT grades and the prognostic value may be limited.
- Post-infusion peak concentrations of soluble factors associated with inflammation were correlated with CRS and iiNT incidence and grade, and were consistent with the mechanisms of action of ide-cel and etiology of CRS and iiNT.

Tumor associated factors

- Day of infusion sBCMA levels were positively correlated with a subset of high tumor burden or high-risk tumor features, and grade of CRS and iiNT in the ide-cel arm.
- Day of infusion levels of serum sBCMA were higher in subjects not achieving a response (<PR) and in subjects with < CR vs CR/sCR in both treatment arms, indicating the association may not be specific to the BCMA-directed CAR T mechanism of action.
- sBCMA clearance was observed in both treatment arms. Nadir levels were deeper and occurred earlier with ide-cel treated subjects vs standard regimens. sBCMA nadir correlated with depth of clinical response.
- The nadir and frequency of sBCMA clearance was not different across dose subgroups, but the frequency of subjects clearing sBCMA < lower limit of quantification was higher in

subjects who received 2 prior regimens vs 3 to 4 prior regimens supporting the benefit of ide-cel for patients in earlier treatment lines.

- sBCMA clearance at 2 months post-infusion (Month 3 Day 1 visit) and ongoing clearance at 6 months (Month 7 Day 1 visit) post-infusion were associated with more favorable mPFS in the ide-cel arm. Detectable sBCMA at these timepoints identified subjects at higher risk of progression.
- Evidence of BCMA expression (directly via BCMA+ immunohistochemistry result, or indirectly via detectable sBCMA) was observed in all evaluable subjects in the ide-cel arm at screening, and in 97.6% (82/84) of evaluable subjects at the time of progression, suggesting antigen loss was not a primary driver of treatment resistance/relapse after ide-cel treatment.

In summary, univariate analyses of the relationship between 27 cytokines and dose category or incidence/grade of CRS or iiNT were conducted. Pre-infusion and peak post-infusion (Cmax) levels of all evaluated cytokines and chemokines were found to be similar across the dose categories of 300 to 460 and > 460 to 540 $\times 10^6$ CAR+ T cells; interpretation was limited for dose category < 300 $\times 10^6$ CAR+ T cells due to the limited number of subjects (n = 3) in this group. Pre-infusion Ang-2 levels were found to be positively associated with CRS grade; pre-infusion Ang-2 and IL-8 levels were positively associated with iiNT incidence and grade. Cmax levels of a number of cytokines and chemokines associated with T cell activation and function were associated with CRS and iiNT incidence and/or grade, consistent with the etiology of these toxicities. In almost all cases, peak concentrations were higher for any vs no CRS/iiNT and showed a positive association with CRS/iiNT grade subgroup.

6.4 Dose Response Regression Analysis of Safety

The dose-response regression analyses were conducted using both data from MM-003 and pooled data (MM-003 and MM-002 [Cohort 1]) to address the feedback received from FDA during the Type B content and format interaction on 12-Oct-2021 (CRMTS #13613).

Model-based analyses showed no statistically significant relationship between dose and iiNT(Grade 2+). A statistically non-significant positive relationship was also found between dose and tCRS/sCRS. The linear regression model suggested a positive significant relationship between dose and CRS (Grade 3+), which should be interpreted with caution as the visual inspection suggested potential inconsistency between data and model prediction at the high doses.

Several significant covariates were identified from the multivariable dose-response regression analyses based on MM-003 data from the ide-cel arm:

- Higher baseline sBCMA was found to be associated with higher iiNT(Grade 2+) rate. (Note: Baseline sBCMA refers to day of infusion sBCMA in the dose-response regression analyses.)
- Baseline sBCMA and body weight were found to be positively and negatively associated with CRS (Grade 3+) rate, respectively. However, the significant covariate effects on CRS (Grade 3+) should be interpreted with caution.

Sensitivity analyses suggested that the findings on dose-response relationships and covariate effects for tCRS and sCRS using the pooled data (MM-003 and MM-002 [Cohort 1]) were overall consistent with the findings obtained with data from MM-003. However, non-significant covariate effect of baseline sBCMA on iiNT (Grade 2+) and significant covariate effect of body weight on tCRS were found using the pooled data.

6.5 Drug-Biologic Interactions Related to Risk Mitigation Medications or Lymphodepletion

Neither tocilizumab/siltuximab nor corticosteroids used to manage CRS had a negative impact on ide-cel PK. In MM-003, patients with CRS treated with tocilizumab/siltuximab had higher cellular expansion levels, as measured by 3.1-fold and 2.9-fold higher median Cmax (N=156) and AUC0-28D (N=155), respectively, compared to patients who did not receive tocilizumab/siltuximab (N=64 for Cmax and N=63 for AUC0-28D). Similarly, patients with CRS treated with corticosteroids had higher ide-cel cellular expansion levels, as measured by 2.3-fold and 2.4-fold higher median Cmax (N=60) and AUC0-28D (N=60), respectively, compared to patients who did not receive corticosteroids (N=160 for Cmax and N=158 for AUC0-28D).

Lymphodepleting chemotherapy in MM-003 and MM-002 consisted of cyclophosphamide and fludarabine, starting 5 days prior to the target infusion date of ide-cel. Fludarabine was dose-reduced for renal insufficiency. The effect of lymphodepletion on PK was not evaluated as the same body-surface-area-based dose regimens of cyclophosphamide and fludarabine were consistently applied to all patients treated with ide-cel in MM-003 and MM-002.

6.6 Alternate Dosing Regimens for Specific Sub-Populations

The clinical pharmacology analyses suggest that no alternate dosing regimens are needed for specific sub-populations. The multivariable logistic regression analyses for MM-003 and the pooled data of MM-003 and MM-002, Cohort 1 revealed that body weight, age, and sex have limited covariate effects on ide-cel PK parameters.

The covariate effect of body weight on PK exposure was estimated to be modest, with the estimated change within 40% at the 5th and 95th percentiles of baseline body weight, considerably lower than the observed inter-subject variability (>~200% Geometric CV) in exposure parameters in MM-003. Thus, the overall effect of body weight on the ide-cel PK is not considered to be clinically relevant.

The covariate effects of age and sex were not found to significantly influence ide-cel PK. The covariate effects of race and ethnicity on PK using the MM-003 and pooled data were not evaluated due either to missing values or to less than 10% of subjects falling into the related categories.

The FDA's Assessment:

Presented below is a brief summary from the Clinical Pharmacology review memo:

Pharmacokinetics/Cellular Kinetics

- In KarMMa-3, ide-cel arm, following a single dose infusion of ide-cel (dose range: 175 to 529 x 10^6 CAR+ T cells), the cells proliferated and underwent rapid multi-log expansion, with the maximum peak expansion occurring at a median of 11 days across the ide-cel actual doses. The extent of cell expansion during the first month post-infusion ($AUC_{0\text{-}28D}$) represents more than 80% of the cumulative exposure at 3 months ($AUC_{0\text{-}3M}$) post-infusion. High inter-subject variability was observed in the PK profiles of ide-cel.

- Age, ethnicity, race, and sex had no obvious impact on exposure of ide-cel. No dose-adjustment is needed for specific populations.

- The exposure of ide-cel was comparable between the dose categories of 300 to 460 and 460 to 540 x 10^6 CAR+T cells.

- In general, immune-related soluble factors characteristic of T cell activation were induced after ide-cel; peak elevation was generally observed within the first 7 days after infusion, and levels subsequently returned to baseline. Both pre-infusion and peak post-infusion (C_{max}) levels of evaluated soluble factors were similar across the 2 dose subgroups of 300 to 460 × 10^6 CAR+ T cells and > 460 to 540 × 10^6 CAR+ T cells.

Please refer to the clinical pharmacology review memo for additional details.

7 Sources of Clinical Data

7.1 Table of Clinical Studies

Table 4. Applicant - Listing of Clinical Studies Relevant to this sBLA

Study	Design/ *Primary Objective*	Population	Regimen and Dose	Study Status/ Number of Subjects	Data Cutoff Dates
Phase 3					
BB2121-MM-003 NCT03651128 Countries: 12 Sites: 49	Randomized, open-label study comparing the efficacy and safety of ide-cel vs standard regimens *PFS per IRC*	Subjects (≥ 18 years), with RRMM who had received 2-4 prior myeloma regimens including DARA, an IMiD, and a PI, with documented disease progression during or within 60 days after the last prior therapy	**Ide-cel:** Planned Dose Range: 150 to 450 × 10^6 CAR+ T cells/IV infusion after LD chemotherapy **Standard Regimens**[a]	Ongoing for follow-up (enrollment closed) **Randomized:** 386 **Treated:** 376 Ide-cel: 250 Standard Regimens: 126 **Safety Population:** 351 Ide-cel: 225 Standard Regimens: 126	18-Apr-2022
Phase 2					
BB2121-MM-001 NCT03361748 Countries: 7 Sites: 20	Open-label, single-arm study *ORR per IRC*	Subjects (≥ 18 years) with RRMM who had received at least 3 prior therapies, including: an IMiD, a PI, and an anti-CD38 antibody, and who were refractory to their last prior treatment regimen	**Dose Range**: 150 to 450 × 10^6 CAR+ T cells/IV infusion after LD chemotherapy	Ongoing for follow-up (enrollment closed) **Enrolled:** 140 **Treated:** 128	Efficacy: 14-Jan-2020 Safety: 16-Oct-2019
BB2121-MM-001-Japan NCT03361748	Open-label, single-arm study *ORR*	Subjects (≥ 18 years) who had received least 3 prior therapies, including: an IMiD, a PI, and an anti-CD38 antibody, and who were	Planned Dose Range: 150 to 450 × 10^6 CAR+ T cells/IV infusion after LD chemotherapy	Ongoing (enrollment closed) **Enrolled:** 9 **Treated:** 9[b]	21-Dec-2020

Study	Design/ *Primary Objective*	Population	Regimen and Dose	Study Status/ Number of Subjects	Data Cutoff Dates
Countries: 1 Sites: 4		refractory to their last prior treatment regimen			
BB2121-MM-002 NCT03601078 Countries: 5 Sites: 21	Multicohort, open-label, study *To evaluate the efficacy of ide-cel*	Subjects (≥ 18 years) with: Cohort 1: RRMM and ≥ 3 prior AMT regimens, including an IMiD, a PI, and an anti-CD38 mAb Cohort 2a and 2b: early relapse after 1 prior AMT with or without ASCT Cohort 2c and Cohort 3: NDMM who have achieved suboptimal response after induction and ASCT	Planned Dose Range: 150 to 450 × 10^6 CAR+ T cells/IV infusion after LD chemotherapy	Ongoing (enrollment ongoing) 235 planned **Enrolled / Treated** Total: 182 / 167 Cohort 1: 76 / 68 Cohort 2a: 39 / 37 Cohort 2b: 35 / 31 Cohort 2c: 32 / 31	14-Mar-2022
Phase 1					
CRB-401 NCT02658929 Countries: 1 Sites: 9	Open-label, single-arm, 2-part (dose escalation [Part A] and dose expansion [Part B]), study *Part A: determine the MTD of ide-cel* *Part B: confirm the safety of the dose(s) chosen in Part A*	Subjects (≥ 18 years) with: Part A: RRMM who had received at least 3 different prior lines of therapy, including a PI and IMiD or had double refractory disease to a PI and IMiD Part B: RRMM who had previous exposure to a PI, IMiD, and DARA and was refractory (based on IMWG criteria) to their last line of prior therapy.	Part A (dose escalation) 50, 150, 450, or 800 × 10^6 CAR+ T cells Part B (dose expansion) 150 to 450 × 10^6 CAR+ T cells	LPLV achieved **Enrolled / Treated** Part A: 24 / 21 Part B: 43 / 41	07-Apr-2020
BB2121-MM-004 NCT04196491 Countries: 1 Sites: 8	Open-label, single-arm study *Safety and determine the optimal dose of ide-cel*	Subjects (≥ 18 years) with high-risk (R-ISS stage III) NDMM	Part A (dose finding) 150, 300, 450, or 800 × 10^6 CAR+ T cells after LD chemotherapy Starting dose: 450 × 10^6 CAR+ T cells Part B (dose expansion) Closed	Ongoing (enrollment closed) **Enrolled / Treated** 13 / 13	15-Apr-2022

Study	Design/ *Primary Objective*	Population	Regimen and Dose	Study Status/ Number of Subjects	Data Cutoff Dates
Long-term Follow-up					
LTF-305 (aligns with parent study CRB-401) NCT02786511 Countries: 1 Sites: 5	Open-label, non-randomized, long-term safety and efficacy follow-up	Subjects with RRMM who were treated with ide-cel in Study CRB-401	No treatment administered	Enrollment completed Study closed Enrolled: 20	Safety: 22-Jul-2019
GC-LTFU-001 NCT03435796 Countries: 6 Sites: 16	Open-label, non-randomized, long-term safety and efficacy follow-up	Subjects previously treated with gene- modified T cells in Sponsor's studies	No treatment administered	Ongoing Enrolled: 46	Aligns with parent study

Note: Ide-cel doses exceeding 20% of the upper dose limit constituted an overdose. LD chemotherapy was 3 consecutive days of fludarabine 30 mg/m^2 and cyclophosphamide 300 mg/m^2 IV

[a] The choice of study treatment is dependent on the subject's most recent antimyeloma treatment regimen. Regimens included DARA + POM + dex (DPd), DARA + BTZ + dex (DVd), IXA + LEN + dex (IRd), CFZ + dex (Kd), or ELO + POM + dex (EPd)

[b] All Japan subjects were treated at the target dose of 450 × 10^6 CAR+ T cells.

The FDA's Assessment:

FDA agrees with the Applicant's listing of clinical trials relevant to this submission.

8 Statistical and Clinical Evaluation

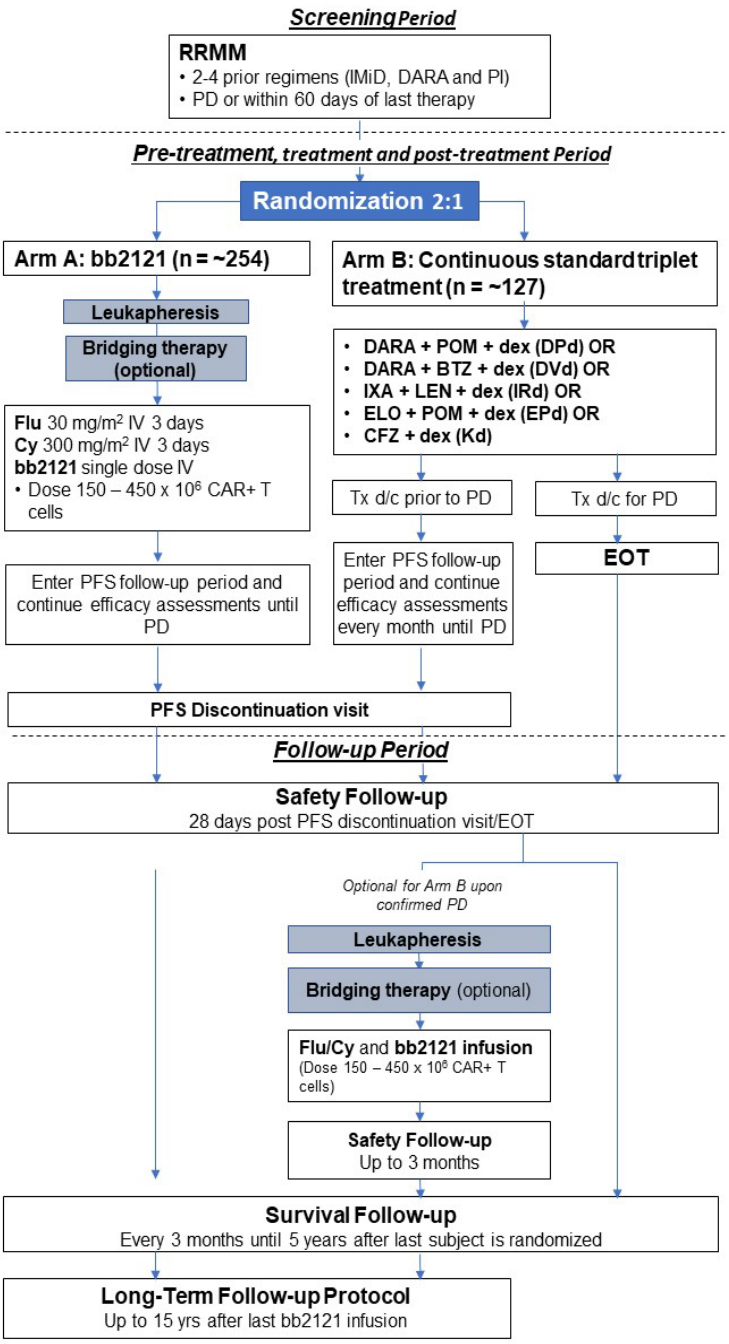
8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1 Pivotal Phase 3 Study BB2121-MM-003 (MM-003)

Trial Design

The Applicant's Description:

Figure 1. Applicant - Overall Study Design for MM-003



MM-003 is an ongoing, open-label, multi-center, global, randomized, controlled Phase 3 study comparing the efficacy and safety of ide-cel vs standard regimens in subjects with RRMM. Subjects were to have received at least 2 but no greater than 4 prior MM regimens, including DARA, an immunomodulatory agent, and a PI. Documented disease progression was required during or within 60 days of last dose of prior therapy.

Note: Based on the evolving treatment landscape for the patient population included in this study, 2 additional standard regimen options (EPd and Kd) were added via protocol Amendment 2.0 dated 17-Dec-2019.

Table 5. Applicant - MM-003 Study Design Details

Design Aspect	Description	
Eligibility Criteria	These inclusion/exclusion criteria are in line with other CAR T clinical trials in RRMM. Subjects eligible for this study were intended to be representative of the TCE early line relapse MM population by:	

Design Aspect	Description	
	• Not requiring an upper age limit and not limiting eligibility based on gender, race, or ethnicity • Requiring disease characteristics based on prior therapies, in alignment with the protocol identified unmet medical need population • Including safety requirements (i.e., laboratory abnormalities, organ function, clinically relevant coexisting conditions and concomitant treatments) driven by the known safety profiles of the study treatments	
Trial location	49 sites in 12 countries	
Choice of control group	The standard regimens allowed in the study consisted of DPd, DVd, or IRD, and from Protocol Amendment 2.0 (17-Dec-2019) onwards, additionally EPd or Kd. DKd was not included as a standard regimen option as it did not receive FDA approval until 20-Aug-2020, and 2 DARA triplets were already included in the study. There is no therapeutic option approved in TCE early line relapse patients. As such, the conventional therapies used in this disease consist of regimens evaluated in and approved for the treatment of double class exposed patients (ie, IMiD and PI), based on the within or between class switch treatment paradigm in RRMM and regional treatment guidelines. These standard regimens represented an appropriately broad choice to ensure the external validity of this global study data, by enabling investigators to select a regimen most appropriate to each subject, in line with this treatment paradigm. Although the use of 5 regimens introduced a degree of heterogeneity in the control arm efficacy and safety outcomes, the Sponsor's decision to include these regimens addressed Health Authority feedback and was in alignment with advice received from MM clinical expert advisors. As such, the study design incorporating an investigator's choice control arm containing an option of standard regimens is consistent with concepts for drug development discussed (and subsequently published) at an Office of Oncologic Disease symposium in 2019.[26] To avoid bias in the selection of a standard regimen for the control arm subjects, investigators chose a standard regimen prior to randomization. Investigator's choices were governed by the RRMM therapeutic guidelines (ie, subject's clinical features and disease history) as well as by protocol requirements prohibiting the reuse of regimens used as most recent prior therapy. The assigned regimen could have been used as bridging therapy if the subject were randomized to the ide-cel arm, or as control arm therapy if the subject were randomized to the standard regimens arm. As expected, no subject in the standard regimens arm received the same regimen as their last prior regimen. All standard regimens arm subjects received at least one agent that was different from the ones in the last prior regimen. This is particularly relevant to subjects refractory to DARA, in whom within class switches are not available. Emerging data in DARA-refractory patients indicate that reintroduction of a previously failed IMiD while retaining DARA as a backbone can overcome refractoriness to both classes, which is likely due to the synergistic effect between IMiDs and DARA.[27,28] The most frequently selected standard regimen having been DPd (~33% subjects), given 69% of subjects were DARA refractory in the most recent prior regimen, likely reflects that these data might have been a consideration the investigators used. Therefore, the regimens received by subjects in the	

Design Aspect	Description	
	standard regimens arm reflect the fact that study investigators optimized treatment selection based on the patients' treatment history.	
Diagnostic criteria	The diagnostic criteria and definitions to enroll patients in this study are reflective of: • Standard treatments given in frontline and early line relapse myeloma • IMWG definition of refractory disease • IMWG definition of measurable disease • The RRMM population in which ide-cel and the study standard regimens are considered to be safe to administer based on their known safety profile	
Key inclusion/ exclusion criteria	Inclusion 1. ≥ 18 years of age at the time of signing the ICF. 2. Documented diagnosis of MM and measurable disease, defined as: • M-protein: sPEP ≥ 0.5 g/dL or uPEP ≥ 200 mg/24 hours and/or • Light chain MM without measurable disease in the serum or urine: Serum immunoglobulin free light chain ≥ 10 mg/dL (100 mg/L) and abnormal serum immunoglobulin kappa lambda free light chain ratio 3. Received at least 2 but no greater than 4 prior MM regimens. 4. Received prior treatment with DARA, a PI and an IMiD for at least 2 consecutive cycles. 5. Refractory to the last treatment regimen, defined as documented progressive disease during or within 60 days (measured from the last dose of any drug within the regimen) of completing treatment with the last anti-myeloma regimen before study entry. 6. Achieved a response (MR or better) to at least 1 prior treatment regimen. 7. ECOG performance status of 0 or 1. Exclusion 1. Any of the following laboratory abnormalities: • ANC < 1,000/µL • Platelet count: < 75,000/µL in subjects in whom < 50% of bone marrow nucleated cells are plasma cells and platelet count < 50,000/µL in subjects in whom ≥ 50% of bone marrow nucleated cells are plasma cells (it is not permissible to transfuse a subject to reach this level) • Hemoglobin < 8 g/dL (< 4.9 mmol/L) (it is not permissible to transfuse a subject to reach this level) • Serum CrCl < 45 mL/min • Corrected serum calcium > 13.5 mg/dL (> 3.4 mmol/L) • Serum AST or ALT > 2.5 × ULN • Serum total bilirubin > 1.5 × ULN or > 3.0 mg/dL for subjects with documented Gilbert's syndrome • International normalized ratio or aPTT > 1.5 × ULN, or history of Grade ≥ 2 hemorrhage within 30 days, or subject requires ongoing treatment with chronic,	

Design Aspect	Description	
	therapeutic dosing of anticoagulants (eg, warfarin, low molecular weight heparin, Factor Xa inhibitors) 2. Active or history of plasma cell leukemia, Waldenstrom's macroglobulinemia, POEMS syndrome or amyloidosis. 3. Known central nervous system involvement with myeloma. 4. Uncontrolled systemic fungal, bacterial, viral or other infection (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antimicrobial treatment) or requiring IV antimicrobials for management.	
Dose selection	A dose range of 150 to 450 x 10^6 CAR+ T cells was chosen for MM-003 based on the results of Phase 1 study CRB-401.	
Study treatments	Ide-cel arm: Single IV infusion of 150 to 450 x 10^6 CAR+ T cells (dose exceeding 20% of the upper limit constituted overdose) after LD chemotherapy (3 consecutive days of fludarabine 30 mg/m^2 and cyclophosphamide 300 mg/m^2 IV) Standard regimens: DPd, DVd, IRd, Kd, or EPd doses and dosing regimens per approved labels, given until confirmed progression, unacceptable toxicity, or consent withdrawal.	
Assignment to treatment	Subjects were randomized 2:1 to ide-cel or standard regimens using IRT, stratified by: • Age: < 65 vs ≥ 65 years. • Number of prior antimyeloma regimens: 2 vs 3 or 4. • High risk cytogenetic abnormalities; t(4;14) or t(14;16) or del 17p: presence vs absence or unknown presence.	
Blinding	Investigators and subjects were unblinded to treatment assignments for individual subjects. IRC members have been blinded to treatment assignments. The clinical team from the sponsor, statisticians, and statistical programmers had access only to individual treatment assignments when reviewing subject-level clinical data; however, IA1 (futility) was performed by an independent statistical organization and the results were presented to the DSMB for review. The study team did not have access to IA1.	
Dose modification, dose discontinuation	Ide-cel: Not applicable as ide-cel was administered as a single IV infusion. Standard regimens: At the Investigator's discretion per the full prescribing information and labeling	
Administrative structure	An IRC reviewed all data for response assessment and determined response to therapy based on IMWG Uniform Response Criteria, blinded to treatment allocation.[29] An independent DSMB reviewed cumulative data over the course of the study to evaluate safety and efficacy, protocol conduct, and scientific validity and integrity of the study. A SSC was implemented to oversee the conduct of this trial; the SSC served in an advisory capacity to the Sponsor.	
Concurrent medications	Subjects with myeloma-associated bone disease could receive bisphosphonate therapy prior to study entry and it was permitted throughout the study. Platelet/RBC transfusions and hematopoietic growth factors were also permitted. Concurrent use of hormones for noncancer-related conditions was acceptable. For subjects treated with ide-cel, up to 1 cycle of DPd or DVd or IRd or Kd or EPd was allowed as bridging therapy while ide-cel was being manufactured.	

Design Aspect	Description	
Treatment compliance	Monitored by drug accountability, as well as subject's medical record and eCRF.	
Rescue medication	No rescue medications were planned.	
Subject completion, discontinuation, or withdrawal	Subjects randomized to ide-cel were followed for efficacy until confirmed PD or withdrawal of consent. Subjects randomized to standard regimens received study treatment until confirmed PD, unacceptable toxicity, or withdrawal of consent. Subjects who permanently discontinued treatment with DPd, DVd, IRd, Kd or EPd prior to confirmed PD were followed (PFS-follow-up period) until confirmed PD. If requested by the Investigator, subjects in the standard regimens arm had the option to receive ide-cel upon confirmation of PD by the IRC and confirmed eligibility. Subjects on both treatment arms were followed for survival status on the study from time of documented disease progression (or after 3 months post Treatment Follow-up for Treatment Arm B subjects that have received ide-cel) up to 5 years after the last subject has been randomized. All subjects who received ide-cel and completed the survival follow-up period specified in the protocol or withdrew from this study were asked to enroll in Study GC-LTFU-001. As specified in the SAP, safety data from GC-LTFU-001 for subjects who are from MM-003 were combined with the parent study, as appropriate. Subjects who withdrew from the study were not replaced so the intent-to-treat population could be retained for between arm comparison. Their survival status and last known alive/death date were collected based on the data availability legal allowance. The collected data are included in survival analysis as specified in the SAP.	

Key procedures and schedule:

Table 6. Applicant – MM-003 Procedures and Schedule

	AEs	SAEs	SPM
Screening	Required	Required	-
Treatment	Continuous	Continuous	Continuous
PFS Follow-up	Continuous[a]	Continuous[a]	Continuous
Follow-up	Every 3 months	Every 3 months	Every 3 months

[a] All AEs were collected continuously from informed consent signature (for AESI from ide-cel infusion) for a minimum of 6 months post ide-cel infusion (through Month 6). Grade ≥ 3 AEs, all SAEs, and all AESIs were collected from Month 7 until 28 days after PFS Discontinuation Visit.

The FDA's Assessment:

Overall, FDA agrees with the Applicant's description of the study design, eligibility criteria, and treatment outlined above with the following additions.

1. The availability of five different regimens in the SOC arm broadened the therapeutic options for a heavily pre-treated myeloma population; however, this created significant heterogeneity in the SOC arm. The study was not powered to compare the efficacy of ide-cel arm to each of the treatment subgroups in the SOC arm or to compare the outcome of each regimen in the SOC arm.

2. Prior to randomization, investigators selected one of the five protocol specified regimens to be administered as treatment in the SOC arm or as bridging therapy (BT) in the ide-cel arm based on similar clinical criteria. The role of BT is to stabilize the disease while awaiting product manufacture.

3. For the subjects who received ide-cel upon cross over from the SOC arm, all AEs were collected for 3 months post-infusion. This was followed by survival follow-up during which all secondary primary malignancies, all possibly related Grade 3 and higher AEs, SAEs, and AESIs were collected until the end of the study. Since ide-cel was administered as a subsequent therapy in the SOC arm, the AE collection beyond 3 months post-infusion for this subgroup was different than the upfront ide-cel arm.

4. In addition to the assessment for eligibility at the time of screening, subjects in the ide-cel arm were evaluated prior to leukapheresis, prior to administration of lymphodepleting chemotherapy, and prior to ide-cel infusion to ensure that they were suitable for CAR T infusion.

Study Endpoints

The Applicant's Description:

Parameters chosen to monitor efficacy were based on appropriate standard of care and response guidelines for patients with MM. Response assessments were evaluated using the IMWG Uniform Response Criteria,[29] based on data generated at central laboratories and from local imaging, and assessed by the IRC in blinded fashion. The ITT population, which included all subjects randomized to one of the two treatment arms, was used for the primary analysis for efficacy.

The primary endpoint of the study was PFS ()which is a standard efficacy endpoint used in oncology clinical trials and has been utilized as a primary endpoint in most randomized Phase 3 trials that form the basis of approval of new therapies in MM. Per the primary definition, PFS was calculated as the time from randomization to the first documented progression or death due to any cause on study, whichever occurs first. The progression date was assigned to the earliest time when any progression was observed without prior missing assessments during the study. If withdrawal from the study due to adverse events or change of therapy occurs before documented progression or death, then these observations were censored at the date when the last complete myeloma response assessment determined a lack of progression.

The median PFS (9 months vs 14 months for Arm B vs Arm A) in the statistical assumption was calculated from randomization for both treatment arms. Considering the potential non-proportional hazard function due to the delayed study treatment in Treatment Arm A (ide-cel) by approximately 1 month post randomization, the statistical power was still estimated to be > 85%. Assuming a 76% event rate, a total of 381 subjects (254 in Arm A and 127 in Arm B) were to be randomized.

The key secondary endpoints included ORR and OS. ORR was defined as the percentage of randomized subjects who achieved a best response of at least PR. OS was defined as the time from randomization to the date of death from any cause. OS was censored at the last date known alive for subjects who are alive at the time of analysis.

Table 7. Applicant - MM-003 Key Endpoints

Endpoint	Description
Primary	
PFS by IRC	Time from randomization to the first documentation of progressive disease, or death due to any cause, whichever occurs first
Key Secondary Endpoints (Hierarchically Tested)	
ORR by IRC	Percentage of subjects who achieved PR or better
OS[a]	Time from randomization to time of death due to any cause
Other Secondary Endpoints	
CR rate by IRC	Percentage of subjects who achieved CR or better.
DoR	Time from first documentation of response (PR or better) to first documentation of disease progression or death from any cause, whichever occurs first
TTR	Time from randomization to the first documentation of response (PR or better)
EFS	Time from randomization to the first documentation of PD, first day when subject receives another antimyeloma treatment or death due to any cause, whichever occurs first
PFS2	Time from randomization to second objective PD on subsequent therapy (Ide-cel Arm: PD observed after the next antimyeloma regimen that is different from ide-cel regimen; Standard Regimens: subsequent therapy including ide-cel) or death from any cause, whichever is first
Time to next antimyeloma treatment	Calculated as the time from randomization to the first day when subjects receive another antimyeloma treatment, which includes ide-cel for subjects in the standard regimens arm.

[a] The p-value for OS did not cross the significance boundaries for either efficacy superiority or futility and the study team remains blinded.

The FDA's Assessment:

FDA agrees with the Applicant's description of key study endpoints with the following additional comments.

- With final OS analysis at 222 events, KarMMa-3 was powered to detect a HR of 0.74 with 50% power, which would translate into a 7-month difference between the two arms.

- The Applicant originally proposed a single control arm of DPd. The statistical assumption of 9 months for the median PFS and 50% for the ORR in the SOC arm was based on the efficacy data for the registrational trial, EQUULEUS, which evaluated DPd in patients who had received lenalidomide and bortezomib after at least two prior lines but were pomalidomide and daratumumab naïve. This study demonstrated a median PFS of 9.9 months and ORR of 66%. (Facon T et al. 2017). Since KarMMa-3 enrolled a more heavily pre-treated population, the assumptions for the median PFS and ORR were considered acceptable. In July 2018, the

Applicant expanded the SOC arm to include two additional regimens: DVd and IRd in addition to DPd. Subsequently, two additional regimens (EPd, and Kd) were added in December 2019 based on an evolving treatment landscape. The registrational trials of these four regimens (DVd, IRd, Kd, and EPd) include a less advanced myeloma population in earlier lines of therapy and, therefore, did not inform the statistical assumptions of the SOC arm.

Statistical Analysis Plan and Amendments

The Applicant's Description:

Primary efficacy analyses were performed on the ITT population (all randomized subjects). The primary endpoint (PFS) and key secondary endpoints (ORR and OS) were tested in a hierarchical order from PFS to ORR and then to OS to control type I error rate. Two interim analyses, one for futility and one for superiority of efficacy, were planned for the primary efficacy endpoint PFS. The first interim analysis was conducted at approximately 33% information for futility, the second interim at approximately 80% information for superiority.

Since both the PFS and ORR analysis crossed the pre-specified significance boundary at PFS IA2 for superiority of efficacy, OS formal testing was performed by the DSMB. However, the p-value did not cross the boundaries for either efficacy superiority or futility and the study team remains blinded.

The following algorithms were considered for missing data: 1) The stratification based on data from CRF and centralized lab analysis with missing values imputed by the values from IRT was used for stratified analyses and subgroup analyses using the stratification factors; 2) Subjects without a best overall response assessment are considered as non-responders in the analysis of ORR; 3) In PFS analysis, PD or death right after missing 2 (or more) consecutive scheduled assessments is censored using last adequate efficacy assessment date with no evidence of PD; 4) Adverse events with a missing relationship to study drug (bridging therapy, LD chemotherapy, bb2121, study medication in standard regimens) are presented in the summary table as "treatment-related" for the corresponding treatment administered; 5) Partially missing data is imputed as described in SAP Section 18.2.1. No imputation was conducted for other missing data.

The original SAP (version 1.0, dated 19-Aug-2021) was submitted to the FDA as part of Type B Written Response Only Meeting Package, CRMTS #13613. The most recent SAP (version 2.0) based on protocol amendment 4 was submitted to the FDA on 28-Jan-2022. The SAP was not changed thereafter and was considered as finalized before the DSMB reviewed the data on 09-Aug-2022 and the trial data were subsequently unblinded.

The FDA's Assessment:

The statistical analysis plan (SAP) was updated to Version 2.0 dated December 19, 2021, to incorporate FDA WRO CRMTS #13613 from October 12, 2021. The following major revisions were made to the SAP:

- The information fraction was updated from 67% to 80% for the primary PFS analysis

(second interim) to support a regulatory submission.

- Statistical analyses were added to address the impact of treatment cross-over on OS.

- Two interim analyses were added for OS: first analysis at the time of the second interim PFS analysis at 80% IF and the second analysis at the time of the final PFS analysis. Both the analyses would be conducted regardless of whether PFS and ORR demonstrated statistical significance. The OS analyses will assess for any potential OS detriment given the toxicity of CAR T products since OS is an important metric for safety in addition to efficacy.

- For the primary efficacy analysis, the event, and censoring rules for PFS were aligned with the FDA Guidance For Clinical Trial Endpoints For The Approval of Oncology Drugs and Biologics.

- Addition of supportive analysis on the primary endpoint to evaluate the imbalance in the dropout rate and informative censoring between two treatment arms.

On August 5, 2022, the Data and Safety Monitoring Board (DSMB) reviewed the data from PFS IA2 (second interim analysis). Progression-free survival and ORR crossed the superiority boundaries with p-values <0.0001. The other key secondary efficacy endpoint, OS, did not cross the efficacy boundary or the futility boundary. The study team remained blinded to the OS data per the SAP.

An independent team within the company was assembled to handle the unblinded OS data. At the time of the PFS IA2 (primary PFS analysis), approximately 10% of the subjects (39 out of 386 randomized subjects) had missing OS data as patients had discontinued the study due to various reasons: voluntary withdrawal, physician decision, and lost to follow-up. Consequently, the Applicant conducted an additional post-hoc OS interim analysis using the 90-day safety update data cutoff date, (October 3, 2022). For this additional OS interim analysis, an administrative alpha corresponding to a superiority boundary of 0.001 was spent. An addendum to the SAP version 2.0 was made on January 6, 2023, to document this additional OS interim analysis.

Protocol Amendments

The Applicant's Description:

The original protocol was dated 13-Jul-2018. As of the data cutoff (18-Apr-2022), there were 4 global protocol amendments. None of the changes impacted the overall quality or outcome of the study.

Table 8. Applicant - Summary of Key Changes to MM-003 Study Protocol

Document (Amendment) Date	Summary of Key Changes	Rationale	Planned Sample Size	Subjects Randomized
Amendment 1.0 11-Dec-2018	Added an independent DSMB to review cumulative study data quarterly over the course of the study to evaluate safety and efficacy, protocol conduct, and scientific validity and integrity of the study. Also added: • Interim analysis, AEs and mortality data to provide evidence for potential early stopping in the event of unacceptable toxicity. • Safety and efficacy data to be monitored by the Sponsor Medical Monitor, Clinical Research Scientist and Safety Physician on an ongoing basis throughout the study. • Should a significant safety or efficacy issue be identified, immediately notify all Investigators and expeditiously convene the DSMB for recommendation on future conduct of the study. • Based on the changes above, the criteria for pausing the study were removed from the protocol.	N/A	381	0
Amendment 2.0 17-Dec-2019	Added 2 additional standard regimen options: EPd and Kd. Subjects in Treatment Arm B were given the opportunity to receive ide-cel treatment following IRC confirmed progression on the standard regimen in Treatment Arm B and confirmed eligibility. Subjects in Treatment Arm B who	These changes were based on the evolving treatment landscape for the patient population included in this study and feedback received from Investigators and Health Authorities.	381	68

Document (Amendment) Date	Summary of Key Changes	Rationale	Planned Sample Size	Subjects Randomized
	received ide-cel were to be followed for safety for a period of 3 months post-ide-cel infusion.			
Amendment 3.0 21-Aug-2020	Revised Management Guidelines for CRS and Neurologic Toxicities.	Clarified guidance and management options for subjects who rapidly deteriorate despite first line interventions and was prompted by reports of non-relapse mortality within the first 2 months of ide-cel infusion.	381	168
Amendment 4.0 08-Nov-2021	The second IA for the primary endpoint, PFS, at approximately 67% information fraction (or approximately 193 PFS events) was replaced by an IA at approximately 80% information fraction (or approximately 232 PFS events)	Per FDA recommendation received on 12-Oct-2021 to perform an interim analysis for superiority with a higher information fraction allowing for an accurate and reproducible estimate of treatment effect.	381	382
	The timing for OS interim analyses was adjusted. The superiority and futility boundaries for PFS and OS interim and final analyses were updated accordingly	Per FDA feedback, OS analysis was to be conducted at the second PFS interim analysis and the PFS final analysis for safety and efficacy considerations regardless of whether PFS and ORR were tested positive. The rationale was that OS is not only an efficacy but also an important safety endpoint.		

Subjects randomized at the time of the protocol amendment.

The FDA's Assessment:

FDA agrees with the Applicant's summary of the protocol amendments for KarMMa-3.

8.1.2 Study Results

Compliance with Good Clinical Practices

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

The FDA's Assessment:
The transport files for all ADaM and legacy datasets for KarMMa-3 in the original submission suffered from a dataset corruption issue. Corrected transport files were created and submitted under amendment #2 on March 20, 2023 (ADaM dataset) and under amendment #4 on March 24, 2023 (legacy datasets).

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

After consideration of factors including subject enrollment, protocol deviations, financial disclosures, and inspection history, three clinical sites (covering approximately 11% of subjects enrolled in KarMMa-3) were selected for inspection and verification of submitted data by FDA's bioresearch monitoring (BIMO) team:

- Site 132: M.D.Anderson Cancer center, Houston, Texas.
- Site 114: Washington University School of medicine, St. Louis, MO.
- Site 131: Winship Cancer Institute, Atlanta, GA.

No significant BIMO inspectional findings were noted. No forms FDA-483 were issued, and all inspections were classified as No Action Indicated (NAI).

Financial Disclosure

The Applicant's Position:
Financial disclosure information was collected and reported for the Investigators (Primary Investigators and Sub-investigators) in MM-003. Bias mitigation has been done for all reported financial interests.

The FDA's Assessment:
See Section 18.2 for details.

Patient Disposition

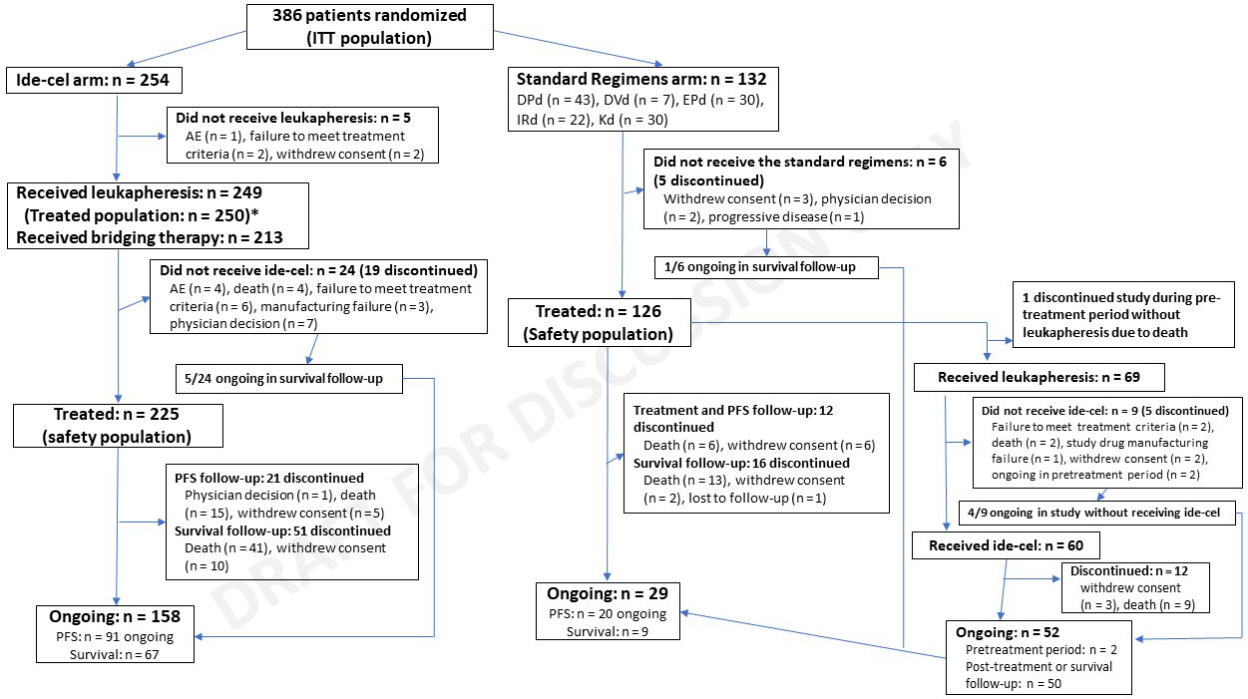
Data:

Table 9. Applicant - Key Dates and Follow-up in MM-003

Last Subject Randomized Date for Ide-cel Arm (Arm A)	04-Feb-2022
Last Subject Randomized Date for Standard Regimens Arm (Arm B)	08-Apr-2022
Clinical Cutoff Date (LPLV)	18-Apr-2022
Database Lock	14-Jul-2022
Minimum Follow-up, months	0.4
Ide-cel Arm	2.4
Standard regimens Arm	0.4
Median Follow-up, months[a]	18.6
Ide-cel arm	18.7
Standard regimens arm	18.1

[a] Follow-up duration using cutoff date (Cutoff date -randomization date + 1)/30.4375 for ITT population.

Figure 2. Applicant - Subject Disposition in MM-003



*One subject in the treated population received bridging therapy, but not leukapheresis

Table 10. Applicant - Analysis Populations in MM-003

Population[a]	Ide-cel Arm (N = 254) n (%)	Standard Regimens Arm (N = 132) n (%)	Total (N = 386) n (%)
Intent-to-Treat[b]	254 (100.0)	132 (100.0)	386 (100.0)
Treated[c]	250 (98.4)	126 (95.5)	376 (97.4)
Safety[d]	225 (88.6)	126 (95.5)	351 (90.9)

[a] Percentages are based on the ITT Population.

[b] ITT Population: all subjects who are randomized to one of the two treatment arms.

[c] Treated population: all subjects in the ITT population who underwent leukapheresis, bringing therapy, lymphodepleting chemotherapy or ide-cel infusion in Ide-cel Arm, and those who receive any dose of DARA, POM, LEN, BTZ, IXA, CFZ, ELO, or dex in standard regimens arm.

[d] Safety Population: all subjects in the Treated Population who received any study treatment, including ide-cel infusion for ide-cel arm and any dose of DARA, POM, LEN, BTZ, IXA, CFZ, ELO, or dex for standard regimens arm.

Source: ADSL

The Applicant's Position:

At the DBL, the majority of the randomized subjects remained ongoing in the study. Death was the most common reason for study discontinuation in both treatment arms.

The FDA's Assessment:

Out of 490 subjects that were screened, 386 subjects were enrolled in KarMMa-3. Overall, 29 out of 254 (11.4%) subjects in the ide-cel arm were randomized but did not receive ide-cel infusion. Six out of 132 subjects (4.5%) were randomized to the SOC arm but did not receive the intended treatment.

Ide-cel arm:

We generally agree with the Applicant's presentation of the study population disposition with the following additional comments:

- Out of the 227 subjects that underwent leukapheresis and received LD (lymphodepleting chemotherapy), two subjects received LD but did not receive ide-cel. One subject with history of congestive heart failure developed Grade 3 CHF after LD and discontinued further therapy. The second subject developed altered mental status after receiving LD and discontinued further therapy.

- FDA conducted efficacy analysis on the ITT population. FDA conducted safety analysis on subjects that received conformal ide-cel in the ide-cel arm and subjects that received any SOC treatment in the SOC arm. FDA also analyzed the safety of the subjects that crossed over from the SOC arm and received conformal ide-cel.

- At the time of the primary efficacy and safety analysis (data cutoff date, April 18, 2022), 69 subjects (52%) crossed over from the SOC arm to undergo leukapheresis and 60 subjects (45%) had received ide-cel. This includes two subjects that received non-conformal ide-cel. At the time of the final PFS analysis, (data cutoff date, April 23, 2023) 82 subjects (62%)

crossed over to undergo leukapheresis and 74 subjects (56%) received ide-cel. This includes two subjects that received non-conformal ide-cel.

Table 11 below shows the reasons for the study discontinuation by the treatment arm:

Table 11. FDA – Reasons for Study Discontinuation by the Treatment Arm

Reason for Study Discontinuation	Ide-cel N=254 n (%)	SOC N=132 n (%)
Death	75 (30%)	33 (25%)
Withdrawal by subject	19 (7%)	16 (12%)
Physician decision	2 (0.8%)	1 (0.8%)
Lost to follow-up	0	1 (0.8%)
Total	96 (38%)	51 (39%)

Source: FDA analysis, April 18, 2022, data cutoff.

Table 12. FDA – Reason for Treatment Discontinuation, Standard of Care Arm:

Reason for Treatment Discontinuation	SOC, N=126 n (%)
Progressive disease	87 (69)
Withdrawal by subject	7 (6)
Death	5 (4)
Adverse Events	1 (0.8)
Total	100 (79)

Source: FDA analysis and Applicant IR. April 18, 2022, data cutoff.

- The study had a 21% screen failure rate which may indicate the fairly restrictive eligibility criteria for study entry.
- Ninety-five percent of the randomized subjects were able to receive SOC treatment in the SOC arm compared to 89% in the ide-cel arm who were able to receive ide-cel infusion. The higher rate of subject attrition in the ide-cel arm occurred at multiple steps between randomization and CAR T cell infusion. This was due to disease progression or death while awaiting product manufacture, manufacture failure, need for repeat leukapheresis resulting in subject ineligibility due to delay in product availability, physician decision, and subject withdrawal from the study.
- At the time of the primary efficacy analysis, 62% of the subjects remained on the study and 38% discontinued the study (Table 4). The rate of study discontinuation was similar between in the two arms (38% in the ide-cel arm and 39% in the SOC arm). The most common reason for study discontinuation was death, followed by withdrawal by subjects.

- Treatment discontinuation is only relevant to the SOC arm given that ide-cel is administered as a single infusion. As shown in Table 5, 79% of the subjects in the SOC arm discontinued treatment at the time of the primary efficacy analysis. The most common reason for treatment discontinuation was disease progression.

Protocol Violations/Deviations

Data:

Table 13. Applicant - Important Protocol Deviations - ITT Population in MM-003

	Ide-cel Arm					Standard Regimens Arm
Categories Subcategories	**Prior to Rand (N=254) n (%)**	**Rand to Before LDC (N=254) n (%)**	**LDC to before Infusion (N=227) n (%)**	**On/after Infusion (N=225) n (%)**	**Overall (N=254) n (%)**	**Overall (N=132) n (%)**
Subjects with at Least one IPD	19 (7.5)	40 (15.7)	17 (7.5)	101 (44.9)	141 (55.5)	58 (43.9)
Laboratory	3 (1.2)	19 (7.5)	7 (3.1)	71 (31.6)	93 (36.6)	30 (22.7)
Top 2 Subcategories						
Labs, PK/PD samples not collected per protocol	1 (0.4)	10 (3.9)	0	54 (24.0)	64 (25.2)	18 (13.6)
Procedures not done per protocol	2 (0.8)	8 (3.1)	6 (2.6)	15 (6.7)	29 (11.4)	13 (9.8)
Other	2 (0.8)	10 (3.9)	4 (1.8)	21 (9.3)	32 (12.6)	9 (6.8)
Top 2 Subcategories						
Failure to report SAEs/SUSARs per regulations	1 (0.4)	9 (3.5)	1 (0.4)	15 (6.7)	26 (10.2)	4 (3.0)
GCP - other	1 (0.4)	1 (0.4)	0	6 (2.7)	8 (3.1)	3 (2.3)
Visit schedule	2 (0.8)	2 (0.8)	1 (0.4)	26 (11.6)	28 (11.0)	13 (9.8)
Top 2 Subcategories						
Visit not done	0	0	0	15 (6.7)	15 (5.9)	2 (1.5)
Missing safety or efficacy assessment	2 (0.8)	1 (0.4)	0	11 (4.9)	13 (5.1)	11 (8.3)
ICF Issues	7 (2.8)	0	3 (1.3)	9 (4.0)	16 (6.3)	5 (3.8)
Top 2 Subcategories						
Revised ICF not signed at next study visit	0	0	1 (0.4)	9 (4.0)	10 (3.9)	3 (2.3)
ICF not signed prior to study assessments	6 (2.4)	0	0	0	6 (2.4)	2 (1.5)
Study drug	1 (0.4)	10 (3.9)	2 (0.9)	1 (0.4)	13 (5.1)	18 (13.6)
Top 2 Subcategories						
Study drug - other	0	6 (2.4)	0	0	6 (2.4)	6 (4.5)
MNC product related deviation	0	3 (1.2)	0	0	3 (1.2)	0
Inclusion / Exclusion	4 (1.6)	5 (2.0)	0	0	9 (3.5)	4 (3.0)
CC medication	0	1 (0.4)	1 (0.4)	1 (0.4)	2 (0.8)	0

Note: For Standard Regimens Arm, all data are included for those subjects who did not receive leukapheresis, but only data before leukapheresis are included for those subjects who planned to receive ide-cel infusion.
Source: ADSL, ADDV

The Applicant's Position:

Important Protocol Deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. A review of all of the important protocol deviations () was performed by the study team including the Clinical Trial Physician during the study. The largest category of IPDs was Laboratory, which includes samples not collected and procedures not done per protocol including central laboratory samples for efficacy, local samples for safety, and PK/PD samples. Review of each of the Laboratory IPDs did not find substantial impact on the assessment of primary and key secondary endpoints, or on the assessment of the adequacy of the trial conduct. The second most reported category was 'other' which mostly included SAE reporting not having occurred within the protocol required timeframe. Other IPD categories of note were related to study visit not having been performed within the required timeframe, and ICF deviations (related to timing of signing of ICF versions and timing of signing in relation to study assessments). None of these deviations had an impact on interpretation of the data or subjects' safety.

The FDA's Assessment:

The rate of important protocol deviation (IPD) as defined by the Applicant were higher in the ide-cel arm (56%) compared to the SOC arm (44%). FDA agrees with the Applicant assessment that the most common IPD was laboratory assessment and procedures. This category was more common in the ide-cel arm (37%) compared to the SOC arm (23%). The IPDs for efficacy laboratory and imaging were further reviewed. The common causes included missed 24-hour urine assessment for protein electrophoresis (required monthly until Month 25 and every 3 months thereafter) and missed imaging assessment at baseline evaluation (after BT and prior to CAR T infusion). In addition, lack of completion of protocol-specified bone marrow assessments were another cause of IPD. Failure to report SAEs and suspected unexpected adverse reactions per regulations was observed in 10% of subjects in the ide-cel arm compared to 3% in the SOC arm. IPD violations for study drug administration were higher in the SOC arm (14%) compared to ide-cel arm (5%), Many of these IPDs were related to dexamethasone dosing as premedication for daratumumab or pomalidomide dosing. COVID-19-related protocol deviations were balanced between the two arms.

- In addition to the requirement for bone marrow biopsy at the time of suspected CR/sCR and progressive disease (PD) per IMWG 2016 (Kumar S et al. 2016), the protocol required that bone marrow biopsy be performed at prespecified time points of Month 2, 7, and 9. Some subjects may have considered bone marrow biopsies to be optional and not mandatory, resulting in lack of compliance with the procedure.

- The IRC adjudicated events based on clinical expertise and the totality of clinical evidence in cases of missed efficacy assessments in accordance with the IRC charter and IMWG 2016 guidelines. In case all necessary data for response assessment was missing for a particular visit, the adjudicator could select the assessment as not evaluable. In addition, prespecified study rules for censoring if two or more consecutive scheduled assessments were missing was applied uniformly to both the arms. The reviewer agrees with the Applicant that the missed assessment did not impact the interpretation of the efficacy results of the study or the safety of the study participants.

Table of Demographic Characteristics

Data:

Table 14. Applicant - Key Demographics and Baseline Characteristics Summary - ITT Population in MM-003

Parameters	Ide-cel Arm (N = 254)	Standard Regimens Arm (N = 132)	Total (N = 386)
Age (years)			
Median (Min, Max)	63.0 (30.0, 81.0)	63.0 (42.0, 83.0)	63.0 (30.0, 83.0)
Age Categories (years), n (%)			
<65	150 (59.1)	78 (59.1)	228 (59.1)
65-74	92 (36.2)	45 (34.1)	137 (35.5)
75-84	12 (4.7)	9 (6.8)	21 (5.4)
Sex, n (%)			
Male	156 (61.4)	79 (59.8)	235 (60.9)
Female	98 (38.6)	53 (40.2)	151 (39.1)
Race, n (%)			
American Indian or Alaska Native	1 (0.4)	0	1 (0.3)
Asian	7 (2.8)	5 (3.8)	12 (3.1)
Black or African American	18 (7.1)	18 (13.6)	36 (9.3)
Native Hawaiian or Other Pacific Islander	0	1 (0.8)	1 (0.3)
White	172 (67.7)	78 (59.1)	250 (64.8)
Other	2 (0.8)	3 (2.3)	5 (1.3)
Not Collected or Reported	54 (21.3)	27 (20.5)	81 (21.0)
Ethnicity, n (%)			
Hispanic or Latino	11 (4.3)	8 (6.1)	19 (4.9)
Not Hispanic or Latino	188 (74.0)	98 (74.2)	286 (74.1)
Not Reported	54 (21.3)	26 (19.7)	80 (20.7)
Unknown / Missing	1 (0.4)	0	1 (0.3)
Weight (kg)			
Median (Min, Max)	82.0 (41.1, 144.1)	85.5 (45.1, 177.8)	82.6 (41.1, 177.8)

Parameters	Ide-cel Arm (N = 254)	Standard Regimens Arm (N = 132)	Total (N = 386)
Region			
Europe	106 (41.7)	45 (34.1)	151 (39.1)
Belgium	5 (2.0)	2 (1.5)	7 (1.8)
France	33 (13.0)	14 (10.6)	47 (12.2)
Germany	11 (4.3)	9 (6.8)	20 (5.2)
Italy	11 (4.3)	6 (4.5)	17 (4.4)
Netherlands	10 (3.9)	2 (1.5)	12 (3.1)
Norway	7 (2.8)	2 (1.5)	9 (2.3)
Spain	19 (7.5)	7 (5.3)	26 (6.7)
Switzerland	5 (2.0)	1 (0.8)	6 (1.6)
United Kingdom	5 (2.0)	2 (1.5)	7 (1.8)
North America	144 (56.7)	82 (62.1)	226 (58.5)
Canada	10 (3.9)	9 (6.8)	19 (4.9)
United States of America	134 (52.8)	73 (55.3)	207 (53.6)
Asia	4 (1.6)	5 (3.8)	9 (2.3)
Japan	4 (1.6)	5 (3.8)	9 (2.3)

Note: Baseline value is defined as the last non-missing value before or on the date of first leukapheresis for ide-cel arm and before or on Month 1 Day 1 for Standard Regimens Arm. If a subject does not perform leukapheresis in ide-cel arm or is not treated in Standard Regimens Arm, then the last assessment on or before randomization +7 days is used as baseline value.
Source: ADSL

The Applicant's Position:

Subjects were enrolled at 49 sites in 12 countries (). Baseline demographics were generally balanced between the ide-cel and standard regimens arms (); an exception, by chance, was the distribution of Black or African American subjects (7.1% vs 13.6%, respectively; n = 36 total). Of the 207 subjects recruited in the US, 36 (16.9%) were African American, which is representative of the general US MM population.

Race and ethnicity were not collected or reported in 21.0% and 20.7% of the ITT population, respectively, mainly due to restrictions in the collection of data in several participating countries.

The FDA's Assessment:

Overall, the older population (75 years and older) and racial and ethnic minorities were underrepresented in the study. The median age of the study population was 63 years which is younger than the median age of 69 years at diagnosis in the U.S. Only 5% of the study population was 75 years or older compared to the higher prevalence (35%) of multiple myeloma in 75 years and older population in the U.S. (Rosko et al. 2017). Overall, only 9% of the study population was Black or African American. A lower proportion of Black or African American subjects were on the ide-cel arm compared to the SOC arm (7% versus 14%). Otherwise, the demographic characteristics were balanced between the two arms. Race was

not collected or reported in 21% of the enrolled population, despite, 60% of the study population enrolled in the United States.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

Table 15. Applicant - Key Baseline Disease Characteristics - ITT Population in MM-003

Parameters	Ide-cel Arm (N=254)	Standard Regimens Arm (N=132)	Total (N=386)
ECOG Performance Status, n (%)[a]			
0	120 (47.2)	66 (50.0)	186 (48.2)
1	133 (52.4)	62 (47.0)	195 (50.5)
2	0	3 (2.3)	3 (0.8)
3	1 (0.4)	1 (0.8)	2 (0.5)
Time since Initial Diagnosis (year)			
n	251	131	382
Median (Min, Max)	4.1 (0.2, 21.8)	4.0 (0.7, 17.7)	4.1 (0.2, 21.8)
R-ISS at Baseline (Derived), n (%)[b]			
Stage I	50 (19.7)	26 (19.7)	76 (19.7)
Stage II	150 (59.1)	82 (62.1)	232 (60.1)
Stage III	31 (12.2)	14 (10.6)	45 (11.7)
Missing/Unknown	23 (9.1)	10 (7.6)	33 (8.5)
Baseline Cytogenetic Abnormalities, n (%)[c]			
High Risk	107 (42.1)	61 (46.2)	168 (43.5)
Non-High Risk	114 (44.9)	55 (41.7)	169 (43.8)
Not Evaluable/Missing	33 (13.0)	16 (12.1)	49 (12.7)
Presence of Bone Lesions, n (%)			
Yes	194 (76.4)	104 (78.8)	298 (77.2)
No	59 (23.2)	28 (21.2)	87 (22.5)
Missing/Unknown	1 (0.4)	0	1 (0.3)
Presence of Extramedullary Plasmacytoma, n (%)			
Yes	61 (24.0)	32 (24.2)	93 (24.1)
Radiological Only	6 (2.4)	2 (1.5)	8 (2.1)
Both Clinical and Radiological	55 (21.7)	30 (22.7)	85 (22.0)
No	192 (75.6)	100 (75.8)	292 (75.6)
Missing/Unknown	1 (0.4)	0	1 (0.3)
Tumor Burden, n (%)[d]			
Low	172 (67.7)	90 (68.2)	262 (67.9)
High	71 (28.0)	34 (25.8)	105 (27.2)
Missing/Unknown	11 (4.3)	8 (6.1)	19 (4.9)
Prior Autologous Stem Cell Transplant for Multiple Myeloma, n (%)			
Yes	214 (84.3)	114 (86.4)	328 (85.0)
No	40 (15.7)	18 (13.6)	58 (15.0)
Number of Prior Anti-myeloma Regimens			
Median (Min, Max)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)
Distribution of Prior Antimyeloma Regimens, n (%)			

Parameters	Ide-cel Arm (N=254)	Standard Regimens Arm (N=132)	Total (N=386)
2	78 (30.7)	39 (29.5)	117 (30.3)
3	95 (37.4)	49 (37.1)	144 (37.3)
4	81 (31.9)	44 (33.3)	125 (32.4)
Number of Prior Antimyeloma Regimens per Year Since Diagnosis, n	251	131	382
Median (Min, Max)	0.7 (0.1, 8.1[e])	0.7 (0.2, 3.2)	0.7 (0.1, 8.1[e])
Refractory Status to Prior Therapies, n (%)			
IMiD	224 (88.2)	124 (93.9)	348 (90.2)
Lenalidomide	186 (73.2)	104 (78.8)	290 (75.1)
Pomalidomide	127 (50.0)	70 (53.0)	197 (51.0)
Thalidomide	10 (3.9)	2 (1.5)	12 (3.1)
PI	189 (74.4)	95 (72.0)	284 (73.6)
Bortezomib	112 (44.1)	60 (45.5)	172 (44.6)
Carfilzomib	104 (40.9)	43 (32.6)	147 (38.1)
Ixazomib/Ixazomib Citrate	35 (13.8)	23 (17.4)	58 (15.0)
Anti-CD38 Antibodies	242 (95.3)	124 (93.9)	366 (94.8)
Daratumumab	242 (95.3)	123 (93.2)	365 (94.6)
Isatuximab	1 (0.4)	1 (0.8)	2 (0.5)
Time to Progression on Last Prior Anti-Myeloma Therapy (Months)[f]			
Median (Min, Max)	7.1 (0.7, 67.7)	6.9 (0.4, 66.0)	6.9 (0.4, 67.7)

Note: Baseline value is defined as the last non-missing value before or on the date of first leukapheresis for Ide-cel Arm and before or on Month 1 Day 1 for Standard Regimens Arm. If a subject does not perform leukapheresis in Ide-cel Arm or is not treated in standard regimens arm, then the last assessment on or before randomization +7 days is used as baseline value.

[a] All subjects had ECOG score 0 or 1 at screening, but the ECOG score may be >1 at baseline.

[b] Derived ISS is calculated using baseline values of Albumin and Beta-2-microglobulin. R-ISS is derived using baseline ISS stage, cytogenetic abnormality, and serum lactate dehydrogenase.

[c] To determine cytogenetic risks, the centralized lab data at screening will be considered first, if centralized data are not available, the last value from historical tests including at diagnosis collected on the CRF will be used. If neither the centralized lab nor the CRF data are available, the data will be imputed from the IRT system. Cytogenetic risk 'High' is defined as presence of any of the following abnormality: del17p13 (a probe reflective of del17p), t(14;16) or t(4;14); 'Not High' risk is defined as absence of all three abnormalities. The cytogenetic risk is not evaluable or missing if the status of one or more probes is not available.

[d] Tumor burden is determined by the higher value between bone marrow aspiration and bone marrow biopsy CD138+ plasma cell. Low tumor burden: < 50%, High tumor burden: ≥ 50%.

[e] Range maximum reflects data entry error; corrected after database lock.

[f] Time to progression calculated based on summary statistics instead of Kaplan-Meier estimator.

Source: ADSL

The Applicant's Position:

The ITT population was reflective of a high-risk RRMM patient population with previous exposure to 3 classes of conventional therapies reflected by the high percentages of patients who harbored high risk cytogenetic abnormalities, had extramedullary disease, and had high tumor burden at baseline. The rate of high risk cytogenetics in MM-003 (43.5%) was higher than typical for TCE populations (18.5% to 23.7%).[30] There was a higher percentage of subjects with extramedullary disease in MM-003 (24.1%) than is usually seen in relapsed myeloma, where the reported incidence of extramedullary disease is 3.4% to 14%.[31,32] The refractory nature and difficult-to-treat disease course in this patient population is evident based on the short median TTP on the

last prior regimen before study entry and the high median number of antimyeloma regimens per year since diagnosis.

All subjects received 2 to 4 prior antimyeloma regimens (median 3.0) and, per protocol, had received an IMiD, PI, and DARA. Given the treatment until progression paradigm in myeloma, the majority of subjects were also refractory to the 3 classes of therapy they were required to have been exposed to. Refractory to each agent was ascertained relative to the most recent regimen the respective agent was part of. Refractoriness to that agent was defined as the subject either having been nonresponsive on therapy (defined as failure to achieve at least a minimal response) or having progressed while on or within 60 days of the last dose of the respective agent. The most common (≥ 25% of subjects) last non-steroid agents received by subjects across both treatment arms before entering the study were DARA (72.3%) and pomalidomide (38.1%). 94.6% of subjects were refractory to DARA; of which, 69.9% of subjects were refractory to DARA received as part of their last prior antimyeloma regimen (immediately before study entry) and 24.6% of subjects were refractory to DARA as part of an earlier antimyeloma regimen.

The baseline disease characteristics were generally balanced between treatment arms, indicating that differences in efficacy outcomes observed between the treatment arms are free of confounding and should be attributed to the treatment effect.

The randomized patient population is representative of the general patient population of RRMM patients who received 2 to 4 prior regimens and are TCE. Therefore, the efficacy data from MM-003 are generalizable to the patient population in this disease setting

The FDA's Assessment:

- FDA agrees with the Applicant's assessment that baseline disease factors that are indicative of poor prognosis, such as high-risk cytogenetics, revised International Staging System (ISS) stage 3, and presence of extramedullary plasmacytoma were balanced between the two arms. The median number of prior lines of therapy was three and 95% of the patients were refractory to anti CD38 monoclonal antibody. An equal proportion of subjects in each arm had received two, three, or four prior lines of therapy. The study did not enroll any patients who had received only 1 prior line of therapy.

- The study population was triple-class exposed population and 66% of the subjects were triple class refractory. This population has few effective treatment options.

- One-third of the study population had received four prior lines of therapy, a population for which ide-cel is commercially available.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

All study treatments were administered by trained medical personnel at each site and administration was recorded in source documents and on the appropriate CRFs. Treatment

compliance was monitored by routine monitoring of clinical source documentation and drug accountability, as well as the subject's medical record and CRF.

No subjects in the ide-cel arm had an infusion interruption of ide-cel during administration. 37 (14.8%) subjects in the ide-cel arm who received fludarabine had at least 1 dose adjustment. In the standard regimens arm dose interruptions or reductions due to AEs were to be done per the respective approved labels.

In the safety population, all subjects in both treatment arms received at least 1 concomitant medication and most subjects (ide-cel: 208 [92.4%]; standard regimens 96 [76.2%]) received at least 1 concomitant procedure/surgery.

All 225 subjects in the ide-cel arm, safety population, received at least 1 concomitant medication of interest and 122 (54.2%) had at least 1 concomitant procedure of interest (*Source: ADSL, ADCM, ADPR*).

- The most commonly used concomitant medications of interest included antivirals (98.7%), antibiotics (98.2%), antimycotics (71.6%), anti-cytokine drugs (72.0%), CSFs (58.7%), and IVIGs (32.9%).

- The anti-cytokine drugs tocilizumab, anakinra, and siltuximab were received by 72.0%, 4.4%, and 1.3% of subjects, respectively.

- Erythropoietin stimulating agents and thrombopoietin mimetics were used by 7.1% and 2.7% of subjects, respectively.

- The most frequently reported concomitant procedures of interest included RBC transfusions (48.4%) and platelet transfusions (31.6%).

In the standard regimens arm, safety population, 123 (97.6%) subjects had at least 1 concomitant medication of interest and 27 (21.4%) had at least 1 concomitant procedure of interest (*Source: ADSL, ADCM, ADPR*).

- The most commonly used concomitant medications of interest included antivirals (96.0%), antibiotics (71.4%), and CSFs (34.1%).
- Erythropoietin stimulating agents and thrombopoietin mimetics were used by 10.3% and 1.6% of subjects, respectively.
- The most frequently reported concomitant procedures of interest included RBC transfusions (9.0%) and platelet transfusions (7.9%).

<u>The Applicant's Position:</u>

Concomitant medications/procedures received by subjects during the study were consistent with the permitted, prohibited, and required usages specified in the protocol, and were reflective of the underlying medical conditions and AEs that were reported in the study.

The FDA's Assessment:

Overall, FDA agrees with Applicant's assessment. The 222 subjects that received conformal ide-cel constitute the safety population for FDA's analysis. FDA's review of bridging therapy is summarized below.

Bridging Therapy:

Table 16 compares bridging therapy (BT) to SOC regimen. SOC regimen is the definitive treatment, whereas bridging in the ide-cel arm is only for disease stabilization until the product can be manufactured. The protocol specified up to one cycle of BT at investigator discretion.

Table 16. FDA – Regimens in SOC Arm and Bridging Therapy for Ide-cel Arm

Regimens	SOC (N=132) n (%)	Ide-cel (N=254) n (%)
EPd	30 (23)	61 (24)
DPd	41 (31)	50 (20)
Kd	28 (21)	29 (11)
IRd	20 (15)	26 (10)
DVd	7 (5)	21 (8)
Other bridging therapies*	N/A	26 (10)
Received SOC or bridging	126 (95)	213 (84)
No SOC/bridging	6 (4.5)	41 (16)

Source: FDA analysis and Applicant IR.
*Non-protocol specified bridging therapy

Overall, 84% of subjects in the ide-cel arm received BT. The median (min, max) duration of BT was 22.0 days (1.0, 101). Ten percent of the subjects received non-protocol-specified BT.

The time from randomization to initiation of BT was a median of 8 days (range 1 to 267 days). Most of the subjects (79%) received 1 cycle of bridging, 14% received 2 cycles, 1% received >2 cycles, and 7% is missing this information. The most common regimen used as bridging was EPd followed DPd. The non-protocol-specified BT included doublet regimens such as pom+dex, len+dex, elo+dex, dara+dex, single agent daratumumab, and cytoxan in combination with anti-myeloma agents. The ORR to BT was low and ranged from 4% to 21%, depending on the regimen that was used.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Table 17. Applicant - Results of the Statistical Testing Hierarchy - ITT Population in MM-003

	p-Value Threshold	Actual p-Value	Met the Threshold
Primary Objective: Compare PFS per IRC of ide-cel vs standard regimens	0.014	< 0.0001	Yes
Hierarchically Tested Secondary Objectives:			
1. Compare ORR of ide-cel vs standard regimens	0.014	<0.0001	Yes
2. Compare OS of ide-cel vs standard regimens	0.001[a]	NA	No

[a] SAP defined threshold. p-value for OS did not cross the significance boundaries for either superiority of efficacy or futility (one-sided critical p-value <0.001 need for statistical significance and p-value >0.8 for futility). The study team remains blinded to OS results.

Source: ADSL, ADTTE, ADRS

Table 18. Applicant - Primary Efficacy Endpoint of PFS per IRC - ITT Population in MM-003

	Ide-cel Arm (N=254)	Standard Regimens Arm (N=132)
Events (Progressed/Died), n (%)	149 (58.7)	93 (70.5)
Censored, n (%)	105 (41.3)	39 (29.5)
Median PFS (95% CI),[a] mo	13.3 (11.8, 16.1)	4.4 (3.4, 5.9)
Stratified HR (97.2% CI),[b] one-sided p-value[c]	0.493 (0.365, 0.666); p < 0.0001	
Stratified HR (95% CI)[b]	0.493 (0.377, 0.645)	
Event-free rate % (SE)[d]		
6-month	73.4 (2.8)	40.3 (4.6)
12-month	54.5 (3.3)	30.2 (4.4)

[a] Median and corresponding 95% confidence interval are based on Kaplan-Meier approach.

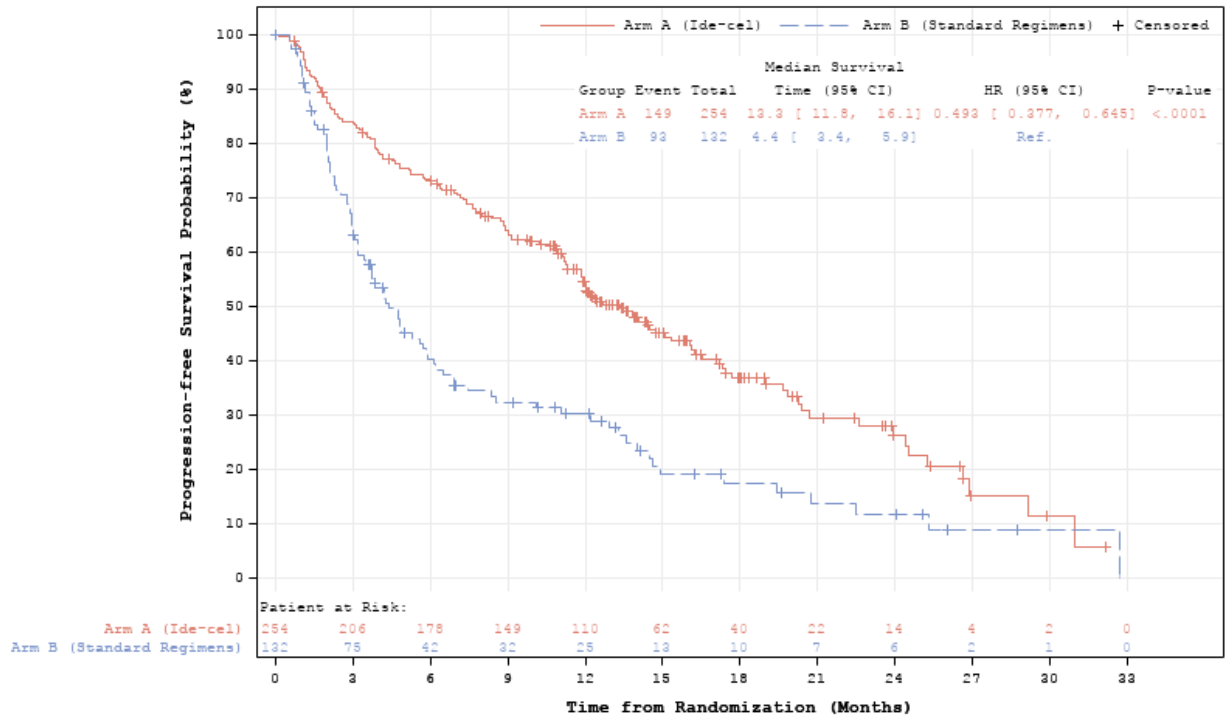
[b] Stratified and unstratified HR are based on the univariate Cox proportional hazards model. Confidence interval is two-sided. Additional two-sided 97.2% CI for stratified HR is to match the one-sided superiority boundary 0.014 in p-value scale used for this interim analysis.

[c] P-value is one-sided based on a log-rank test stratified by stratification factors (age, < 65 vs ≥ 65; Number of prior anti-myeloma regimens, 2 vs 3 or 4; High risk cytogenetic abnormalities, t(4;14) or t(14;16) or del 17p presence vs absence/unknown).

[d] SE is based on Greenwood formula.

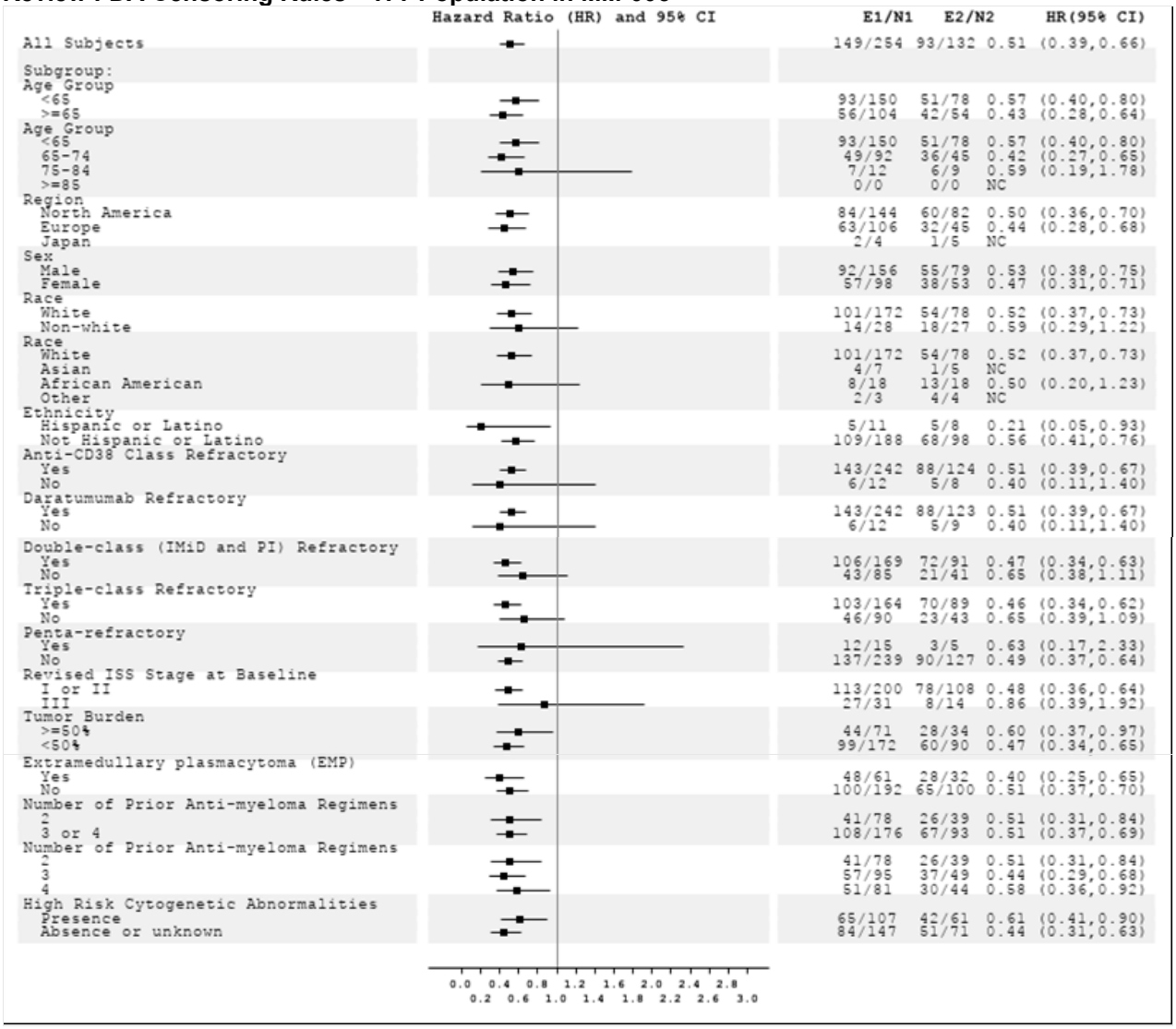
Source: ADSL, ADTTE

Figure 3. Applicant – K-M Curve of PFS Based on IMWG Criteria – IRC Review, FDA Censoring Rules, ITT Population in MM-003



Source: ADSL, ADTTE

Figure 4. Applicant – Forest Plot for PFS Hazard Ratios Based on IMWG Criteria – IRC Review FDA Censoring Rules – ITT Population in MM-003



E1/N1 = number of events/number of subjects assigned to ide-cel arm in the subgroup.
E2/N2 = number of events/number of subjects assigned to standard regimens arm in the subgroup.
Note: HR is unstratified HR for ide-cel arm vs standard regimens arm based on the univariate Cox proportional hazards model. CI is two-sided. HR is not computed for subgroups if both N1 and N2 are less than 10. NC = Not calculated.
Source: ADSL, ADEXSUM, ADTTE

The Applicant's Position:

At data cutoff (18-Apr-2022) for the pre-planned PFS IA2 analysis, the median follow-up was 18.6 months (). In the ITT population, ide-cel demonstrated a statistically significant improvement in PFS, per IRC assessment, with a stratified log-rank test p-value of < 0.0001 (). Separation of the KM curves favoring ide-cel over standard regimens occurred early, and this treatment effect was sustained through the period of follow up (). Median PFS was longer and event-free rates were higher with ide-cel compared with standard regimens ().

HRs for PFS (per IRC) for all predefined subgroups favored ide-cel over standard regimens (HR < 1) including difficult to treat subgroups (eg, double-class refractory, triple-class refractory, high risk cytogenetics, high tumor burden, or EMP) (Figure 4), thus supporting the internal consistency of the study results, although interpretation in some subgroups is limited by small numbers of subjects. The PFS benefit of ide-cel over standard regimens was consistent regardless of the number of prior regimens received (ie, 2, 3, or 4 prior lines of therapy). Median PFS per IRC assessment across the pre-planned ide-cel subgroup dose ranges of 300 to 460 × 10^6 and > 460 to 540 × 10^6 was similar and consistent to that of the overall ide-cel arm.

Despite the imbalanced distribution of African American subjects between the treatment arms, the benefit of ide-cel over standard regimens among African American subjects was consistent with the overall study population for PFS (mPFS: 20.3 [95% CI: 8.9, NA] vs 6.9 [95% CI: 3.7, 22.5] months; HR = 0.5) (*Source: ADSL, ADEX, ADEXSUM*).

The FDA's Assessment:

- We agree with the Applicant's assessment that KarMMa-3 met its primary endpoint to demonstrate a statistically significant improvement in PFS. We also agree that the treatment effect on PFS generally appears consistent across subgroups.

  Table 19 below shows the PFS analysis per IRC analysis.

Table 19. FDA – PFS analysis in KarMMa-3

Variable	Ide-cel N=254	SOC N=132
Subjects with PFS event, n (%)	149 (59%)	93 (70%)
Progression	129 (51%)	89 (67%)
Death	20 (8%)	4 (3%)
Subjects censored, n (%)	105 (41%)	39 (30%)
Median PFS (95% CI)	13.3 (11.8, 16.1)	4.4 (3.4, 5.9)
Hazard ratio[1] (95% CI)	0.495 (0.379 to 0.647)	
p-value [2]	<.0001	

Source: FDA analysis. Data cutoff April 18, 2022
[1]Stratified Cox proportional hazards model. One-sided stratified log-rank test

Table 20 below shows the refractory and exposure status to each agent in the different treatment subgroups in the SOC arm.

Table 20. FDA – Refractory Status to Agents in SOC Regimen (ITT Population)

SOC regimen	Refractory status is each agent*	Prior Exposure to each agent
IRD n=22	Ixazomib =1 (4.5%) Lenalidomide: 17 (77%)	Ixazomib =1 (4.5%) Lenalidomide: 22 (100%)
DVd n=7	Daratumumab: n=7 (100%) Bortezomib: n=2 (29%)	Daratumumab: n=7 (100%) Bortezomib: n=6 (86%)
EPd n=30	Elotuzumab: n=0 Pomalidomide: n=13 (43%)	Elotuzumab: n=1 (3%) Pomalidomide: n=15 (50%)
DPd n=43	Daratumumab: n=41 (95%) Pomalidomide: n=12 (28%)	Daratumumab: n=43 (100%) Pomalidomide: n=13 (30%)
Kd n=30	Carfilzomib: n=3 (10%)	Carfilzomib: n=5 (17%)

Source: FDA analysis and Applicant IR.
Refractory status is assessed in the last line including the respective agent

We have the following additional comments regarding the PFS analysis:

- The median PFS in the SOC arm (4.4 months) is lower than the statistical assumption (9 months). However, the absolute magnitude of median PFS (mPFS) difference (8.9 months) between the two arms is considered clinically meaningful in the RRMM setting.

- A higher proportion of PFS events in the ide-cel arm were attributed to deaths compared to the SOC arm (ide-cel arm: 8%, n=20; SOC arm: 3%, n=4). In the ide-cel arm, 8 out of 20 deaths occurred in subjects who did not receive ide-cel; the remaining 12 deaths were attributable to TEAEs. In the SOC arm, three out of the four deaths were attributable to TEAEs.

  Our analyses indicate differences in the mPFS across regimens used in the SOC arm, ranging from 2.8 months to 10.1 months (DPd: n=43, mPFS is 8.5 months [95% CI: 3.7, 14.6]; DVd: n=7, mPFS is 3.2 months [95% CI: 0.8, 4.3], Kd: n=30, mPFS is 10.1 months [95% CI: 3.2, 14.9]; EPd: n=30, mPFS is 2.8 months [95% CI: 2.0, 4.7]; IRD: n=22, mPFS is 3.7 months [95% CI: 1.1, 6.9]). The study was not powered to compare the outcome between each of the treatment groups. Any comparison between these subgroups is limited by the small sample size and may be affected by the imbalance in the disease characteristics within these subgroups. It is, however, notable that median PFS with EPd was only 2.8 months, although none of the subjects in this subgroup were refractory to elotuzumab, only one subject was exposed to elotuzumab, and 57% were not refractory to pomalidomide. Although 95% of the subjects in the DPd subgroup were refractory to daratumumab, the median PFS of this subgroup was higher than the overall median PFS of the SOC arm. Efficacy results from each of these subgroups are considered exploratory and hypothesis generating.

- The first post-treatment efficacy assessment (Month 2, Day1) was to occur 1 month after CAR T infusion in the ide-cel arm and one month after treatment initiation in the SOC arm. Subsequent post-treatment efficacy assessments were monthly for two years and then every 3 months thereafter.

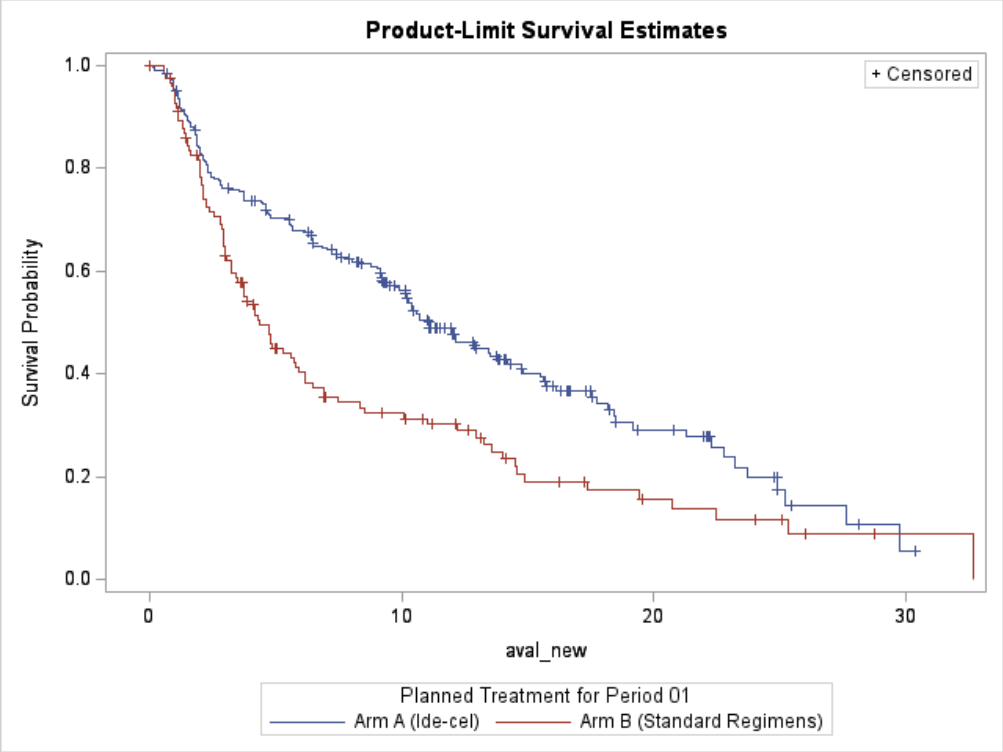
  Due to the time required to manufacture ide-cel, the actual time from randomization to the treatment was longer in the ide-cel arm (median: 55 days; range: 36, 121) compared to the SOC arm (median: 6 days; range: 1, 25). Consequently, the median time from randomization to Month 2 Day 1 (M2D1) efficacy assessment was also longer for the Ide-cel arm (83 days) compared to the SOC arm (34 days). Since PFS is determined from randomization, the misaligned post-treatment disease assessment introduced a lead time ascertainment bias in favor of the ide-cel arm.

  FDA conducted a sensitivity analysis to address this lead time bias.

  The starting point of the PFS measurement was changed from randomization to the date of ide-cel infusion for the PFS events that occurred after CAR T infusion. The early PFS events prior to the CAR T infusion were retained per the original PFS analysis. This eliminated the bias introduced by later post-infusion disease assessments in the ide-cel arm. With this analysis, the median time to M2D1 assessment for the Ide-cel arm was 29

days which was similar to the median time to M2D1 assessment of the SOC arm (34 days). For SOC patients, the original PFS analysis was used.

Figure 5. FDA – Sensitivity Analysis for Lead-Time Bias:



Source: FDA Statistical reviewer.

Figure 5 shows the Kaplan-Meier (KM) curves for the two treatment arms after realignment of disease assessment. This analysis continues to show PFS advantage with the ide-cel arm compared to the SOC arm with a hazard ratio was 0.573 (95% CI: 0.439, 0.748) and a stratified log-rank test p-value <0.0001.

Sensitivity analysis: FDA conducted a second sensitivity analysis on 40 subjects with readjudicated response assessment. This included 30 subjects in the ide-cel arm and 10 subjects in the SOC arm. The basis for the readjudication and sensitivity analysis is summarized below:

a) Discrepant Adjudication between Investigator and IRC for disease progression (PD): Four subjects with PD per investigator and FDA reviewer assessment were adjudicated as stable disease by the IRC. Three out of these four events occurred prior to CAR T infusion.

b) Discrepant adjudication between IRC members and final IRC adjudication of PD in the

SOC arm: Five subjects in the SOC arm were adjudicated by the IRC as disease progression based on increase in serum free light chain (FLC). However, FDA's assessment of the efficacy laboratory data does not demonstrate that the difference in the FLC met the IMWG 2016 criteria for PD (increase of 25% from the lowest response value in difference between involved and uninvolved FLC levels and absolute increase must be >10 mg/dl).

c) IRC response assessment discrepant from the IMWG 2016 consensus criteria per FDA assessment: This category includes 11 subjects in the ide-cel arm and 1 subject in the SOC arm.

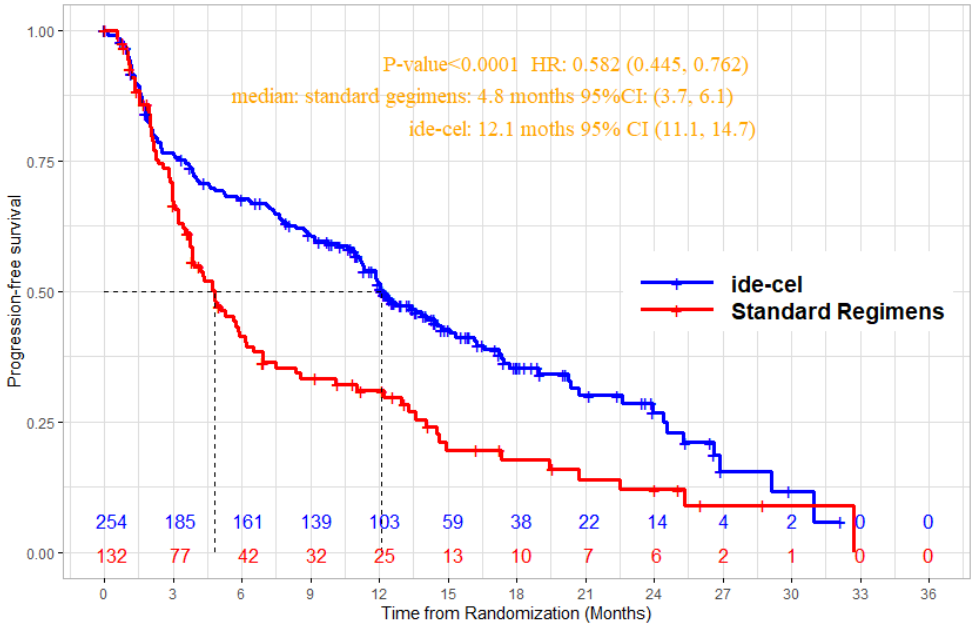
d) Subjects in the ide-cel arm with PD based on imaging but IRC assessed as non-PD: Nine subjects with early PD events based on imaging prior to CAR T infusion were adjudicated as stable disease by the IRC. These responses were readjudicated for the sensitivity analyses.

e) Assessment of PD following two or more missed consecutive scheduled assessment for a parameter which determined PD: Three subjects in the SOC arm and one subject in the ide-cel arm were considered as PD immediately following two or more missed consecutive scheduled assessment for a parameter which ultimately determined PD. These subjects were readjudicated as censored at the last adequate assessment of the PD parameter at a date that did not show PD.

f) PD based on single read biochemical assessment demonstrating disease progression without confirmation: One subject in the SOC arm and four subjects in the SOC arm were assessed as PD based on a single biochemical assessment of PD. These subjects did not have subsequent efficacy assessment to allow for confirmation of PD. Per the IMWG 2016 criteria, these subjects should not be considered as PD given the lack of confirmation of biochemical assessment of disease progression. Therefore, these subjects were censored at the date of last adequate disease assessment.

g) Lack of follow-up imaging for extramedullary plasmacytoma (EMP) present on screening imaging: One subject with EMP at screening with no follow up imaging post-screening was assessed by the IRC as PD on study day 90 based on biochemical progression. This subject was censored at randomization as lack of follow-up imaging for EMP renders this subject in-evaluable for efficacy.(Figure 6).

Figure 6. FDA – Sensitivity Analysis Based on FDA Readjudication



Source: FDA statistical reviewer

The sensitivity analysis for these subjects using FDA adjudication demonstrates statistically significant improvement in PFS compared to the SOC arm, indicating that the PFS improvement was robust. The statistical reviewer concluded that the sensitivity analysis confirmed the robustness of the PFS results.

In summary, results of the two sensitivity analyses described above demonstrate a consistent and robust PFS benefit of ide-cell compared to the SOC arm.

Efficacy analysis based on the line of therapy: This was prespecified subgroup analysis. There was a balanced distribution of prior lines of therapy across KarMMa-3; 30%: 2L (prior lines of therapy), 37%: 3 L and 32%:4L. Expectedly, the proportion of triple class refractory patients increased with more lines of therapy (50% with 2L, 61% with 3L, and 85% with 4L). A similar improvement in median PFS and ORR was observed across the different line of therapy subgroups as shown below:

Table 21. FDA – PFS analysis based on Line of Therapy, KarMMa-3

	2 Prior Lines Ide-cel n=78	2 Prior Lines SOC n=39	3 Prior Lines Ide-cel n=95	3 Prior Lines SOC n=49	4 Prior Lines Ide-cel n=81	4 Prior Lines SOC n=44
Median PFS	15.1	4.8	12.5	3.2	11.2	4.9
95% CI	(12.7, 19.7)	(3.2, 13.3)	(10.8, 17.7)	(2.3, 5.7)	(7.4, 14.1)	(3.2, 6.9)
Unstratified HR (95% CI)	0.51 (0.31, 0.84)		0.45 (0.29, 0.68)		0.58 (0.36, .92)	
ORR (%)	74	51	70	35	70	41
95% CI	(64.7, 84)	(36, 67)	(60.2, 78.7)	(21.4, 48)	(60.4, 80.3)	(26.4, 55.4)

Source: KarMMa-3 Clinical Study Report, S BLA 125736/218

The PFS benefit with ide-cel was observed across all prior lines of therapy (2 to 4). KarMMa-3 was not powered to compare the efficacy outcomes across different lines of therapy. Therefore, any comparisons across these three subgroups are considered exploratory.

Data Quality and Integrity

The Applicant's Position:

There were no concerns identified for data quality or integrity from MM-003. An independent DSMB reviewed cumulative study data quarterly over the course of the study to evaluate protocol conduct, and scientific validity and integrity of the study and did not request any modifications of study conduct.

Per protocol, investigators are not allowed to disclose data from study participants without written approval. In 2022, the Sponsor became aware of 2 unauthorized publications of data. Cross-functional review of both cases concluded that there was no impact on data integrity, no bias has been introduced or impacted the results of the study. No significant GCP deviations impacting the study or Serious Breaches were reported.

The FDA's Assessment:

Please refer to FDA assessment of data quality and integrity under Section 8.2.2.

Efficacy Results – Secondary and other relevant endpoints

Data:

Table 22. Applicant – Summary of Secondary Efficacy Results – ITT population in MM-003

	Ide-cel (N=254)	Standard Regimens (N=132)
Key Secondary Endpoint (Hierarchically Tested)		
ORR per IRC[a]		
N responders (%)	181 (71.3)	55 (41.7)
95% CI[b]	65.7, 76.8	33.3, 50.1
Common rate difference[c] (97.2% CI)	29.3 (18.1, 40.5); p < 0.0001[d]	
Common rate difference[c] (95.0% CI)	29.3 (19.3, 39.3)	
Common odds ratio[c] (97.2% CI)	3.54 (2.14, 5.85)	
Common odds ratio[c] (95.0% CI)	3.54 (2.26, 5.54)	
sCR, n (%)	90 (35.4)	6 (4.5)
CR, n (%)	8 (3.1)	1 (0.8)
VGPR, n (%)	55 (21.7)	13 (9.8)
PR, n (%)	28 (11.0)	35 (26.5)
MR, n (%)	4 (1.6)	9 (6.8)
SD, n (%)	31 (12.2)	48 (36.4)
PD, n (%)	24 (9.4)	10 (7.6)
Other Secondary Endpoints		
CR Rate per IRC[a], n (%)	98 (38.6)	7 (5.3)
95% CI[b]	32.6, 44.6	1.5, 9.1
TTR per IRC, n	181	55
Median TTR[e], mo (Min, Max)	2.9 (0.5, 13.0)	2.1 (0.9, 9.4)
DoR per IRC, n	181	55
Median DoR[e], mo (95% CI)	14.8 (12.0, 18.6)	9.7 (5.4, 16.3)
EFS per IRC		
Events, n (%)	156 (61.4)	101 (76.5)
Censored, n (%)	98 (38.6)	31 (23.5)
Median EFS, mo (95%CI)[f]	12.5 (11.3, 14.7)	3.9 (3.1, 5.3)
Stratified HR (95% CI)[g]	0.480 (0.371, 0.623)	
Event-free rate % (SE)[h]		
6-month	72.2 (2.8)	36.9 (4.4)
12-month	53.0 (3.2)	27.7 (4.2)
Time to next antimyeloma treatment		
Median, mo (95% CI)[f]	20.3 (16.2, 24.5)	6.9 (5.3, 8.1)
Stratified HR (95% CI)[g]	0.348 (0.259, 0.467)	
PFS2		
Progressed/Died, n (%)	112 (44.1)	62 (47.0)
Censored, n (%)	142 (55.9)	70 (53.0)
Median PFS2 (95% CI),[f] mo	20.0 (17.3, 24.0)	15.9 (11.8, 21.5)
Stratified HR (95% CI)[g]	0.744 (0.543, 1.021)	
Event-free rate % (SE)[h]		
6-month	85.1 (2.3)	84.4 (3.3)
12-month	72.1 (2.9)	57.8 (4.7)
MRD-negative status and ≥ CR by NGS, n (%)[i]	51 (20.1)	1 (0.8)
95% CI	(15.2, 25.0)	(0.0, 2.2)

[a] Overall response rate is defined as the rate of subjects whose response is PR or better (i.e. sCR or CR or VGPR or PR); Complete response rate is defined as the rate of subjects whose response is CR or better (i.e. sCR or CR). The denominator used for rate calculation is the number of subjects in the designated study population.

[b] Two-sided Wald confidence interval.

[c] Unstratified rate difference and odds ratio are calculated based on the observed response rate with two-sided Wald CI. Common rate difference, odds ratio and CI are based on Mantel-Haenszel estimate. Additional two-sided 97.2% CI for common risk difference and odds ratio is to match the one-sided superiority boundary 0.014 in p-value scale used for this interim analysis.

[d] One-sided p-value from CMH test stratified by stratification factors.

[e] Median is based on the Kaplan-Meier estimation.

F Median and corresponding 95% confidence interval are based on Kaplan-Meier approach.

G Stratified and unstratified HR are based on the univariate Cox proportional hazards model. Confidence interval is two-sided. Additional two-sided 97.2% CI for stratified HR is to match the one-sided superiority boundary 0.014 in p-value scale used for this interim analysis.

[h] SE is based on Greenwood formula.

[if] Negative MRD values post randomization are considered. MRD negativity is determined by at least one negative MRD value within 3 months prior to achieving CR or above until time of progression/death (exclusive). ITT population is used as a denominator. The primary analysis for MRD negative response uses the sensitivity of 10^{-5}.

Source: ADSL, ADTTE, ADRS, ADMRD

Figure 7. Applicant – Forest Plot for ORR Odds Ratio between Ide-cel and Standard Regimens Arms Based on IMWG Criteria per IRC Review – ITT Population in MM-003

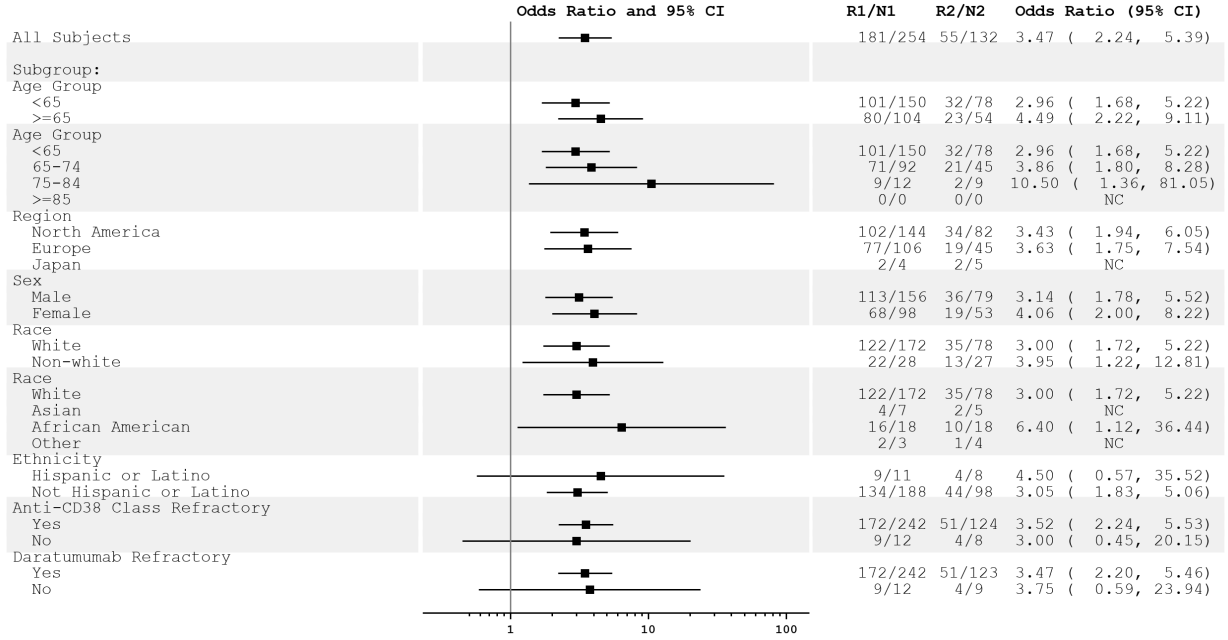
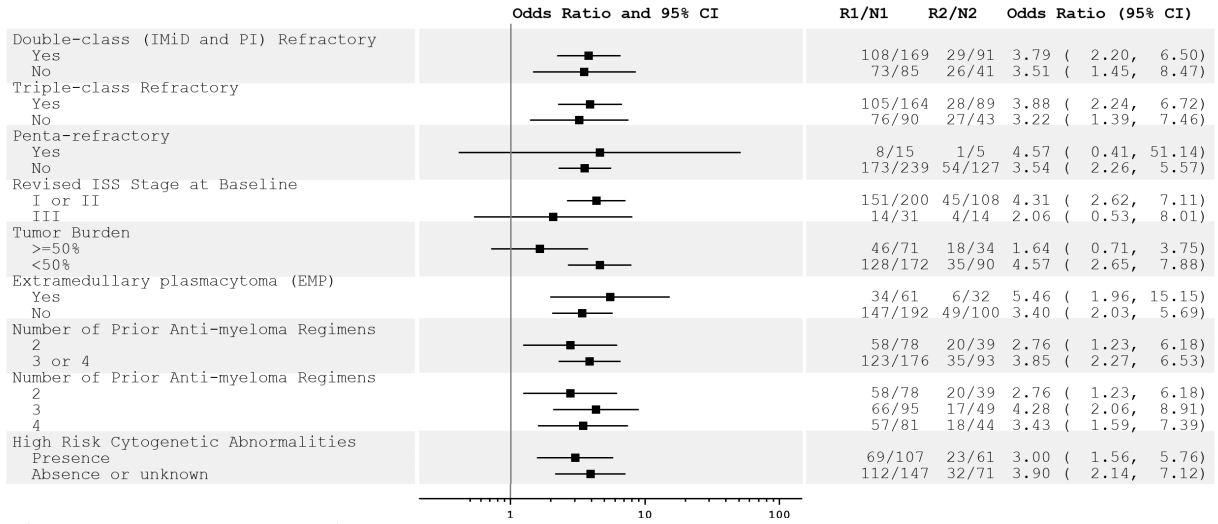


Figure 8. Applicant – Forest Plot for ORR Odds Ratio between Ide-cel and Standard Regimens Arms Based on IMWG Criteria per IRC Review – ITT Population in MM-003



R1/N1 = number of responders/number of subjects assigned to Ide-cel Arm in the subgroup.
R2/N2 = number of responders/number of subjects assigned to Standard Regimens Arm in the subgroup.
Odds ratio is unstratified and based on the observed response rate. Confidence interval (CI) is two-sided Wald CI.
Odds ratio is not computed for subgroups if both N1 and N2 are less than 10.
Source: ADSL, ADEXSUM, ADRS

The Applicant's Position:

Key Secondary Endpoints (Hierarchically Tested): In the ITT population, for the key secondary endpoint of ORR per IRC assessment, ide-cel demonstrated a statistically significant improvement compared with standard regimens: Cochran-Mantel-Haenszel test p-value < 0.0001 (Table 17, Table 18). Ide-cel demonstrated a 3.54 (95% CI: 2.26, 5.54) fold higher odds of achieving a response compared to standard regimens.

At data cutoff, the p-value for OS did not cross the significance boundaries for either superiority of efficacy or futility (one sided critical p-value <0.001 needed for statistical significance and p-value >0.8 needed for futility); therefore the study team remains blinded to OS results.

Other Secondary Endpoints: In the ITT population, efficacy favored ide-cel over standard regimens across all other secondary efficacy endpoints analyzed, including CR, DoR, and EFS, as well as MRD negativity rate.

Subgroups: The unstratified odds ratios for ORRs (per IRC) favored ide-cel (odds ratio > 1) over standard regimens in most predefined subgroups, although interpretation in some subgroups is limited by small numbers of subjects. Similar to PFS, the ide-cel ORR benefit over standard regimens was also consistent regardless of the number of prior regimens received. Median ORR per IRC assessment across the pre-planned ide-cel subgroup dose ranges of 300 to 460 × 10^6 and > 460 to 540 × 10^6 were similar and consistent to that of the overall ide-cel arm. Despite the imbalanced distribution of African American subjects between the treatment arms, the benefit of ide-cel over standard regimens among African American subjects was consistent with the overall study population for ORR (88.9% [95% CI: 74.4, 100.0] vs 55.6% [95% CI: 32.6, 78.5], respectively; Odds Ratio = 6.40) (, *Source: ADSL, ADEXSUM, ADRS*).

The FDA's Assessment:
Overall Response Rate:

FDA agrees with Applicant's assessment that ORR was statistically significant, as shown above in Table 22. While the efficacy results of PFS and ORR in the subpopulations were consistent with the ITT efficacy data, these data should be interpreted with caution given the small sample size of the subgroups and exploratory nature of such analyses.

Overall Survival:
Results of three OS analyses submitted by the Applicant are summarized below in Table 23. The first interim OS analysis was prespecified and was conducted at the time of primary PFS analysis. The Applicant conducted and submitted to the Biologics License Application, the results of an unplanned, post-hoc analysis of OS performed at the time of the 90-day safety update (refer to the Appendix for the OS KM Figure 13). A second OS interim analysis was prespecified to occur at the time of the final analysis of PFS. During FDA's review of KarMMa-3, the Applicant provided results from the second interim OS analysis.

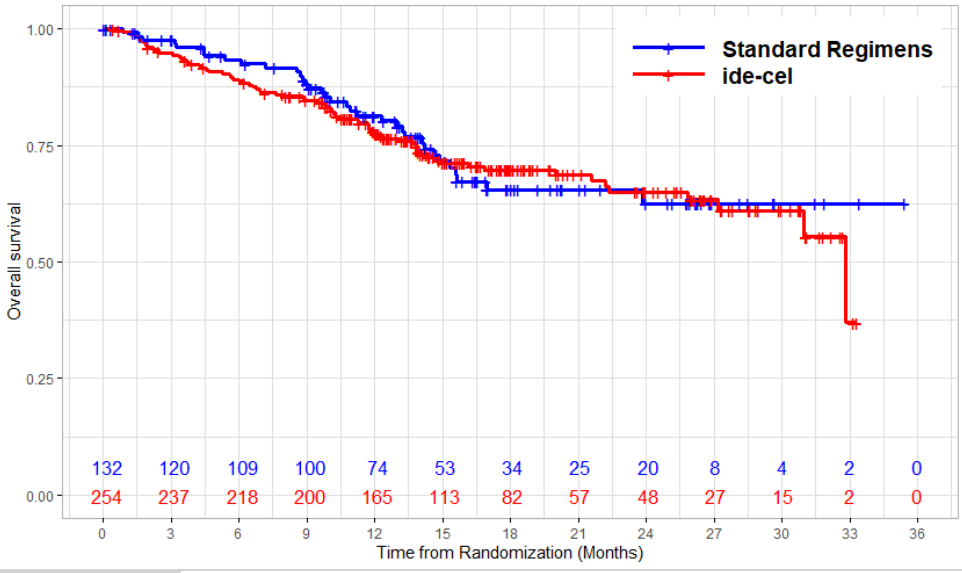
Table 23. FDA – Analyses of Overall Survival, ITT, KarMMa 3

	Pre-specified		**Post-Hoc**		**Pre-Specified**	
	First Interim Analysis		**Interim Analysis**		**Second Interim Analysis**	
Variable	**Ide-cel N=254**	**SOC N=132**	**Ide-cel N=254**	**SOC N=132**	**Ide-cel N=254**	**SOC N=132**
OS analysis	**Planned at Interim PFS analysis**		***Unplanned at Safety Update**		**Planned at Final PFS analysis**	
IF	**49%**		**67%**		**74%**	
Deaths, n(%)	75 (29.5)	34 (25.8)	92 (36.2)	57 (43.2)	106 (41.7)	58 (43.9)
Censored, n(%)	179 (70.5)	98 (74.2)	162 (63.8)	75 (56.8)	148 (58.3)	74 (56.1)
Median OS (95% CI)	32.8 (30.9, NA)	NA	NA (29.4, NA)	27.6 (20.9, NA)	41.4 (30.9, NA)	37.9 (23.4, NA)
Median follow-up (95% CI)	17.6 (15.9, 18.4)	16.4 (14.3, 17.8)	23.5 (22.1, 24.3)	23.2 (20.6, 26.5)	30.3 (28.9, 31.3)	29.2 (26.8, 31.2)
Hazard ratio (95% CI)	1.093 (0.727, 1.645)		0.891 (0.637,1.246)		1.012 (0.731, 1.400)	

Source: FDA analysis
Data cut off for first interim analysis, April 18, 2022. Data cut off for post-hoc interim analysis, October 3, 2022. Data cut off for second interim analysis April 28, 2023.
IF: Information Fraction * Unplanned and post-hoc OS analysis done at the time of Safety update.

The first interim OS analysis was performed at the time of the primary PFS analysis (i.e., data cutoff of April 18, 2022) with a median follow up of 16.9 months (95% CI:15.9, 17.9) and 49% IF. Visual inspection of the Kaplan Meier plot indicates OS detriment up to 15 months; heavy censoring from Month 9 onward indicates that data are immature.

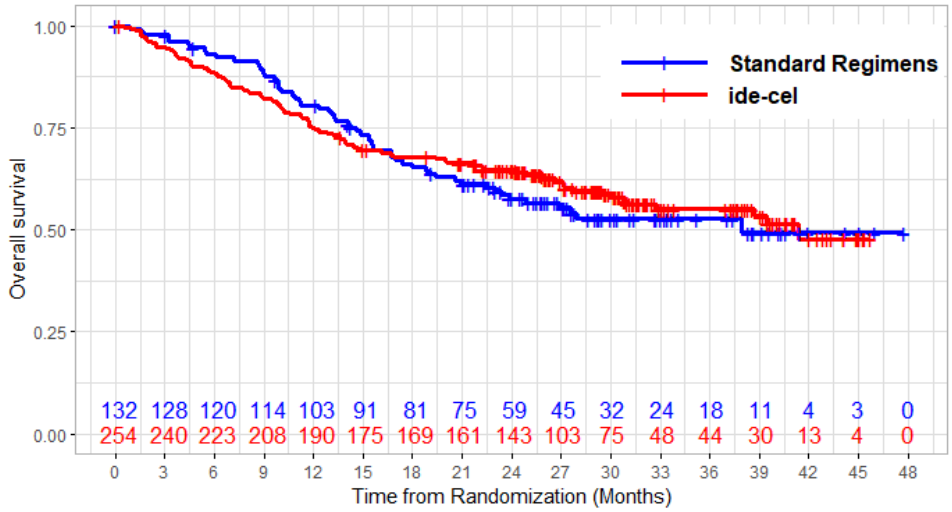
Figure 9 FDA – Overall Survival, ITT Population, Interim Analysis #1



Source: FDA analysis.
Data cutoff=April 18, 2022

The second prespecified interim OS analysis (Figure 10) was performed at the time of the final PFS analysis with a data cutoff of April 28, 2023. With an estimated median follow-up of 29.7 months (95% CI: 28.7, 30.9) and 74 % IF, the OS data are shown in Figure 10 below. At this time, 42% of the subjects in the ide-cel arm and 44 % of the subjects in the SOC arm have died. The median OS in the ide-cel arm is 41.4 months (95 % CI: 30.9, NA) and 37.9 months in the SOC arm (95% CI: 23.4, NA). Fifty-six percent of the subjects in the SOC arm crossed over and received ide-cel.

Figure 10. FDA – Overall Survival, ITT Population, Interim Analysis #2



Source: FDA analysis ,Data cutoff=April 28, 2023

- Visual inspection of the KM OS curve suggests a lower OS in the ide-cel arm compared to the SOC arm for up to 15 months. Overall, 28% of the study population had died at the time of the primary PFS analysis. The number of deaths were higher in the ide-cel arm compared to the SOC arm as shown in Table 23 above.

- In the second interim analysis for OS (see Figure 4) provided more mature OS data reflecting an additional year of follow-up for OS. These results were consistent with the first interim OS analysis with persistent OS detriment for approximately 15 months after randomization. Forty-two percent of the subjects randomized to the ide-cel arm and 44% of the subjects randomized to the SOC arm had died. The median OS in the ide-cel arm is 41.4 months (95 % CI: 30.9, NA) and 37.9 months in the SOC arm (95% CI: 23.4, NA). At the time of this analysis, 56% (74/132) of subjects in the SOC arm had crossed over and received ide-cel. Out of these 74 subjects, 69 had progressed prior to cross over.

- Kaplan Meier plot for OS represents a crossing of the curves which indicates that the treatment effect constancy assumption cannot be made (i.e., there is non-proportional hazards). In this scenario, average HR is an unreliable summary statistic to quantify the treatment effect.

- Overall, these OS results raised concerns regarding the safety of ide-cel particularly for the increased risk of early death. FDA conducted additional analysis of deaths in the first 15 months. Please refer to the Section :Additional Analyses Conducted on the Individual Trial'.

- For the impact of cross-over on overall survival analysis, please refer to Section 9.1, Statistical Issues; impact of cross-over on overall survival.

  Minimal Residual Disease:

  Minimal residual disease (MRD) negative rate was a secondary endpoint in the study and is defined as the proportion of subjects who achieved CR or better and MRD negative status at any time point within 3 months prior to achieving CR until the time of PD/death based on the ITT population. MRD was assessed in the bone marrow samples using a clonoSEQ assay (NGS methodology). An MRD threshold of 10e-5 was prespecified in the study with sensitivity based on a limit of detection (LOD) of (b) (4) with a DNA input of at least (b) (4) micrograms. The clonoSEQ Assay is an in-vitro diagnostic test that was originally approved for use in MM as a De Novo (DEN170080) on September 28, 2018 in patient's bone marrow for monitoring burden of disease before and after treatment

  MRD was assessed at screening, between leukapheresis and LD chemotherapy, and at Months 2, 7, and 13 in the ide-cel arm; and at screening and Months 2, 7, and 13 for

subjects in the SOC arm, independent of IMWG response. In addition, bone marrow aspirate for MRD assessments was performed at CR or sCR and at confirmed PD.

A subject was considered MRD evaluable if calibration was achieved and if there was at least one post-randomization MRD assessment with a result at 10e-5 sensitivity level.

In total, 161 subjects (63%) were MRD evaluable in the ide-cel arm and 53 subjects (40%) were MRD evaluable in the SOC arm. Subjects were MRD in-evaluable due to calibration assay failure, missing of calibration samples, calibration not attempted because no post-treatment MRD samples were collected, or if there were no post randomization MRD results.

Calibration was attempted in 213 subjects (84%) in the ide-cel arm and 81 subjects (61%) in the SOC arm. Calibration was not attempted due to lack of pre-treatment or post-treatment bone marrow aspirate samples in the remaining subjects. Calibration was achieved in 166 (65%) and failed in 47 (19%) in the ide-cel arm. In the SOC arm, calibration was achieved in 60 patients (46%) and failed in 21 (16%) in the SOC arm in the ITT population.

For subjects in whom calibration was attempted, calibration was successful in 78% in the ide-cel arm and 74% in the SOC arm.

Overall, 20% of the subjects in the ide-cel arm attained MRD negativity compared to 0.8% in SOC arm.

- Overall, only 63% of the population in the ide-cel arm was MRD evaluable compared to 40% in the SOC arm. The reasons for MRD in evaluability was due to lack of bone marrow sample availability for calibration, calibration assay failure or no post-randomization MRD data. The Applicant reported a successful calibration rate of only 65% in the ide-cel arm and 46% in the SOC arm in the ITT population.

- The high calibration failure rate raises concerns regarding the reliability of the MRD response assessments for regulatory purposes. The rate of calibration failure is higher (>90%) than the reported rates with the clonoSEQ NGS assay (Costa et al. 2021). These significant issues that were noted have an impact on the strength and validity of the MRD results. Therefore, the MRD data was not considered robust to support inclusion in the USPI.

Dose/Dose Response

Data:

Table 24. Applicant - PFS and ORR by CAR+ T cell Dose Range (Ide-cel Arm only) - Safety Population in MM-003

Endpoint	300 to 460 × 10^6 CAR+ T cells (N = 143)	> 460 to 510 × 10^6 CAR+ T cells (N = 69)
PFS per IRC		
Censored, n (%)	56 (39.2)	34 (49.3)
Progressed/Died, n (%)	87 (60.8)	35 (50.7)
Progressed, n (%)	79 (55.2)	32 (46.4)
Died Without Progression, n (%)	8 (5.6)	3 (4.3)
Progression-Free Survival Time, mo [a]		
25th Percentile (95% CI)	7.2 (4.2, 9.2)	8.8 (4.8, 11.3)
Median PFS (95% CI)	14.7 (11.9, 19.0)	14.4 (12.0, NA)
75th Percentile (95% CI)	25.3 (20.4, 30.9)	24.5 (17.3, NA)
Event-free Rate % (SE)[b]		
3-months	90.2 (2.5)	91.3 (3.4)
6-months	79.0 (3.4)	84.0 (4.4)
12-months	57.4 (4.2)	63.8 (6.0)
ORR[c]		
N responders (%)	116 (81.1)	57 (82.6)
95% CI[d]	74.7, 87.5	73.7, 91.6
sCR, n (%)	61 (42.7)	27 (39.1)
CR, n (%)	4 (2.8)	3 (4.3)
VGPR, n (%)	34 (23.8)	17 (24.6)
PR, n (%)	17 (11.9)	10 (14.5)

Note: For ORR, only the assessments after study treatment and before the first progressive disease are included in the analysis. The assessments after the start of a new antimyeloma therapy are not considered.

[a] The 25th and 75th percentile, median and corresponding 95% confidence interval are based on Kaplan-Meier approach.

[b] SE is based on Greenwood formula.

[c] Overall response rate is defined as the rate of subjects whose response is PR or better (i.e. sCR or CR or VGPR or PR); Complete response rate is defined as the rate of subjects whose response is CR or better (i.e. sCR or CR). The denominator used for rate calculation is the number of subjects in the designated study population.

[d] Two-sided Wald CI.

Source: ADSL, ADEXSUM, ADTTE, ADRS

The Applicant's Position:

Based on the prespecified subgroup analyses, median PFS and ORR were similar across the ide-cel subgroup dose ranges of 300 to 460 × 10^6 and > 460 to 540 × 10^6 CAR+ T cells. To support the proposed dose range expansion, post-hoc analyses for subgroups of 300 to 460 × 10^6 and > 460 to 510 × 10^6 CAR+ T cells were performed; median PFS and ORR per IRC assessment across the ide-cel subgroup dose ranges were similar and consistent to that of the overall ide-cel arm (Table).

The FDA's Assessment:

Sixty-nine subjects (31%) in the ide-cel treated population received a dose of >460 to 510 x10e6 CAR+ T cells which is the dose expansion requested in the sBLA. FDA agrees with the Applicant's assessment that the median PFS and ORR per IRC assessment in this dose cohort was similar to the that of the approved ide-cel dose cohort of 300 to 460 x10e6 CAR+ T cells and to the overall ide-cel arm.

Durability of Response

Data:
In the ide-cel arm, the median DoR among responders was 14.8 months (95% CI: 12.0, 18.6) compared with a median DoR of 9.7 months (95% CI: 5.4, 16.3) in the standard regimens arm (Table

The Applicant's Position:
Clinically meaningful durable responses were observed with ide-cel compared with standard regimens, supporting the long-term benefit of treatment with ide-cel.

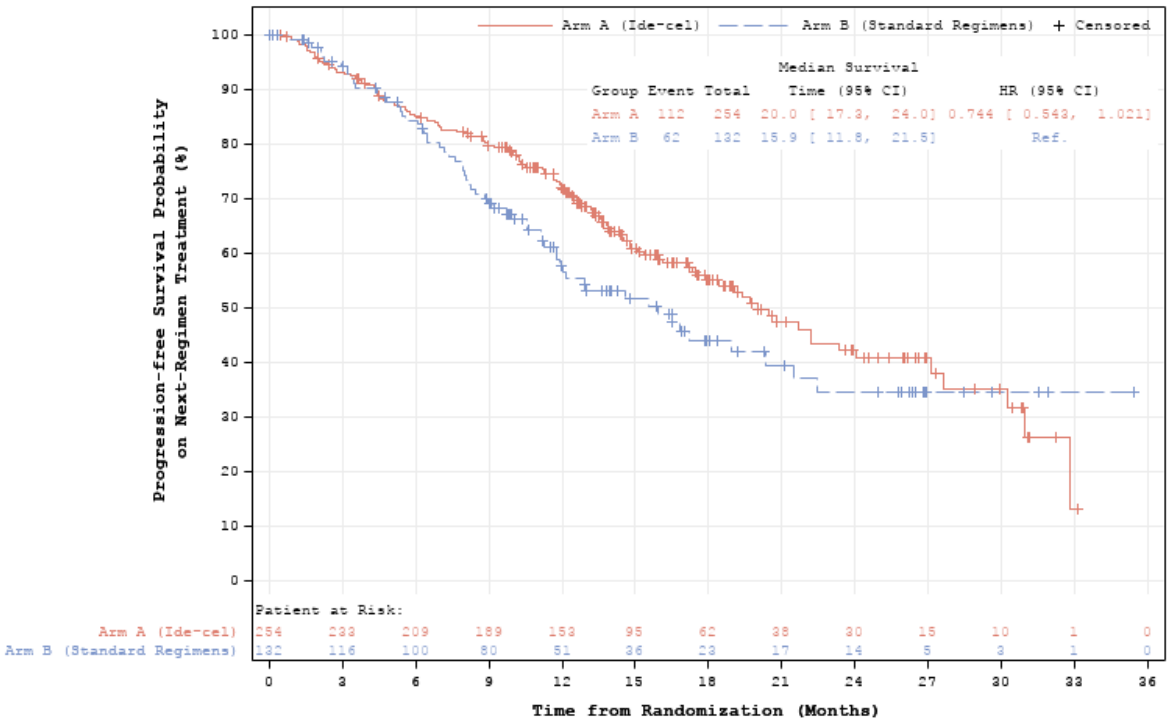
The FDA's Assessment:
The comparison of DOR between the two arms is a responder analysis that does not compare a population that is well balanced in terms of prognostic factors. Therefore, the review team does not agree with such a comparative analysis. Instead, a stand-alone analysis of DOR in the ide-cel arm was done which demonstrates that the median duration of response (DOR) was 14.8 months (95% CI: 12.0, 18.6) in patients with partial response (PR) or better. In those patients with CR or better, the median DOR was 20 months (95% CI: 15.8, 24.3).

The duration of response correlates with the depth of response with ide-cel. This information will be included in the USPI as it may be useful to the prescribers.

Persistence of Effect

Data:

Figure 11. Applicant - K-M Curve of PFS on Next-Regimen Treatment (PFS2) - ITT Population in MM-003



Source: ADSL, ADTTE

At the time of the data cutoff, in the ITT population, a higher percentage of subjects in the standard regimens arm received subsequent AMT (68.9% vs 39.0% in the ide-cel arm).

The Applicant's Position:

TTNT and PFS2 are endpoints that support measurement of longer-term clinical benefit. As an indicator of duration of clinical benefit, TTNT reflects not only the duration of treatment efficacy on disease and symptom control, but also accounts for patient compliance and tolerance to the study treatment. TTNT was defined as the time to next anti-myeloma treatment calculated from the time of randomization. Median TTNT was longer in the ide-cel arm compared to the standard regimens arm, and the HR favored the ide-cel arm over the standard regimens arm (Table). The TTNT results highlight the longer, clinically meaningful treatment-free period achieved with ide-cel treatment as compared to standard regimens.

PFS2 has been shown to correlate with OS.[33,34] PFS2 was defined as time to randomization to second objective disease progression or death from any cause. Median PFS2 per Investigator assessment was longer in the ide-cel arm than the standard regimens arm, and the HR favored the ide-cel arm over the standard regimens arm (). The longer PFS2 for ide-cel compared with standard regimens suggests that subsequent disease control is not compromised by ide-cel therapy.

The FDA's Assessment:

Time to next treatment and PFS2 were exploratory endpoints in KarMMa-3 and cannot support regulatory decision-making. Therefore, FDA relied on primary PFS and OS data to verify the safety and efficacy of ide-cel in KarMMa-3.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:

Completion and Compliance Rates Over Time: Completion and compliance rates were equivalent across clinical outcome assessments with compliance rates >80% at most visits. Rates were similar between the 2 treatment arms.

The Applicant's Position:

Mean Changes from Baseline: Clinically meaningful improvements in ide-cel arm were observed on the group-level mean change from baseline on EORTC QLQ-C30 domains (Fatigue, Pain, Physical Functioning, Cognitive Functioning, and Global Health Status/QoL) consistently, whereas in the standard regimen arm, group-level mean changes either stayed stable or deteriorated. After a transient decline on Day 1, Fatigue, functioning domains (physical, role, cognitive), and Global Health Status/QoL in particular, showed clinically meaningful improvements from baseline with ide-cel as well as differences between arms, in favor of the ide-cel arm. Additionally, clinically meaningful improvements or stability over time were observed in the EORTC QLQ-C30 Pain domain and EORTC QLQ-MY20 Disease Symptoms in the ide-cel arm. Perceived side effects based on the EORTC QLQ-MY20 remained stable for ide-cel with a trend towards worsening in the standard regimens arm. Findings were similar in the remaining EORTC domains. The EQ-5D-5L VAS showed meaningful improvements in the ide-cel arm only.

Proportion of Subjects Meeting Pre-specified Responder Definitions: The proportion of subjects reporting meaningful improvement, no change, or worsening compared to baseline was evaluated for post-baseline visits. After Month 2, consistently higher proportions of subjects in the ide-cel arm improved or were stable compared with the standard regimens arm, particularly for the EORTC QLQ-C30 Physical and Cognitive Functioning, Fatigue, and Global Health Status/QoL domains. Similarly, either no deterioration or improvement in the EORTC QLQ-C30 Pain domain and MY20 Disease symptoms was observed in a greater proportion of subjects in the ide-cel arm compared with the standard regimens arm. After Day 1, the MY20 Side Effects domain showed higher proportions of subjects that were stable or improved with ide-cel compared with standard regimens. Based on the EQ-5D-5L VAS, a consistently higher proportion of subjects improved in the ide-cel arm compared with the standard regimens arm after Month 2.

Cumulative Distribution Function Curves: Based on cumulative distribution function evaluation, there were noteworthy differences in the proportion of subjects in the ide-cel arm with meaningful improvement in Fatigue, Global Health Status/QoL, and the VAS at Month 6, and Fatigue also at Month 12. Similarly, differences favoring ide-cel over standard regimens were found in the proportion of subjects who had worsening in Fatigue, Physical Functioning, Cognitive Functioning, and the EQ 5D-5L VAS at Month 6.

The FDA's Assessment:

Patient-generated data was collected monthly in KarMMa 3 using the European Organization for Research and Treatment of Care (EORTC)-Quality of Life Questionnair-C30 and EORTC-MY-20 measures. Patient-reported outcome (PRO) endpoints were included in the trial as exploratory and were not included in the statistical hierarchy. FDA therefore approached this data as purely exploratory and descriptive information.

- In examining mean change in scores from baseline, FDA noted a short-term worsening of treatment-related symptoms (e.g., fatigue), physical functioning, and role functioning observed at month 1 and 2 for the Ide-cel arm compared to SOC, but these patients improved after month 2. Patients in the SOC arm did not experience major changes from baseline. Overall, mean change from baseline results from fatigue, physical functioning, and side effect domains were directionally favorable in the Ide-cel arm after month 3. The longitudinal trajectory of these curves likely represents the early toxicity of Ide-cel followed by a period of no active treatment compared to ongoing combination therapy in the SOC arm.

- There was no appreciable difference between arms in terms of disease-related symptoms as measured by the EORTC-Quality of Life Questionnaire-MY20 primary domains.

- Interpretation of this PRO data has the following substantial limitations: (1) the small number of patients in the control arm beyond month 6; (2) the infrequent assessment of PROs, particularly early in the trial (within 2 to 3 weeks of CAR T infusion) when patients experience tolerability issues with CAR T; and (3) longitudinal PRO data does not include the experience of patients who died early in the trial and is therefore subject to selection bias.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:
Not applicable.

The FDA's Assessment:
Increased Rate of Early Deaths in the ide-cel Arm:

FDA's analysis of deaths that occurred in the first 15 months in the study demonstrated a higher rate of death in the ide-cel arm in the first 9 months post randomization. As shown in the table, 18% of patients in the ide-cel arm died in the first 9 months compared to 11% in the SOC arm. This includes a higher rate of death from disease progression, any AEs, and unknown causes.

Table 25. FDA – Deaths, ITT Population

Variable	Ide-cel N=254 n (%)	SOC N=132 n (%)
Total deaths in ITT population (treated and untreated)	106[1] (42)	58[1] (44)
Death from PD	60 (24)	36 (27)
Deaths from AE	29 (11)	14 (11)
Unknown	17 (7)	8 (6)
All deaths in the first 9 months (treated and untreated)	45 (18)	15 (11)
Death from PD	25 (10)	9 (7)
Death from AE	14 (6)	6[2] (4.5)
Unknown	6 (2.4)	0

Variable	Ide-cel N=254 n (%)	SOC N=132 n (%)
All deaths from 9-18 months	36 (14)	29 (22)
Death from PD	20 (8)	19 (14)
Death from AE	10 (3.9)	7[3] (5)
Unknown	6 (2.4)	3 (2.3)
All deaths after 18 months	25 (10)	14 (11)
Death from PD	15 (6)	8 (6)
Death from AE	5[4](2)	1 (0.8)
Unknown	5 (2)	5 (3.8)

Source: FDA analysis: April 28, 2023, data cutoff date. Death day is calculated from randomization. Table includes deaths in all randomized subjects including two subjects who received nonconformal ide-cel
Table includes all deaths after treatment from AEs including infection related AEs following disease progression and subsequent AMT.
[1]Out of the 106 deaths in the ide-cel arm, 25 never received the intended treatment; (20 of these deaths were in the first 9 months) compared to 4 deaths in the SOC arm.
[2] Includes one death from ide-cel neurotoxicity after crossover
[3] Includes three deaths from AE post ide-cel: two deaths from sepsis, one death from carcinoma of unknown primary
[4] Includes death in recipient of nonconformal ide-cel from amyotrophic lateral sclerosis in the setting of renal cell carcinoma.
The cause of death in 25 subjects who did not receive ide-cel treatment include: infection, respiratory failure, disease progression and unknown. The cause of death in four subjects who did not receive SOC treatment include: Grade 5 CRS on another clinical trial, ventricular tachycardia and unknown.

Given the higher rate of death in the ide-cel arm in the first 9 months from randomization, FDA further analyzed these deaths. This is shown below in Table 26.

It is notable that 8% of the patients (20 patients) randomized to the ide-cel arm died without receiving the intended CAR T cell infusion within 9 months of randomization compared to none such patients in the SOC arm. The most common cause of death was disease progression followed by AEs and unknown causes. Within the ide-cel treated patients and patients who received SOC therapy, the rate of death and deaths from AEs was similar between the two arms in the ITT population.

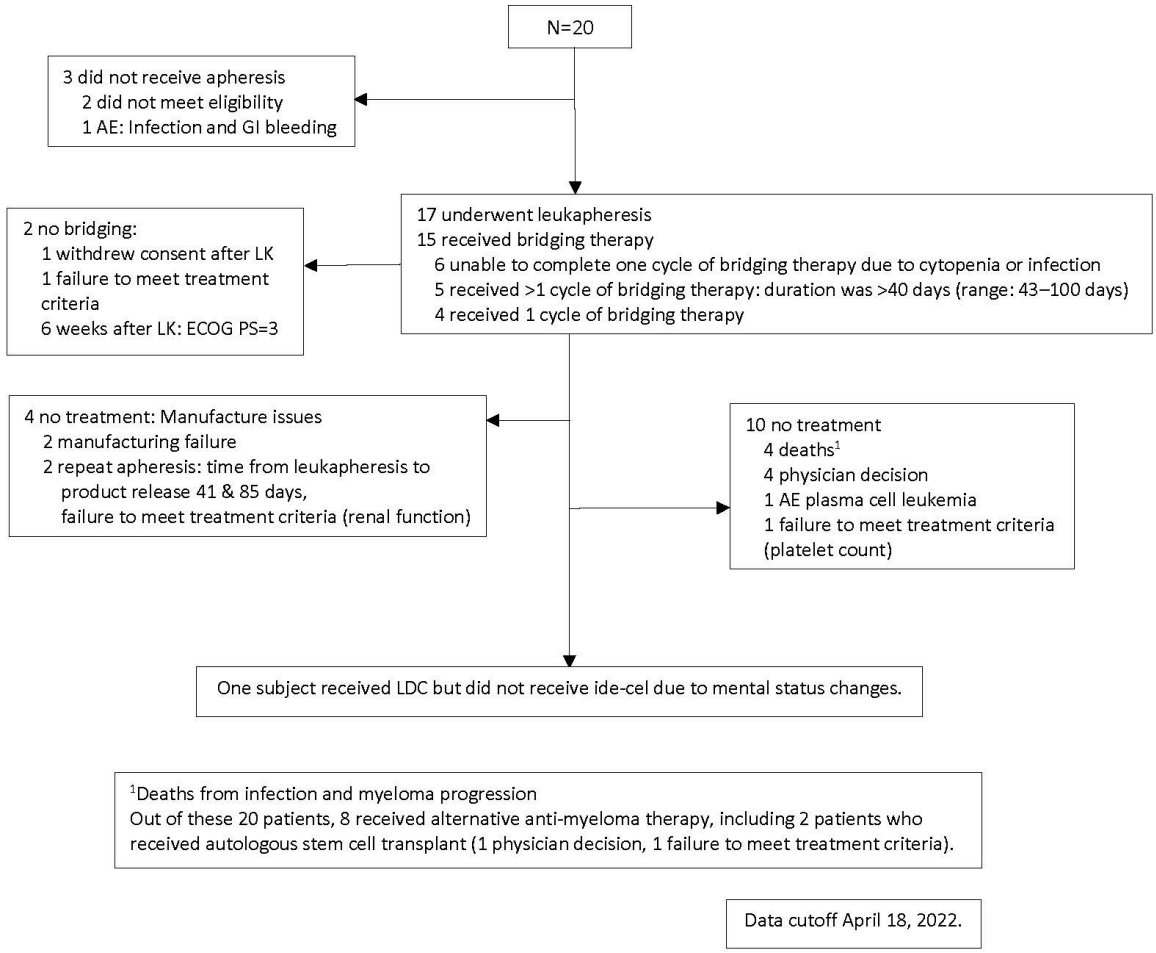
Table 26. FDA –Deaths in First 9 Months in ITT Population

	ide-cel (N=254) n(%)	SOC (N=132) n(%)
Total	**45 (18)**	**15 (11)**
Prior to ide-cel/SOC	**20 (8)**	**0**
Disease progression	15 (6)	0
Adverse event	3 (1.2)	0
Unknown cause	2 (0.8)	0
After ide-cel/SOC	**25 (10)**	**15 (11)**
Disease progression	10 (4)	9 (7)
Adverse event	11(4.3)	6 (4.5)
Unknown cause	4 (1.6)	0

Source: FDA.
Data cut off: April 28,2023
3 out of 6 deaths after crossover to ide-cel arm

Analysis of the 20 patients who died prior to ide-cel infusion within 9 months of randomization demonstrates that patient attrition occurred at different steps in the process to CAR T cell infusion. This is demonstrated in (Figure 12) below:

Figure 12. FDA – Disposition of 20 Subjects Who Did Not Receive Ide-cel and Died Within 9 Months



Source: FDA

Since the majority of patients died from disease progression prior to ide-cel infusion, FDA analyzed the BT administration in this subgroup of 20 patients who died prior to ide-cel infusion within 9 months of randomization and compared it to the patients who did receive ide-cel.

Table 27. FDA – Bridging Therapy

	ide-cel (N=254)	
	ide-cel (N=225)	No ide-cel* (N=20)
Received BT (%)	85	75

	ide-cel (N=254)	
	ide-cel (N=225)	No ide-cel* (N=20)
Time from randomization to BT start Median in days (range)	8 (1-51)	7 (2-33)
Type of BT (%) Protocol specified Non-protocol specified	76 10	75 0
Duration of BT (days) Median (range)	22 (1-88)	24 (1-100)
Number of cycles (%) 1 2 > 2 Missing/unknown	70 11 0 5	40 15 10 10
Time from leukapheresis to product release (days) Median (range)	35 (24-102)	30 (26-85)

Source: FDA and Applicant analysis
*Death within 9 months

Overall, the rate of BT administration was comparable between these two groups. The median time from randomization to start of BT and the median duration of BT were also similar between the two groups. There was a higher proportion of patients who received two or more cycles in this group of early mortality prior to ide-cel compared to the treated group.

- Bridging therapy cycles were truncated and modified in the event of cytopenia or infections and in some instances more than one regimen was administered as bridging.
- Overall, no significant difference was found between the median time from leukapheresis (LK) to product release in the two groups.
- In all, this analysis indicates that BT administration was similar between the early mortality subgroup that did not receive ide-cel and ide-cel treated patients. In addition, investigators used clinical judgment to tailor BT including administering more than 1 cycle and non-protocol-specified BT to meet patients' individual clinical needs in KarMMa 3.
- FDA conducted exploratory analyses to assess whether any particular prognostic subgroup was associated with a higher early mortality in the ide-cel arm (refer to Table 81 in Appendix). No particular prognostic subgroup was associated with or was driving this observed higher early mortality. The study was not designed to characterize a heterogeneous study population which may have contributed to higher early mortality with ide-cel.

8.1.3 Integrated Review of Effectiveness

The FDA's Assessment:

The varying study design and differences in the primary endpoint in the pivotal study KarMMa-

3 with the supporting studies (KarMMa and KarMMa-2) does not allow for an integrated efficacy assessment. However, see FDA's assessment under Section 8.1.4 regarding the pooled analysis of ORR and CR rate to support dose expansion.

8.1.4 Assessment of Efficacy Across Trials

Primary Endpoints

Data:

Table 28. Applicant - Summary of ORR, CR Rate, and DoR by Dose Intervals (× 10^6 CAR+ T Cells) Using IMWG Criteria, FDA Censoring Rules - Pooled Analyses and MM-003 Ide-cel Arm

Pooled Data from MM-001, MM-002 Cohort 1 and MM-003 Ide-cel Arm												
Parameters[a]	**< 300 (N=26)**	**300-460 (N=283)**	**>460-470 (N=23)**	**>470-480 (N=16)**	**>480-490 (N=12)**	**>490-500 (N=18)**	**>500-510 (N=23)**	**>510-520 (N=11)**	**>520-530 (N=4)**	**>530-540 (N=0)**	**>540 (N=1)**	**Total (N=417)**
ORR, n (%)[b]	14 (53.8)	215 (76.0)	18 (78.3)	13 (81.3)	9 (75.0)	16 (88.9)	20 (87.0)	9 (81.8)	4 (100.0)	0	1 (100.0)	319 (76.5)
95% CI[c]	33.4, 73.4	70.6, 80.8	56.3, 92.5	54.4, 96.0	42.8, 94.5	65.3, 98.6	66.4, 97.2	48.2, 97.7	39.8, 100.0	NA	2.5,100.0	72.1, 80.5
CR Rate, n (%)[d]	5 (19.2)	109 (38.5)	10 (43.5)	7 (43.8)	5 (41.7)	11 (61.1)	7 (30.4)	1 (9.1)	2 (50.0)	0	0	157 (37.6)
95% CI[c]	6.6, 39.4	32.8, 44.5	23.2, 65.5	19.8, 70.1	15.2, 72.3	35.7, 82.7	13.2, 52.9	0.2, 41.3	6.8, 93.2	NA	0.0, 97.5	33.0, 42.5
Median DoR, mo[e,f,g]	7.5	13.4	11.1	16.8	NA	NA	10.2	4.5	NA	NA	9.5	13.4
95% CI	2.8, 16.7	11.3, 16.8	7.5, NA	3.5, NA	4.7, NA	15.2, NA	6.1, NA	1.7, NA	9.6, NA	NA, NA	NA, NA	11.3, 16.7
MM-003 Ide-cel Arm												
Parameters[a]	**< 300 (N=3)**	**300-460 (N=141)**	**>460-470 (N=15)**	**>470-480 (N=11)**	**>480-490 (N=9)**	**>490-500 (N=14)**	**>500-510 (N=20)**	**>510-520 (N=5)**	**>520-530 (N=4)**	**>530-540 (N=0)**	**>540 (N=0)**	**Total (N=222)**
ORR, n (%)[b]	1 (33.3)	115 (81.6)	12 (80.0)	8 (72.7)	6 (66.7)	13 (92.9)	18 (90.0)	3 (60.0)	4 (100.0)	0	0	180 (81.1)
95% CI[c]	0.8, 90.6	74.2, 87.6	51.9, 95.7	39.0, 94.0	29.9, 92.5	66.1, 99.8	68.3, 98.8	14.7, 94.7	39.8, 100.0	NA	NA	75.3, 86.0
CR Rate, n (%)[d]	1 (33.3)	64 (45.4)	7 (46.7)	4 (36.4)	3 (33.3)	10 (71.4)	6 (30.0)	0	2 (50.0)	0	0	97 (43.7)
95% CI[c]	0.8, 90.6	37.0, 54.0	21.3, 73.4	10.9, 69.2	7.5, 70.1	41.9, 91.6	11.9, 54.3	0.0, 52.2	6.8, 93.2	NA	NA	37.1, 50.5
Median DoR, mo[e,f,g]	13.9	15.8	11.1	14.8	NA	NA	10.2	8.8	NA	NA	NA	13.9
95% CI	NA, NA	12.0, 18.6	6.8, NA	1.8, NA	4.7, NA	NA, NA	6.1, NA	1.7, NA	9.6, NA	NA, NA	NA, NA	11.2, 17.8

Note: subjects who received non-confirming ide-cel product are excluded from analysis. For MM-001, ORR and CR rate are based on FDA adjudication of responses, as used in the current USPI. For MM-003 and MM-002 Cohort 1, ORR and CR rate are based on IRC adjudication of responses.

[a] Including subjects who did not have any response assessment data, or whose only assessment was response not evaluable.

[b] Overall response rate is defined as the rate of subjects whose response is PR or better (i.e. sCR or CR or VGPR or PR).

[c] Two-sided Clopper-Pearson confidence interval.

[d] Complete response rate is defined as the rate of subjects whose response is CR or better (i.e. sCR or CR).

The denominator used for rate calculation is the number of subjects in the designated study population.

[e] Response is defined as achieving sCR, CR, VGPR or PR.

[f] Only subjects with a response (sCR, CR, VGPR or PR) are included in the analysis.

[g] The median is based on the Kaplan-Meier estimate.

Cut-off dates:MM-001:14-Jan-2020, MM-002:14-Mar-2022, MM-003:18-Apr-2022.
Source: ADSL, ADRS, ADTTEEFF

Table 29. Applicant - ORR, CR Rate, and DoR by Dose Ranges of 300 to 460 × 10^6 CAR+ T cells and > 460 to 510 × 10^6 CAR+ T Cells Using IMWG Criteria, FDA Censoring Rules - MM-001, MM-002 Cohort 1, and MM-003 Ide-cel Arm, and Pooled Analyses

	Ide cel 300 - 460 x 10^6				Ide cel > 460 - 510 x 10^6			
	MM-001 (N=100)	MM-002 C1 (N=42)	MM-003 (N=141)	Pooled (N=283)	MM-001 (N=2)	MM-002 C1 (N=21)	MM-003 (N=69)	Pooled (N=92)
ORR - n (%)[a]	72 (72.0)	28 (66.7)	115 (81.6)	215 (76.0)	1 (50.0)	18 (85.7)	57 (82.6)	76 (82.6)
95% CI[b]	62.1, 80.5	50.5, 80.4	74.2, 87.6	70.6, 80.8	1.3, 98.7	63.7, 97.0	71.6, 90.7	73.3, 89.7
CR Rate - n (%)[a]	28 (28.0)	17 (40.5)	64 (45.4)	109 (38.5)	0 (0.0)	10 (47.6)	30 (43.5)	40 (43.5)
95% CI[b]	19.5, 37.9	25.6, 56.7	37.0, 54.0	32.8, 44.5	0.0, 84.2	25.7, 70.2	31.6, 56.0	33.2, 54.2
DoR, n	72	28	115	215	1	18	57	76
Median DoR, mo[c,d]	11.0	18.9	15.8	13.4	6.7	20.3	14.8	15.2
95% CI	10.3, 11.4	15.0, NA	12.0, 18.6	11.3, 16.8	NA, NA	10.3, NA	9.3, NA	10.3, 21.4

Note: For MM-001, ORR and CR rate are based on FDA adjudication of responses, as used in the current USPI. For MM-003 and MM-002 Cohort 1, ORR and CR rate are based on IRC adjudication of responses.

[a] Overall response rate is defined as the rate of subjects whose response is PR or better (ie, sCR or CR or VGPR or PR); Complete response rate is defined as the rate of subjects whose response is CR or better (ie, sCR or CR). The denominator used for rate calculation is the number of subjects in the designated study population.

[b] Clopper-Pearson confidence interval (CI).

[c] Only subjects with a response (sCR, CR, VGPR, or PR) are included in the analysis.

[d] The median is based on the Kaplan-Meier estimate.

Cut-off dates:MM-001: 14-Jan-2020, MM-002: 14-Mar-2022, MM-003: 18-Apr-2022.

Source: ADSL, ADRS, ADTTEEFF

The Applicant's Position:

Additional analyses were conducted to support the requested expansion of ide-cel dose range in the USPI for subjects with TCE RRMM. Data from Study MM-001 and MM-002 Cohort 1 along with MM-003 ide-cel arm have been pooled for these analyses based on similar eligibility requirements, types and schedules of assessments, and planned ide-cel dose range. Subjects who received non-conforming products were excluded from these analyses. Conformance was defined as meeting the pre-established product release quality specifications. The efficacy endpoints used in these analyses were ORR and CR rate because PFS was assessed based on different anchoring points in the Phase 3 MM-003 study (ie, from randomization) compared to the two Phase 2 studies, MM-001 and MM-002 Cohort 1 (ie, from time of infusion).

The pre-planned pooled efficacy analysis by 2 dose ranges (300 to 460 × 10^6 [current USPI dose range] and > 460 to 540 × 10^6 CAR+ T cells) showed consistent results between the 2 dose ranges.

To provide more data granularity within the > 460 × 10^6 CAR+ T cells dose range, additional analyses were performed by 10 × 10^6 CAR+ T cells dose increments within this dose range, which showed that, in the pooled population, comparable efficacy was observed across these discrete dose groups (Table 16). 23 subjects in the pooled population and 20 subjects in MM-003 received an ide-cel dose of 500 to 510 × 10^6 CAR+ T cells, which was considered adequate for reliable response assessment. The lower bound of the 95% CI for ORR in subjects who received an ide-cel dose of 500 to 510 × 10^6 CAR+ T cells, both in the pooled population and in MM-003 ide-cel arm, exclude the null hypothesis of 50%.

Furthermore, post-hoc analyses of data per FDA request from studies MM-001 and MM-002 Cohort 1 along with MM-003 ide-cel arm showed comparable ORR, CR rates , and DoR between the currently approved ide-cel dose range of 300 to 460 × 10^6 CAR+ T cells and the proposed expanded > 460 to 510 × 10^6 CAR+ T cells dose range, both in the pooled population and across the individual studies (Table 17). Results in subgroups including small numbers of subjects should be interpreted with caution.

The Sponsor believes that the experience at the upper end of the dose range for the pooled population supports a proposed upper dose of 510 × 10^6 CAR+ T cells. This is the highest dose administered to a sufficient number of subjects in the pooled population to enable reliable assessment of efficacy and safety (Section 2.9).

The FDA's Assessment:

Table 30. FDA – Summary of Efficacy Data to support Dose Extension

Parameter	KarMMa	KarMMa-2	KarMMa-3
Trial Design	Single arm	Single arm	Randomized controlled trial
Primary Endpoint	ORR	ORR	PFS
Baseline for Efficacy	Prior to LDC	Prior to LDC	Prior to LK
Number of subjects	2	21	69
Median, no. of prior regimens* (Range)	3 (3-4)	5 (3-10)	3 (2-4)
Triple class refractory	2 (100)	13 (62)	47 (68)

Parameter	KarMMa	KarMMa-2	KarMMa-3
Penta-class refractory	1 (50)	2 (10)	6 (9)
Refractory anti-CD38	2 (66)	14 (7)	69 (100)

Source: FDA analysis
*Based on the subjects included in the Table

The Applicant provided pooled efficacy data (ORR, CR rate and DOR) as assessed by IRC from KarMMa, KarMMa-2, and KarMMa-3 to support expansion of the upper end of the ide-cel dose from 460 to 510x10e6 CAR+ T cells.

There are differences in the study population, study design, and primary endpoints which limit the results of the pooled efficacy analyses between these three studies.

A key difference in efficacy assessment between the single arm trials: KarMMa, KarMMa-2 and the RCT, KarMMa-3, is the definition of baseline used for efficacy assessment. For the single arm trials, baseline was defined as the latest available assessment before the start of lymphodepleting chemotherapy (LDC) and after completion of any BT. However, for KarMMa-3, baseline was defined as assessment before leukapheresis which is prior to BT.

In addition, only 23 subjects were treated in KarMMa and KarMMa-2 combined at the expanded dose range of 460 to 510x10e6. Since, 69 subjects were treated at the higher dose range in KarMMa-3;the main study included in the submission, FDA relied on the efficacy data from KarMMa-3 to determine expansion of dose range. Please refer to Section 8.1.2 regarding the efficacy data at the higher dose range in KarMMa-3 supporting regulatory approval.

Secondary and Other Endpoints

The Applicant's Position:
Not applicable.

The FDA's Assessment: Refer to FDA assessment under Section 8.1.2; Efficacy Results-Secondary and other relevant endpoints.

Subpopulations

The Applicant's Position:
Not applicable.

The FDA's Assessment:
While the efficacy results of PFS and ORR in the subpopulations were consistent with the ITT efficacy data, these data should be interpreted with caution given the small sample size of the subgroups and exploratory nature of such analyses.

Additional Efficacy Considerations

The FDA's Assessment:
See FDA assessment under Section 8.1.5.

8.1.5 .Integrated Assessment of Effectiveness

The Applicant's Position:

MM-003 is a randomized, global, well-controlled, adequately powered clinical trial, and the efficacy data support the proposed indication. MM-003 demonstrates that ide-cel delivers a statistically significant PFS and ORR benefit in RRMM subjects who received 2-4 prior regimens including an IMiD, a PI, and DARA, compared to standard regimens. The estimated 51% risk reduction in PFS events and median PFS benefit of 13.3 months is clinically meaningful in this unmet medical need population. PFS and ORR favored ide-cel across predefined subgroups, including high risk subgroups (ie, high risk cytogenetics, extramedullary disease, high tumor burden, triple class refractoriness) and irrespective of the number of prior regimens received, supporting the internal consistency of the study results.

MM-003 provides substantial evidence of effectiveness for the proposed indication. Bias in treatment allocation and confounding in treatment effect assessment were minimized by IRT randomization, stratified by key prognostic factors, and by allocation of a standard regimen prior to randomization. While the use of multiple standard regimens introduced a level of heterogeneity in the control arm clinical benefit, it also enhanced the external validity of the study given the global lack of standard of care in this disease setting. Efficacy was assessed per the IMWG response guidelines by a blinded IRC to avoid assessment bias and ensure integrity of study results. An independent DSMB has reviewed cumulative study data over the course of the study to evaluate safety and efficacy, protocol conduct, and scientific validity and integrity of the trial. The subjects included in the study were representative of the TCE RRMM patient population in the US in terms of demographics and disease characteristics, and were in line with other clinical trials evaluating T cell directed therapies. To evaluate the OS impact of ide-cel treatment in subjects in the standard regimens arm who received ide-cel upon IRC confirmation of progression, predefined sensitivity analyses have been included in the study SAP. The strength of the study conclusions is further supported by the consistency of ide-cel benefit over standard regimens across all secondary endpoints, as well as through sensitivity analyses.

In the pooled population of TCE RRMM subjects from studies MM-003, MM-001, and MM-002 Cohort 1, the consistent ORR, CR rate, and DoR observed between the currently approved ide-cel dose range of 300 - 460 and the proposed expanded >460 - 510 × 10^6 CAR+ T cells dose range, which were reliably and consistently observed for the latter dose range within 10 x 10^6 CAR+ T cells dose increments, support the expansion of ide-cel dose range to 300 to 510 × 10^6 CAR+ T cells. Ide-cel at the proposed dose range of 300 to 510 × 10^6 CAR+ T cells delivers clinically meaningful and statistically significant benefit for TCE RRMM patients.

The FDA's Assessment:

Clinical benefit is demonstrated in KarMMa -3, a Phase 3, randomized (2:1), open label trial that randomized 386 subjects to either a single infusion of ide-cel preceded by lymphodepleting chemotherapy and up to one cycle BT if clinically indicated or to the control arm. All subjects had RRMM after at least 2 to up to 4 prior lines of therapy, were triple class exposed, and were refractory to last line of therapy. Control arm consisted of five protocol-specified anti-myeloma regimens which were continued until disease progression or toxicity. Prior to randomization,

investigators selected one of the five protocol-specified regimens to be administered as treatment in the SOC arm or as BT in the ide-cel arm based on clinical factors.

The primary endpoint was PFS per blinded IRC assessment, the key secondary endpoints were ORR and OS. Upon IRC confirmed disease progression, at investigator discretion and if eligibility criteria were met, patients from the SOC arm could cross over to the ide-cel arm.

Overall, 66% of the study population had triple class refractory disease and 95% was refractory to anti-CD38 monoclonal antibody. The number of prior lines of therapy was three. Forty-four percent had high-risk cytogenetics, 24% had extramedullary disease, and 12% had R-ISS Stage 3 disease at baseline. All high-risk clinical factors were well balanced in the two arms.

A total of 254 subjects were randomized to the ide-cel arm, out of which 225 subjects (89%) received ide-cel. Three subjects received non-conformal ide-cel. Patient attrition occurred at multiple steps in the process to CAR T infusion; inability to proceed with leukapheresis (n=5), inability to proceed with LDC (n=22), and inability to receive ide-cel after LDC (n=2). 213 subjects (84%) received BT to control the disease during product manufacture. The median duration of BT was 22 days (range: 1 to 88 days). The reasons for patient attrition included disease-related complications which precluded LDC and ide-cel infusion, physician decision, death while awaiting the product, subject withdrawal of consent , manufacture failure, and delays due to the need for repeat apheresis. Compared to the ide-cel arm in which 89% of the randomized subjects received the intended CAR T infusion, 95% of the randomized subjects in the SOC arm underwent definitive treatment.

PFS was significantly improved for the ide-cel arm compared to the SOC arm with a stratified HR of 0.495 (95% CI:0.379, 0.647) and a p-value <0.0001 (April 18, 2022 data cut off). The median PFS in the ide-cel arm was 13.3 months (95% CI: 11.8, 16.1) compared to 4.4 months (95% CI: 3.4, 5.9) in the SOC arm. At the time of the primary PFS analysis, 63% of the study population had a PFS event and 37% were censored. Eight percent of the patients in the ide-cel arm died prior to PD compared to 3% in the SOC arm demonstrating a higher rate of death from ide-cel toxicity prior to disease progression.

The median PFS in the SOC arm demonstrated significant heterogeneity ranging from 2.8 months in the EPd group and 10.1 months in Kd group. Because the trial was not designed to evaluate treatment effects within subgroups defined by the SOC, definitive conclusions cannot be made based on these observed differences. Additionally, many factors, including patient selection, may account for differences across subgroups.

Overall, the observed estimate of the treatment effect on PFS appears reliable based on balanced prognostic factors across treatment arms and the blinded independent assessment of the PFS endpoint. The improvement in PFS was maintained in a sensitivity analysis performed to address the lead-time bias due to delay in administration of ide-cel after randomization due to manufacture compared to treatment start in the SOC arm. A sensitivity analysis of 40 subjects (30 in the ide-cel arm, 10 in the SOC arm) with readjudicated responses continued to

demonstrate a statistically significant improvement in PFS in favor of the ide-cel arm. Overall, the improvement in PFS observed in KarMMa-3 is considered clinically meaningful and robust.

The IRC-assessed ORR was higher at 71% (95% CI: 66, 77) in the ide-cel arm compared to 42% (95% CI: 33, 50) in SOC arm (p-value of <0.0001). This difference in ORR was driven primarily by a higher complete response rate (stringent CR +CR rate) at 39% (95% CI:33, 45) in the ide-cel cel arm compared to 5% (95% CI: 1.5, 9.1) in the SOC arm.

Sixty-nine subjects (31%) in the ide-cel treated population received a dose of >460 to 510 x10e6 CAR+ T cells which is the dose expansion requested in the sBLA. The median PFS and ORR per IRC assessment in this dose cohort was similar to the that of the approved ide-cel dose cohort of 300 to 460 x10e6 CAR+ T cells and to the overall ide-cel arm.

OS was a key secondary endpoint after ORR. The trial was powered at 50% for OS. The first interim OS analysis was performed at the time of the primary PFS analysis with an estimated median follow up of 16.9 months and 49% information fraction (April 18, 2022, data cut off). At the time of the primary PFS analysis, 29.5% of the subjects in the ide-cel arm had died compared to 25.8% of the subjects in the SOC arm. Visual inspection of the Kaplan Meier plot indicated OS detriment up to 15 months with censoring beyond Month 9 indicating immature data. The second prespecified interim OS analysis was performed at the time of the final PFS analysis with an estimated median follow-up of 29.7 months and 74 % IF (data cut off April 28, 2023). The OS results at the second interim were consistent with the first interim OS analysis with persistent OS detriment for approximately 15 months after randomization. There was significant censoring after OS curves crossover. Fifty-six percent of the subjects in the SOC arm crossed over and received ide-cel.

FDA's analysis of deaths that occurred in the first 15 months in the study demonstrated a higher rate of death in the ide-cel arm in the first 9 months post-randomization. Eighteen percent of subjects in the ide-cel arm died in the first 9 months compared to 11% in the SOC arm. This includes a higher rate of death from disease progression, any AEs, and unknown causes.

Further analyses of deaths in the first 9 months indicates that 8% of the patients (20 patients) randomized to the ide-cel arm died without receiving the intended CAR T cell infusion within 9 months of randomization compared to none such patients in the SOC arm which was primarily due to patients who died from disease progression prior to ide-cel treatment. A final OS analysis will be performed when 222 deaths have occurred in KarMMa-3.

FDA convened a meeting of the Oncologic Drugs Advisory Committee (ODAC) to discuss whether the results of KarMMa-3 are sufficient to support a positive risk-benefit of ide-cel for the proposed indication and if the risk of early death associated with ide-cel treatment is acceptable in the context of the PFS benefit. The voting members of the committee were asked to vote on whether the risk-benefit assessment for ide-cel was favorable for the proposed indication. The FDA ODAC voted 8 to 3 in favor of ide-cel for the proposed indication. The

committee determined that the PFS benefit with a single infusion of ide-cel without maintenance or continuous therapy was of clinical benefit for the triple class exposed MM population. While no OS advantage was observed with ide-cel compared to the SOC arm, the 56% cross-over rate from the SOC to the ide-cel arm could impact the interpretability of OS data. The committee discussion highlighted concerns regarding the potential inadequacy of BT in the ide-cel arm and if the treatment breaks built into the ide-cel arm due to apheresis and manufacture may have contributed to disease progression and early deaths. However, the committee recognized that despite these speculations, the exact cause of the early OS detriment observed in KarMMa-3 is not well understood. Overall, the committee identified the need for optimization of BT for CAR T cell therapy. Some of panel members opined that BT was constrained in KarMMa-3 and that it could be better individualized based on clinical context in the real-world setting.

The review team agrees that KarMMa-3 demonstrated a statistically significant improvement in PFS and ORR with ide-cel compared to the control arm in a triple class exposed RRMM population after 2 to 4 prior lines of therapy. The benefit in the median PFS of approximately 8.9 months is clinically meaningful in this study population. However, an OS analysis demonstrated that OS was worse in the ide-cel arm compared to the SOC arm for approximately 15 months after randomization after which the OS curves cross. An increased rate of early deaths was observed in the ide-cel arm for up to 9 months which was primarily due to patients who died from disease progression prior to ide-cel treatment. The higher early mortality with ide-cel was observed across multiple prognostic subgroups and was observed even in the absence of individual poor prognostic factors.

The higher rate of early death observed in ide-cel appears to be the inherent “frontloaded” risk of this therapy which will be individualized by the treating physician based on the clinical context.

Overall, the magnitude of the PFS improvement observed with a single infusion of ide-cel without the need for maintenance or ongoing treatment in a triple class exposed population with an unmet medical need is considered clinical benefit. Because the study enrolled subjects who with at least 2 to up to 4 prior lines of therapy, the recommended indication is modified to reflect the study population (a triple-class exposed population after two or more prior lines of therapy) in which a favorable benefit-risk was demonstrated in KarMMa-3.

8.2 Review of Safety

8.2.1 Safety Review Approach

The Applicant’s Position:

The primary safety data used to characterize the safety profile of ide-cel vs standard regimens in subject with RRMM who have received an immunomodulatory agent, a PI, and daratumumab are from pivotal Study MM-003. Safety summaries were provided for the MM-003 Treated Population and the Safety Population (), as appropriate, unless otherwise specified.

Additionally, supportive safety data from the time of ide-cel infusion from the 5 studies listed in are included for side-by-side and pooled analyses.

The ide-cel safety profile from study MM-003 is consistent with the known safety profile from the original BLA, with no new safety signals. Therefore, there were no issues that warranted increased attention in the safety evaluation.

The FDA's Assessment:

- Safety analysis was performed on all subjects who received conformal ide-cel in the investigational arm (n=222).
- For the standard therapy arm, safety analysis included all subjects who received any study treatment (n=126). All safety events and deaths that occurred after crossover were analyzed under the standard therapy arm as per the initial randomization. This includes the 69 subjects that crossed over and underwent leukapheresis and 60 subjects that received ide-cel upon cross over (including 2 subjects that received non-conformal ide-cel).
- FDA also analyzed the safety of subjects who crossed over and received conformal ide-cel (SOC arm; post ide-cel; n=58).
- The safety review is based on the primary data cutoff of April 18, 2022, with a median follow-up of 12.9 months (range: 0.2, 31.8 months) in the ide-cel arm.
- For the standard therapy arm, the median follow-up for the safety population was 13.6 months (range: 0.2, 35 months). The median follow-up for safety after infusion of conformal ide-cel in the SOC arm was 6.6 months (range: 0, 21).
- The 90-day safety update with data cutoff of October 3, 2022, did not include any additional subjects from KarMMa-3. However, at the time of the safety update, 77 subjects (8 additional subjects) in the SOC arm had undergone leukapheresis and 9 additional subjects received ide-cel. The updated datasets were reviewed and no new safety signals were identified in this update.
- For the ide-cel arm, a comparative safety assessment was performed for the subjects treated with >460 to 510x10e6 CAR T cells compared to the approved dose range of 300 to 460x10e6 CAR+ T cells which is the expanded dose range that the Applicant is seeking.
- All deaths were analyzed using the most updated April 28, 2023, data cutoff.
- Safety analysis includes FDA's adjudication of AEs and deaths.
- Data reviewed included datasets, clinical study report, summary of clinical safety, subject narratives, several IRs, and data in the public domain. (b) (4) was used to reproduce safety analyses based on the submitted safety datasets and to conduct additional exploratory analyses.
- Safety data from KarMMa-2, a Phase 2 study with ide-cel in MM and KarMMa, the single arm licensing study of ide-cel was reviewed. Datasets were scanned to identify any additional safety signals.
- Safety analysis is based on AEs that occurred or worsened on or after ide-cel infusion in the ide-cel arm and on or after the administration of anti-myeloma regimens in the SOC arm.

- The Applicant reported AEs by preferred terms, which may underestimate the incidence of some AEs. To minimize underestimation of AEs, FDA grouped preferred terms that represent the same disease process. The reviewer utilized a grouping strategy for comprehensive analyses of AEs that is consistent with the grouping practices for review of similar agents within this class of therapies.
- Applicant defined TEAE as AEs occurring or worsening on or after the date of randomization and within 6 months from start of ide-cel or SOC arm treatment. Since this definition did not include AEs that occurred more than 6 months after treatment start, the TEAE flag was not used for the safety analyses. Instead, the on and after treatment flag was used for the safety analyses.

Review of the Safety Database

Overall Exposure

Data:

Table 31. Applicant - Safety Population for the Side-by-Side and Pooled Analyses

Clinical Trials		Ide-cel Arm				Standard Regimens Arm
Pivotal Study MM-003		Treated population	Leukapheresis population	Safety population		126
				Conforming Product	Non-Conforming Product[b]	
		250[a]	249	222[c]	3[c]	
CRB-401 (150-450 x 10^6 CAR+ T cells)		-	61	56	0	N/A
MM-001		-	140	127	1	N/A
MM-001-Japan		-	9	8	1	N/A
MM-002	Cohort 1	-	76	68	0	N/A
	Cohort 2	-	106	97	2	
MM-004		-	13	12	1	N/A

[a] The Treated population is defined as all subjects in the ITT population who received leukapheresis, bridging therapy, lymphodepleting chemotherapy, or ide-cel infusion in Ide-cel Arm, and those who receive any dose of DARA, POM, LEN, BTZ, IXA, CFZ, ELO, or dex in standard regimens arm.

[b] In all studies, subjects who received non-conforming CAR+ T cell product were excluded from the side-by-side and pooled safety analyses. Non-conforming CAR+ T cell product is defined as not meeting the pre-established product release quality specifications.

[c] The Safety Population is defined as all subjects in the Treated Population who have received any study treatment, including ide-cel infusion for Ide-cel arm and any dose of DARA, POM, LEN, BTZ, IXA, CFZ, ELO, or dex for standard regimens arm.

Table 32. Applicant - Lymphodepleting Chemotherapy Administration, Ide-cel Arm - Treated Population in MM-003

	Ide-cel Arm, (N=250)
Subjects Who Received Any LDC Regimen, n (%)	227 (90.8)
Subjects Who Received LDC Regimen with Adjusted Dose, n (%)	37 (14.8)
Subjects with Adjusted Fludarabine, n (%)	37 (14.8)

	Ide-cel Arm, (N=250)	
	Fludarabine	**Cyclophosphamide**
Number of Days Dosed (Days), n	227	227
Mean (SD)	3.0 (0.28)	3.0 (0.28)
Median (Min, Max)	3.0 (3.0, 6.0)	3.0 (3.0, 6.0)
Total Cumulative Dose (mg), n	227	227
Mean (SD)	167.1 (31.39)	1757.2 (257.17)
Median (Min, Max)	172.5 (84.0, 279.0)	1800.0 (1197.0, 3480.0)
Actual Daily Dose (mg/day)[a], n	227	227
Mean (SD)	55.4 (10.36)	581.3 (74.83)
Median (Min, Max)	57.5 (26.3, 80.0)	598.0 (399.0, 795.0)
Actual Daily Dose by Body Surface Area (mg/m^2/day), n	222	222
Mean (SD)	28.4 (3.37)	299.2 (11.17)
Median (Min, Max)	29.8 (16.5, 32.4)	300.3 (240.6, 324.4)

[a] Actual daily dose is defined as the total cumulative dose divided by number of days dosed.
Source: ADSL, ADEX, ADEXSUM

Table 33. Applicant - Ide-cel Administration, Ide-cel Arm - Safety Population in MM-003

	Ide-cel (N = 225)
Actual CAR+T Cells Infused (10^6 cells), n	225
Mean (SD)	441.8 (52.22)
Median (Min, Max)	445.3 (174.9, 529.0)
Actual CAR+T Cells Infused Grouping (10^6 cells), n (%)	
< 300	3 (1.3)
300 to 460	143 (63.6)
> 460 to 540	79 (35.1)
> 540	0

Note: The allowed dose range was 150 to 450 x 10^6 CAR+ T cells; doses in excess of 20% were considered overdose.
Source: ADSL, ADEXSUM

Table 34. Applicant - Standard Regimen Therapy in the Standard Regimens Arm - Safety Population in MM-003

Standard Regimen (N=126)	DPd	DVd	IRd	Kd	EPd
n (%)	41 (32.5)	7 (5.6)	20 (15.9)	28 (22.2)	30 (23.8)

Source: ADSL, ADEXSUM

Table 35. Applicant - Treatment Duration for Standard Regimens Arm - Safety Population in MM-003

	Arm B (Standard Regimens)				
	DPd (N=41)	**DVd (N=7)**	**IRd (N=20)**	**Kd (N=28)**	**EPd (N=30)**
Treatment Duration (Days)[a]					
Median (Min, Max)	178.0 (11, 967)	86.0 (15, 195)	120.0 (21, 623)	178.0 (28, 604)	119.5 (14, 399)
Number of Cycles Dosed[b]					
Median (Min, Max)	6.0 (1, 35)	5.0 (1, 10)	5.0 (1, 22)	6.5 (2, 21)	4.5 (1, 14)

[a] Treatment duration = Last dose date of the regimen - first dose date of the regimen + 1.

[b] Cycle refers to the "Month" defined per protocol, which is 21 days for DVd, and 28 days for all other standard regimens.

Source: ADSL, ADEX

Antimyeloma Bridging Therapies: In the ITT population, the majority of subjects (83.9%) in the ide-cel arm received bridging therapy for myeloma control during the ide-cel manufacturing period (*Source: ADSL, ADCM*). The median (min, max) duration of bridging therapy was 22.0 days (1.0, 101.0). The most commonly received (≥ 25% of subjects) antimyeloma bridging therapy agents were pomalidomide (48.4%), DARA (31.9%), and elotuzumab (26.4%).

Ide-cel Infusion: The 3 subjects who received non-conforming product are included in MM-003 individual study for analysis between the two treatment arms, but are excluded from analysis when combined with other studies to examine the ide-cel infused subjects only.

The median time (min, max) from leukapheresis to ide-cel administration was 49.0 days (34.0, 117.0) (*Source: ADSL, ADPR*).

The Applicant's Position:

The overall exposure to ide-cel in Study MM-003 is considered adequate to support characterization of the safety profile of this therapy in the intended patient population, and meets the minimum specified in ICH E1A guideline. The overall safety profile of ide-cel in this MM-003 population was consistent with the known safety profile in subjects who had received 4 or more prior lines of therapy. As expected, there were notable differences between ide-cel and standard regimens arms for AESIs that are specific to CAR T-cell therapy. The frequency and severity of AEs, Grade 3 or 4 and SAEs were numerically higher in the ide-cel arm compared with the standard regimens arm.

The AESIs with ide-cel were infrequent and manageable. No new clinically important concerns were identified for ide-cel in line with previous experience.

The FDA's Assessment:

See FDA assessment under Section 8.2.2.

Relevant characteristics of the safety population:

The Applicant's Position:

Baseline demographics in the safety population (*Source: ADSL*) were similar to the ITT population (), and represent a diverse population with respect to age, sex, and race.

The FDA's Assessment:

The reviewer agrees that the baseline demographics in the safety population were similar to the ITT population.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The Applicant's Position:

Baseline disease characteristics in the safety population (*Source: ADSL, ADCM*) were similar to the ITT population, and are representative of a high risk, TCE RRMM population.

The FDA's Assessment:

The reviewer agrees that the baseline disease characteristics in the safety population were

similar to the ITT population.

Adequacy of the safety database:

The Applicant's Position:

The size of the MM-003 safety database and duration of follow-up are considered adequate to provide a reasonable estimate of adverse reactions that may occur with ide-cel treatment. The safety of ide-cel in MM-003 is consistent with the known safety profile from the original BLA.

Together, data from study MM-003 along with the 5 supportive studies (Table 4) allow for a thorough assessment of the ide-cel safety profile in the intended patient population, including characterization of common AEs and SAEs, and informing labeling and risk management strategies.

The FDA's Assessment:

The reviewer agrees that the safety database is considered adequate to identify most common AEs, support the benefit-risk assessment, and represent the target patient population.

8.2.2 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

Data review and quality control checks were implemented by the Sponsor and consisted of site monitoring visits guided by the SMP to review source documents against the eCRF and data validation checks of the eCRF and externally loaded data as per the established Data Review Plan. Data quality review was performed to ensure data completeness and integrity. Any issues or findings were followed up for resolution during Data Review Meetings. The Data Review Plan was used to ensure oversight of Data Management review performed by personnel as detailed in the plan. In addition, a review of the database was performed by BMS Global Biometric and Data Sciences to enhance the quality and ensure completeness of the data. When the database was declared complete and accurate, the Database Lock Checklist was completed, which documented that all prerequisites for the database lock were achieved, and the database was locked.

Multiple measures were taken to minimize the impact of COVID-19 on the conduct of Study MM-003 and other clinical studies and analysis of data. A COVID-19 Safety Surveillance Plan was created by BMS, and newly released MedDRA v23.0 (effective date 04-May-2020) was adopted to retrospectively search for AEs related to COVID-19 in the database. All CRF data entries were completed, and all critical queries were addressed in all countries. Throughout the duration of the study, no site has required an increase in SDV due to compliance issues. Mitigation included increased remote electronic medical records review. Therefore, the outstanding SDVs were assessed as not having a significant impact on the integrity of the data.

The FDA's Assessment:

The original ADAE and ADCM datasets did not include the start and end day of AE or concomitant medication from treatment start and end but only from study start and end. In addition, ADAE dataset did not include signs or symptoms of CRS, which were included in a separate dataset. FDA asked the Applicant to submit updated ADAE dataset that included signs and symptoms of CRS and include start and end day of AE from treatment start and end.

Updated ADCM dataset that included the start and end day of concomitant medications from treatment start and end day and included flags to identify anti-cytokine therapy, corticosteroids, and vasopressor were requested. The Applicant submitted updated ADAE 3 and ADCM2 dataset under amendment 7 on April 25, 2023. Updated ADAE 3 dataset with FDA's adjudication of CRS, NT and infections with flags to identify the treatment day from ide-cel received on cross-over was submitted under amendment 48 on January 10, 2024.

Categorization of Adverse Event

The Applicant's Position:

Study MM-003: The assessment of safety was based on type, frequency, severity of AEs, SAEs, AESIs/Selected AEs, and death. Safety variables included physical examination, vital signs, ECOG, height and weight, routine neurologic examination, mini mental state exam, laboratory assessments for safety parameters, and cardiac assessments. In addition, RCL testing and vector integration site analysis were performed as indicated for Arm A subjects and Arm B subjects who received ide-cel at investigator's request after IRC confirmation of progression.

AEs were coded according to MedDRA version 24.1. Descriptive statistics of safety are presented using NCI-CTCAE v4.03 by treatment arm. AEs ('Combined AEs' [AE CRF combined with the symptoms from the CE-NT CRF]) are summarized by SOC, PT, and period.

All on-study AEs, drug-related AEs, SAEs, drug-related SAEs, AESIs (AESIs include new malignancy or new diagnosis of autoimmune-like, rheumatologic, or new diagnosis of hematologic disorder, Grade ≥ 3 adverse events of CRS, MAS, neurologic toxicity and infection), and selected AEs were tabulated using the worst grade per the NCI-CTCAE v4.03 criteria by SOC and PT. The AE term "neurotoxicity" was entered as the AE on the AE eCRF page and classified as iiNT, while individual signs and symptoms characterizing the iiNT event were captured separately on the Neurotoxicity Details eCRF page and graded according to the NCI CTCAE v4.03. The AE of "neurotoxicity" was graded based on the maximum grade of the associated signs or symptoms. Neurologic Toxicity – Focused, included selected PTs of neurologic toxicity events as determined by the Sponsor with consideration of biological/pharmacological plausibility for a drug-event relationship, known neurologic toxicities reported with this class of drug and consistent with published guidelines for CAR+ T cell encephalopathy, and clinical judgement.

On-study lab parameters including hematology, chemistry, liver function, and renal function were summarized using the worst grade per the NCI-CTCAE v4.03 criterial. Assessments for viral vector safety including RCL testing, monitoring for persistence of vector sequence and detection of vector sequence in second primary malignancy tumor biopsies were conducted for subjects who received ide-cel. Persistence of vector sequence is defined as detection of CAR vector sequences in more than 1% of cells in peripheral blood samples collected at 12 months or any time after 12 months post infusion of ide-cel.

Pooled Analyses: The existing derived variables from each individual study were used, unless otherwise specified. Definitions of variables that were different across studies were explained in the source tables, as appropriate, where such variables were analyzed. Studies CRB-401, MM-001, and MM-001-Japan used MedDRA version (22.0) in the BLA but was updated to version 24.1 for the current analysis. AEs were graded using the NCI-CTCAE version 4.03, except for CRS, which was graded according to a system based on modified criteria.

The FDA's Assessment:
See FDA assessment under section 8.2.3

Routine Clinical Tests

The Applicant's Position:
The pre-dose laboratory testing performed within the MM-003 protocol specified schedules of activities was considered adequate and in line with routine clinical practice.

For subjects receiving ide-cel, routine laboratory assessments were required within 28 days of randomization, ≤ 3 days prior to initiating leukapheresis, within 3 days prior to starting LDC, daily during hospitalization following infusion with ide-cel up to the end of Month 1, and every month thereafter.

For subjects receiving SOC regimens, routine laboratory assessments were required within 28 days of randomization, ≤ 3 days prior to initiating study treatment, and every month thereafter. On Month 1 Day 1 visit, local safety laboratory assessments were required to confirm subject continues to meet the required safety laboratory values prior to initiating study treatment. Additionally, safety laboratory testing at a local laboratory could be performed up to 3 days before the study treatment administration day. Results of these laboratory tests were evaluated before each study treatment administration.

In addition to routine safety lab testing, regular pregnancy testing was required and any pregnancy, suspected pregnancy, or positive pregnancy test were considered immediately reportable events.

Laboratory values considered clinically significant by the investigator or meeting the study definition of SAE were required to be reported as AEs. Additionally, any laboratory values leading to study drug discontinuation, interruption of study drug, or results requiring the subject to receive specific corrective therapy were to be reported as AEs if not otherwise previously reported. AEs were to be managed per the respective current SOC drugs PI, SmPC, or equivalent document for the specific region/country. In the laboratory summary tables, unless otherwise specified, subjects are counted only once for each lab parameter according to their worst on treatment CTC grade.

The FDA's Assessment:
See schedule of assessments (Tables 85 and 86) in the Appendix. Overall, the schedule of testing in KarMMa-3 is considered adequate for the assessment of safety.

8.2.3 Safety Results

Table 36. Applicant - Summary of Safety in MM-003

	No. of Subjects (%)	
	Ide-cel Arm	**Standard Regimens Arm**
ITT Population	**N=254**	**N=132**
Deaths, n (%)	75 (29.5)	34 (25.8)
Primary Reason for Death[a]		
Death from malignant disease under study, or complication due to malignant disease under study, n (%)	44 (17.3)	23 (17.4)

	No. of Subjects (%)			
	Ide-cel Arm		Standard Regimens Arm	
Death from AE, n (%)	15 (5.9)		8 (6.1)	
Death from other cause, n (%)	14 (5.5)		3 (2.3)	
Death from second primary malignant disease, or complication due to second primary malignant disease, n (%)	2 (0.8)		0	
	No. of Subjects (%)			
	Ide-cel Arm		**Standard Regimens Arm**	
	Adverse Event Grades			
Safety Parameters	**Any Grade**	**Grade 3 or 4**	**Any Grade**	**Grade 3 or 4**
Treated Population	**N = 250**		**N = 126**	
SAEs	**130 (52.0)**	**107 (42.8)**	**48 (38.1)**	**43 (34.1)**
Occurring in ≥ 3% of subjects				
General physical health deterioration	17 (6.8)	8 (3.2)	4 (3.2)	2 (1.6)
Pneumonia	16 (6.4)	15 (6.0)	6 (4.8)	15 (6.0)
Pyrexia	12 (4.8)	0	1 (0.8)	1 (0.8)
CRS	10 (4.0)	8 (3.2)	0	0
Febrile neutropenia	10 (4.0)	10 (4.0)	2 (1.6)	2 (1.6)
COVID-19 pneumonia	4 (1.6)	3 (1.2)	4 (3.2)	4 (3.2)
Acute kidney injury	8 (3.2)	6 (2.4)	2 (1.6)	2 (1.6)
AEs	**248 (99.2)**	**233 (93.2)**	**123 (97.6)**	**94 (74.6)**
Occurring in ≥ 20% of subjects				
Cytokine release syndrome	197 (78.8)	10 (4.0)	0	0
Neutropenia	195 (78.0)	189 (75.6)	55 (43.7)	50 (39.7)
Anaemia	165 (66.0)	127 (50.8)	45 (35.7)	23 (18.3)
Thrombocytopenia	136 (54.4)	106 (42.4)	36 (28.6)	22 (17.5)
Nausea	112 (44.8)	4 (1.6)	34 (27.0)	0
Diarrhoea	85 (34.0)	4 (1.6)	30 (23.8)	4 (3.2)
Hypokalaemia	78 (31.2)	12 (4.8)	14 (11.1)	1 (0.8)
Hypophosphataemia	78 (31.2)	50 (20.0)	10 (7.9)	3 (2.4)
Hypomagnesaemia	52 (20.8)	2 (0.8)	6 (4.8)	1 (0.8)
Lymphopenia	73 (29.2)	70 (28.0)	25 (19.8)	23 (18.3)
Leukopenia	72 (28.8)	71 (28.4)	15 (11.9)	11 (8.7)
Constipation	67 (26.8)	0	9 (7.1)	0
Vomiting	51 (20.4)	0	11 (8.7)	0
Fatigue	69 (27.6)	4 (1.6)	44 (34.9)	3 (2.4)
Headache	59 (23.6)	0	24 (19.0)	1 (0.8)
Dyspnoea	44 (17.6)	4 (1.6)	27 (21.4)	2 (1.6)
Safety Population	**N = 225**		**N = 126**	
Treatment-related SAEs	**37 (16.4)**	**31 (13.8)**	**19 (15.1)**	**15 (11.9)**
Occurring in ≥ 1% of subjects				
Sepsis	3 (1.3)	3 (1.3)	0	0
CRS	10 (4.4)	8 (3.6)	0	0
Haemophagocytic lymphohistiocytosis	5 (2.2)	5 (2.2)	0	0
Febrile neutropenia	4 (1.8)	4 (1.8)	1 (0.8)	1 (0.8)
Neutropenia	4 (1.8)	4 (1.8)	1 (0.8)	1 (0.8)
Depressed level of consciousness	4 (1.8)	3 (1.3)	0	0
Aphasia	3 (1.3)	1 (0.4)	0	0
Confusional state	5 (2.2)	2 (0.9)	0	0
Treatment-related AE	**217 (96.4)**	**155 (68.9)**	**104 (82.5)**	**74 (58.7)**
Occurring in ≥ 10% of subjects				

	No. of Subjects (%)			
	Ide-cel Arm		Standard Regimens Arm	
CRS	197 (87.6)	10 (4.4)	0	0
Neutropenia	121 (53.8)	117 (52.0)	48 (38.1)	43 (34.1)
Thrombocytopenia	73 (32.4)	58 (25.8)	30 (23.8)	18 (14.3)
Anaemia	68 (30.2)	50 (22.2)	24 (19.0)	10 (7.9)
Lymphopenia	30 (13.3)	30 (13.3)	18 (14.3)	17 (13.5)
Leukopenia	24 (10.7)	23 (10.2)	13 (10.3)	10 (7.9)
Fatigue	29 (12.9)	0	23 (18.3)	2 (1.6)
Pyrexia	23 (10.2)	0	3 (2.4)	1 (0.8)
Oedema peripheral	3 (1.3)	0	13 (10.3)	3 (2.4)
Nausea	14 (6.2)	0	17 (13.5)	0
Diarrhoea	13 (5.8)	1 (0.4)	15 (11.9)	2 (1.6)
AESIs (Number of subjects with ≥ 1 AESI/selected AE)	225 (100.0)	208 (92.4)	113 (89.7)	82 (65.1)
CRS	197 (87.6)	10 (4.4)	--	--
NT - Broad[c]	159 (70.7)	30 (13.3)	77 (61.1)	16 (12.7)
NT - Focused[d]	85 (37.8)	14 (6.2)	41 (32.5)	8 (6.3)
iiNT	34 (15.1)	7 (3.1)	--	--
Infections - Overall	138 (61.3)	55 (24.4)	68 (54.0)	23 (18.3)
Cytopenia - Overall	206 (91.6)	202 (89.8)	91 (72.2)	76 (60.3)
Cytopenia - Neutropenia	193 (85.8)	189 (84.0)	57 (45.2)	51 (40.5)
Cytopenia - Thrombocytopenia	126 (56.0)	99 (44.0)	37 (29.4)	23 (18.3)
New Malignancies	15 (6.7)	--	5 (4.0)	--
SPM	13 (5.8)		5 (4.0)	
MAS[e]	5 (2.2)	5 (2.2)	0	0
Autoimmune Disorders	1 (0.4)	--	0	--

[a] Primary cause categories are from CRF. Deaths are sorted by descending frequency of primary cause categories first, and then by descending frequency of SOCs within each primary cause category, and then by descending frequency of PTs within each SOC for the last column under Ide-cel Arm.

[b] On/after ide-cel infusion

[c] All PTs within the primary or secondary SOCs of nervous system disorder and psychiatric disorder

[d] Selected PTs of NT events as determined by Sponsor with consideration of biological/pharmacological plausibility for a drug-event relationship, known neurologic toxicities reported with this class of drug and consistent with published guidelines for CAR T encephalopathy, and clinical judgement.

[e] MAS includes the single PT of haemophagocytic lymphohistiocytosis

Source: ADSL, ADAE2, ADAESUM, ADSPM

The FDA's Assessment:

AEs and SAEs were evaluated during clinic visits, hospitalizations, and follow-up visits per protocol-defined guidelines.

FDA reviewed the safety analysis presented by the Applicant in Table 35. The Applicant based the safety analysis on the treated population (all subjects in the ide-cel arm that underwent leukapheresis) for overall safety analysis and the ide-cel treated population (including subject receiving non-conformal ide-cel) for adverse events of special interest (AESI). The Applicant has presented AEs in Table 35 if the AEs were considered related to the investigational therapy. For

the SOC arm, the Applicant has presented only those AEs that occur prior to cross over to the ide-cel arm.

FDA does not agree with this approach and conducted its own safety analysis as described under Section 8.2.1. In summary, FDA'S safety population included recipients of conformal ide-cel (n=222) with focus on AEs that occurred or worsened after start on ide-cel. All treatment-emergent AEs are included in the safety analysis without regard to relatedness. In the SOC arm, safety analysis included AEs before and after cross over to the ide-cel arm.

All 222 subjects (100%) had at least one AE. AEs and SAEs are events that occurred after the administration of ide-cel or treatment in SOC arm. Table presents an overview of all AEs with data cutoff of April 18, 2022. which is similar to the data cut-off used for efficacy analysis. The majority of the maximum toxicity grades were Grade 3 or 4 events. The rates of Grade 4 AEs were higher in the ide-cel arm compared to the SOC arm.

Table 37. FDA – Treatment-Emergent Adverse Events Occurring On and After Treatment, KarMMa-3

TEAE	Ide-cel N=222 n (%)	SOC N=126 n (%)	Ide-cel in the SOC arm N=58 n (%)
Any TEAE	222 (100)	124 (98)	57 (98)
Serious AE	95 (43)	71 (56)	18 (31)
Max Grade 3-5 TEAE	210 (95)	114 (90)	53 (91)
Max Grade 3-4 TEAE	183 (82)	99 (79)	48 (83)
Max Grade 3 TEAE	41 (18)	35 (28)	5 (9)
Max Grade 4 TEAE	142 (64)	64 (51)	43 (74)
Deaths from AE	21 (9)	10 (8)	3 (5)

Source: FDA analysis. Data cutoff date April 18, 2022
Ide-cel columns in the table above represent subjects who received conformal ide-cel

FDA also analyzed the overall safety of the higher dose requested for dose expansion (460 to 510x10e6 CAR+ T cells) compared to the approved dose range (300 to 460x10e6 CAR+ T cells). Overall, the rate of AEs, SAEs and deaths from AEs are similar between the higher dose cohort and the approved dose cohort within the ide-cel arm in KarMMa-3.

Table 38. FDA – TEAEs at the Approved Dose and Higher Dose, Ide-cel arm

Parameter AE/SAE	300-460 million N=141 n (%)	>460-510 N=69 n (%)
All Grade AEs	141 (100)	69 (100%)
Max Grade 3-5 AEs	134 (95%)	64 (93%)
Max Grade 3	30 (21%)	10 (14%)
Max Grade 4	90 (64%)	45 (65%)
Deaths from AE	12 (9%)	7 (10%)
SAEs	60 (43%)	27 (39%)

Source: FDA, Data cutoff date: April 18, 2022

Deaths

The Applicant's Position:

In the ITT population, similar proportions of subjects died in the ide-cel and standard regimens arms (). The causes of death were similar between both arms, with the majority of deaths being due to disease progression in both arms. A similar percentage of subjects died due to Aes in each arm.

The verbatim cause of death in the "death from other cause" category in most subjects in both arms (9 out of 14 in the ide-cel arm and 2 out of 3 in the standard regimens arm) was 'unknown', which was coded under the "General Disorder and administration site condition" SOC.

FDA Assessment:

Deaths:

While the primary safety analysis was conducted using the data cutoff date of April 18, 2022, the reviewer analyzed all deaths in the safety population of both arms using both the April 18, 2022, data cutoff date (primary PFS analysis) and April 23, 2023, data cutoff date (date for final PFS analysis). All deaths after cross over to the ide-cel arm were analyzed and are being presented under the SOC arm as per the initial randomization.

At the time of the primary PFS analysis, 60 subjects (45%) in the SOC arm had crossed over and received ide-cel infusion (including 2 subjects who received nonconformal ide-cel). The most common cause of death in both arms was disease progression. The overall death rate from TEAEs was 9% in the ide-cel arm compared to 8% in the SOC arm. Out of the 10 deaths from TEAE that occurred in the SOC arm, 3 occurred after ide-cel infusion. The TEAE death rate within the first 90 days of treatment start was 2.3% in the ide-cel arm compared to 1.6% in the SOC arm.

Table 39. FDA – Deaths in the Safety Population at Primary PFS Analysis

Parameter	Ide-cel N=222 n (%) (All Deaths)	SOC N=126 n (%) (All Deaths)	SOC Cross over to Ide-cel n (%) N=58
Total deaths	54 (24)	33 (26)	10 (17)
TEAE[1]	21 (9)	10 (8)	3 (5)
Progressive disease	27 (12)	22 (17)	7 (12)
Unknown	6 (2.7)	1 (0.8)	0 (0)

Parameter	Ide-cel N=222 n (%) (All Deaths)	SOC N=126 n (%) (All Deaths)	SOC Cross over to Ide-cel n (%) N=58
Deaths ≤90 days after treatment start	8 (3.6)	4 (3.2)	2 (3.4)
TEAE	5 (2.3)	2 (1.6)	1 (1.7)
Progressive disease	3 (1.4)	2 (1.6)	1 (1.7)
Unknown	0	0	0
Deaths >90 days after treatment start	46 (21)	29 (23)	8 (14)
TEAE	16 (7)	8 (6)	2 (3.4)
Progressive disease	24 (11)	20 (16)	6 (10)
Unknown	6 (2.7)	1 (0.8)	0 (0)

Source: FDA analysis. Data cutoff date April 18, 2022
Cross over to ide-cel: Represents subjects randomized to the SOC arm who crossed over and received conformal ide-cel.

At the time of the final PFS analysis (April 28, 2023, data cutoff), 74 (56%) had received ide-cel infusion (including 2 subjects who received nonconformal ide-cel). The percentage of deaths in the safety population was 36% for the ide-cel arm versus 43% for the SOC arm. The most common cause of death in both arms was disease progression. The overall deaths from TEAE were 11% in the ide-cel arm compared to 10% in the SOC arm. Out of 12 deaths from TEAE that occurred in the SOC arm, 4 deaths occurred after ide-cel infusion. The TEAE death rate within the first 90 days of treatment start was 2.7% in the ide-cel arm compared to 1.6% in the SOC arm.

Table 40. FDA – Deaths in the Safety Population at the Final PFS Analysis:

Parameter	Ide-cel Arm N=222 n (%) (All Deaths)	SOC N=126 n (%) (All Deaths)	SOC (Ide-cel Subgroup) n (%) N=72
Total deaths	79 (36)	54 (43)	21 (29)
TEAE[1]	24 (11)	12 (10)	4 (6)
Progressive disease	42 (19)	36^ (29)	15 (21%)
Unknown	13 (6)	6 (4.8)	2 (2.8)
Deaths ≤90 days after treatment start	9 (4.1)	4 (3.2)	2 (2.8)
TEAE	6 (2.7)	2 (1.6)	1 (1.4)
Progressive disease	3 (1.4)	2 (1.6)	1 (1.4)
Unknown	0	0	0
Deaths >90 days after treatment start	70 (32)	50 (40)	19 (26)
TEAE	18 (8)	10* (8)	3 (4.2)
Progressive disease	39 (18)	34 (27)	14 (19)
Unknown	13 (6)	6 (4.8)	2 (2.8)

Source: FDA analysis; Data cutoff: April 28, 2023
^ includes one death from euthanasia due to myeloma progression

Table 41 below demonstrates the deaths from AEs by dose. Although, there are numerical differences in the deaths between the approved dose and the higher dose, the small number of subjects in each cohort and the small numerical difference in the deaths preclude any conclusion of higher death from toxicity at the higher dose range.

Table 41. FDA – Deaths from AE at the Approved Dose and the Higher Dose

Dose Levels (Million CAR+ T Cells)	Number of Subjects	Death from AE n (%)
300-460	141	14 (10%)
>460-510	69	8 (12%)

Source: FDA, Data cutoff date April 28, 2023

In the safety population, the primary cause of death due to an AE was infection in both the arms as shown in Table 42 below. A summary of the cause of death per subject in each arm for the safety population is included in the Appendix. (Refer to Tables 82-84 in Appendix).

Table 42. FDA – Causes of Death from AE

Characteristic	Ide-cel N=222 n (%)	SOC N=1261 n (%)	Ide-cel in SOC (Subgroup of SOC) N=72 n (%)
Total deaths	79 (36)	54 (43)	21 (29)
Adverse events	24 (11)	12 (10)	4 (6)
CRS and/or HLH/MAS	2 (0.9)	0	0
Neurotoxicity	1 (0.5)	1 (0.8)	1 (1.4)
Infection	14 (6)	8 (6)	2 (2.8)
Second primary malignancy	3 (1.4)	1** (0.8)	1** (1.4)
Hemorrhage	2 (0.9)	0	0
Respiratory failure	0	2 (1.6)	0
Cardiac (coronary artery dissection)	1 (0.5)	0	0
Sudden death	1 (0.5)	0	0
Stroke from atrial fibrillation*	1 (0.5)	0	0

Source: FDA analysis. April 28, 2023
All deaths included in Table are in subjects who received conformal ide-cel.
[1] Includes deaths that have occurred after leukapheresis and ide-cel infusion in SOC arm.
Death due to CRS, HLH/MAS, and invasive candidiasis in one subject in the ide-cel arm is included under both CRS/HLH and infection.
*Atrial fibrillation was sequela of CRS
** Carcinoma of unknown primary

- Given the myelosuppressive effect of CAR T therapy, death from infection and hemorrhage after disease progression and subsequent anti-myeloma therapy were adjudicated as death from AE in both arms.

- Due to the potential risk of secondary malignancy with CAR T therapy, death from any secondary malignancy was also adjudicated as death from AE in both arms.

- Overall, the most common cause of death in the safety population in both the arms was

disease progression. The fatal AE rate at the time of the final PFS analysis is 11% in the ide-cel arm and 10% in the SOC arm.

- At the time of the final PFS analysis, 72 subjects in the SOC arm had crossed over and received conformal ide-cel. 6% of these patients died from an AE.

- Overall, the most common cause of death from AEs in both arms was infection.

- Death due to AEs within 90 days of treatment start was higher in the ide-cel arm compared to the SOC arm: 2.7% versus 1.6%. This includes death from CRS, HLH, neurologic toxicity, infections, and stroke in the ide-cel arm.

- On subject (USUBJID (b) (6)) died 954 days after treatment with non-conformal ide-cel (15 VCN/transduced cells which did not meet the drug product specification of VCN (b) (4) VCN/transduced cell) from amyotrophic lateral sclerosis (ALS) in the setting of radiographically diagnosed renal cell carcinoma. This subject was in sCR at the time of death. This subject developed ALS approximately one year after ide-cel infusion. He had a renal mass since 2016 (preceded ide-cel treatment) with radiographic appearance of renal cell carcinoma. This renal mass progressed radiographically in size requiring treatment with renal artery embolization on day 740.

  Paraneoplastic motor neuron disease has been described in patients with renal cell cancer. Therefore, this fatal AE of ALS may be related to renal cell cancer. No other cases of ALS have been reported in the ide-cel safety database. Overall, this AE of ALS is not considered as related to ide-cel. Given the isolated occurrence of this AE, it was not included in the USPI.

Serious Adverse Events

The Applicant's Position:

The frequencies of SAEs was higher in the ide-cel arm than the standard regimens arm (). The most frequently reported SAEs in the ide-cel arm were general physical health deterioration, pneumonia, pyrexia, CRS, and febrile neutropenia. The most frequently reports SAEs in the standard regimens arm were pneumonia, COVID-19 pneumonia, and general physical health deterioration.

The FDA's Assessment:

FDA 's assessment of SAEs include the safety population in both arms. This analysis is based on FDA 's adjudication and FDA's grouped terms (GT). Among the 222 subjects in the ide-cel safety population, SAEs occurred in 95 subjects (43%), while Grade ≥3 SAEs occurred in 79 subjects (36%). Among the 126 subjects in the SOC safety population, SAEs occurred in 71 subjects (56%), while Grade ≥3 SAEs occurred in 62 subjects (49%).

SAEs occurred in ≥1% of the subjects are presented below in Table 43:

Table 43. FDA – Serious Treatment-Emergent Adverse Events (SAE) Occurring in ≥ 1% of Safety Population

Adverse Events	Ide-cel N-=222 n (%)	SOC arm N=126 n (%)
Pneumonia*	20 (9)	15 (12)
Encephalopathy*	13 (6)	5 (4)
Pyrexia	13 (6)	2 (2)
Sepsis*	12 (5)	11(9)
CRS	10 (5)	0
Renal failure*	9 (4)	3 (2)
General physical health deterioration	8 (4)	6 (5)
Viral infection	8 (4)	9 (7)
Bacterial infection	6 (3)	
Febrile neutropenia	6 (3)	5 (4)
Cardiac arrhythmia*	5 (2)	4 (3)
Dyspnea*	5 (2)	4 (3)
HLH/MAS	5 (2)	0
Musculoskeletal pain*	5 (2)	8 (6)
Neutropenia*	5 (2)	3 (2)
Transaminase elevation*	5 (2)	1 (0.8)
Upper respiratory tract infection*	5 (2)	2 (2)
Hypotension*	4 (2)	1 (0.8)
Hypoxia*	4 (2)	0
Aphasia*	3 (1)	2 (2)
Coagulopathy*	3 (1)	0
Pathological fracture	3 (1)	1 (0.8)
Thrombosis*	2 (0.9)	4 (3)
Pain*	1 (0.5)	3 (2)
Thrombocytopenia*	0	3 (2)
Cardiac failure*	0	2 (2)
Diarrhea*	2 (0.9)	2 (2)
Edema*	0	2 (2)
Gastroenteritis*	1 (0.5)	2 (2)
Cord compression	0	2 (2)
Squamous cell carcinoma	2 (0.9)	2 (2)

Source: FDA analysis of ADAE3 dataset * FDA grouped terms, See Appendix

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Table 44. Applicant - Adverse Reactions in at Least 10% of Patients Treated with ide-cel in MM-003 (N = 222)*

	Any Grade (%)	Grade 3 or Higher (%)
Cardiac disorders		
Tachycardia[a]	13	0
Gastrointestinal disorders		
Diarrhea	29	1.8
Nausea	24	0.9
Constipation	17	0
Vomiting	13	0
General disorders and administration site conditions		
Fatigue[b]	30	1.4
Pyrexia	23	0.9
Edema[c]	15	0.5
Immune system disorders		
Cytokine release syndrome	87	5
Hypogammaglobulinemia[d]	48	0.9
Infections and infestations[e]		
Infections – Pathogen unspecified	33	11
Infections - Viral	17	6
Infections - Bacterial	14	4.5
Metabolism and nutrition disorders		
Decreased appetite	16	1.8
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[f]	35	1.8
Nervous system disorders		
Encephalopathy[g]	21	3.6
Headache[h]	18	0
Dizziness[i]	13	1.8
Psychiatric disorders		
Insomnia	11	0
Renal and urinary disorders		
Renal failure[j]	11	4.1
Respiratory, thoracic, and mediastinal disorders		
Cough[k]	14	0
Dyspnea[l]	14	2.3
Vascular disorders		
Hypotension[m]	16	1.4
Hypertension	14	7

* Subjects who received conforming product only

[a] Tachycardia includes sinus tachycardia, tachycardia.

[b] Fatigue includes asthenia, fatigue, malaise.

[c] Edema includes edema, edema peripheral, generalized edema, peripheral swelling, swelling.

[d] Hypogammaglobulinemia includes patients with adverse events (13%) of blood immunoglobulin G decreased, hypogammaglobulinemia, hypoglobulinemia; and/or patients with laboratory IgG levels below 500 mg/dL following ABECMA infusion (37%).

[e] Infections and infestations System Organ Class Adverse Events are grouped by high level grouped term pathogen type.

[f] Musculoskeletal pain includes arthralgia, back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, spinal pain.

[g] Encephalopathy includes amnesia, cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, dysgraphia, encephalopathy, incoherent, lethargy, memory impairment, mental status changes, somnolence, stupor.
[h] Headache includes headache, head discomfort.
[i] Dizziness includes dizziness, presyncope, syncope, vertigo.
[j] Renal failure includes acute kidney injury, blood creatinine increased, chronic kidney disease, renal failure, renal impairment.
[k] Cough includes cough, productive cough, upper-airway cough syndrome.
[l] Dyspnea includes dyspnea, dyspnea exertional, respiratory failure.
[m] Hypotension includes hypotension, orthostatic hypotension.

Other clinically important adverse reactions that occurred in less than 10% of patients treated with ide-cel include the following:

- Blood and lymphatic system disorders: coagulopathy (6%; includes activated partial thromboplastin time prolonged, coagulopathy, disseminated intravascular coagulation, international normalized ratio increased)
- Cardiac disorders: atrial fibrillation (1.8%)
- Gastrointestinal disorders: gastrointestinal hemorrhage (0.5%)
- Immune system disorders: hemophagocytic lymphohistiocytosis (2.3%)
- Infections and infestations: infections - fungal (5%), sepsis (2.7%; includes bacteremia, sepsis)
- Musculoskeletal and connective tissue disorders: motor dysfunction (8%; dysphonia, muscle spasms, muscular weakness, restless legs syndrome)
- Nervous system disorders: tremor (4.1%; includes resting tremor, tremor), aphasia (3.2%; includes aphasia, dysarthria, slow speech, speech disorder), ataxia (2.3%; ataxia, dysmetria, gait disturbance), seizure (0.5%)
- Psychiatric disorders: anxiety (4.1%), delirium (6.3%; includes agitation, delirium, disorientation, hallucination, restlessness)
- Respiratory, thoracic, and mediastinal disorders: hypoxia (4.1%; hypoxia, oxygen saturation decreased), pulmonary edema (0.5%)
- Vascular disorders: thrombosis (2.7%; includes deep vein thrombosis, pulmonary embolism)

<u>The Applicant's Position:</u>

The most common adverse reactions (incidence greater than or equal to 20%) included CRS, hypogammaglobulinemia, musculoskeletal pain, infections – pathogen unspecified, fatigue, diarrhea, nausea, pyrexia, and encephalopathy. The most common (greater than or equal to 5%) serious adverse reactions included infections-pathogen unspecified, viral infections, and pneumonia. Fatal adverse reactions occurred in 4%.

The FDA's Assessment:

Table 45. FDA – Any-Grade TEAEs Occurring in ≥10% of Subjects, KarMMa 3

Adverse Events	Ide-cel N=222 n (%)		SOC N=126 n (%)	
-	All Grades	Grade 3-4	All Grades	Grade 3-4
Blood and lymphatic system disorders				
Febrile neutropenia	113 (51)	113 (51)	35 (28)	35 (28)
Coagulopathy (GT)	31 (14)	6 (2.7)	6 (4.8)	1 (0.8)
Cardiac disorders				
Cardiac arrhythmia (GT)	15 (7)	6 (2.7)	12 (10)	7 (6)
Tachycardia (GT)	71 (32)	0	27 (21)	0
General disorders and administration site conditions				
Pyrexia	203 (91)	20 (9)	67 (53)	7 (6)
Fatigue (GT)	74 (33)	3 (1.4)	61 (48)	5 (3.9)
Edema (GT)	44 (20)	1 (0.5)	35 (28)	3 (2.4)
Chills	42 (19)	1 (0.5)	17 (13)	0
Pain	39 (18)	6 (2.7)	42 (33)	3 (2.4)
Immune system disorders				
Cytokine release syndrome	202 (91)	9 (4.1)	51 (40)	1 (0.8)
Hypogammaglobulinemia	106 (48)	2 (0.9)	31(25)	0
Gastrointestinal disorders				
Nausea	60 (27)	2 (0.9)	61 (48)	0
Diarrhea (GT)	68 (31)	5 (2.3)	44 (35)	4 (3.2)
Constipation	38 (17)	0	19 (15)	0
Vomiting (GT)	31 (14)	0	22 (17)	0
Abdominal pain (GT)	22 (10)	1 (0.5)	18 (14)	0
Infections and infestations				
Any infection	125 (56)	35 (16)	81 (64)	23 (18)
Infections pathogens unspecified*	78 (35)	20 (9)	50 (40)	14 (11)
Upper respiratory tract infection (GT)	42 (19)	4 (1.8)	21 (17)	1 (0.8)
Viral infections*	40 (18)	12 (5)	35 (28)	8 (6)
Bacterial infections*	33 (15)	9(4)	24 (19)	10 (8)
Pneumonia (GT)	29 (13)	17 (8)	17 (13)	14 (11)
Sepsis (GT)	14 (6)	7 (3.2)	13 (10)	7 (6)
Nervous system disorders				
Dizziness (GT)	32 (14)	4 (1.8)	23 (18)	4 (3.2)
Headache (GT)	54 (24)	0	37 (29)	2 (1.6)
Neuropathy (GT)	23 (10)	0	27 (21)	1 (0.8)
Encephalopathy (GT)	49 (22)	8 (3.6)	26 (21)	6 (4.8)
Motor dysfunction (GT)	19 (9)	2 (0.9)	36 (29)	4 (3.2)
Metabolism and nutrition disorders				
Decreased appetite	37 (17)	4 (1.8)	26 (21)	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain (GT)	81 (36)	4 (1.8)	62 (49)	10 (8)

Adverse Events	Ide-cel N=222 n (%)		SOC N=126 n (%)	
Renal disorders				
Renal failure (GT)	29 (13)	11 (5)	19 (15)	5 (4)
Respiratory, thoracic and mediastinal disorders				
Dyspnea (GT)	46 (21)	4 (1.8)	39 (31)	3 (2.4)
Cough (GT)	32 (14)	0	26 (21)	0
Hypoxia (GT)	41 (18)	13 (6)	10 (8)	2 (1.6)
Vascular disorders				
Hypotension (GT)	79 (36)	5 (2.3)	24 (19)	2 (1.6)
Hypertension (GT)	31 (14)	16 (7)	26 (21)	14 (11)
Sleep disorder				
Sleep disorder(GT)	24 (11)	0	28 (22)	3 (2.)
Skin Disorders				
Rash (GT)	22 (10)	0	24 (19)	1 (0.8)

Source: FDA analysis. Data cutoff April 18, 2022
Grouped term (GT), see Appendix
The incidence of hypogammaglobulinemia is a composite of events reported in ADAE dataset and laboratory values of immunoglobulin G (IgG) < 500 mg/dl following ide-cel administration.
Grade 3 and higher rates of hypogammaglobulinemia are based on AE only.
For febrile neutropenia: rates are calculated using fever overlapping with Grade 3 or higher neutropenia excluded documented infection; this AE could be overlapping with CRS.
Abbreviations: GT, grouped term; TEAE, treatment-emergent adverse event.
AE under Pneumonia and sepsis may also be included under pathogen categories.

- All grade AEs occurring in 10% or more subjects in KarMMa-3 are consistent with those seen with the approved anti-BCMA CAR-T products. These AEs reflect the toxicities of the investigational protocol including lymphodepletion with fludarabine and cyclophosphamide.
- Pain as a grouped term was not included in the label, since we thought it was too broad a category to provide meaningful information to clinicians. This is consistent with labeling of other CAR T approvals.
- The incidence of encephalopathy in Table 45 differs from that in the section on neurologic toxicity given that table 45 includes all reported events of treatment emergent encephalopathy, whether it was adjudicated to be due to the ide-cel. For example, encephalopathy from concomitant medications or sepsis was included in Table 45 above but not under ide-cel NT. In the section on neurologic toxicity, only those events attributed to CAR-T cell toxicity were included.
- Infections: The infections included in Table 46 are classified by the pathogen type based on the high-level group terms (AEHLGT). Infections based on location (upper respiratory tract infection, pneumonia) and serious clinical syndrome such as sepsis are also presented as it would be informative to the prescriber. The label includes

both infections by pathogen type and location, with some infections included in both grouping. This approach was felt to be most useful to the prescribers.

Adverse Events of Special Interest (AESI)

CRS

Table 46. Applicant - Summary of CRS - Ide-cel Arm, Safety Population in MM-003

	Ide-cel Arm (N=225)
Number of Subjects with at Least one CRS Event - n (%)	197 (87.6)
Maximum Reported CRS Grade (Lee Criteria), n (%)	
Grade 1	124 (55.1)
Grade 2	62 (27.6)
Grade 3	6 (2.7)
Grade 4	3 (1.3)
Grade 5	2 (0.9)
Time to first onset of any CRS (days)[a]	
n	197
Median (min, max)	1.0 (1.0, 14.0)
Total Number of CRS Events - n[b]	209
Time of Onset[a]	
After 30 Days Post ide-cel Infusion	0
Duration of CRS (per event) (days)[b]	
n	208
Median (min, max)	3.5 (1.0, 51.0)
Number of events by length of duration (days), n (%)	
1 - 5 days	155 (74.2)
6 - 10 days	44 (21.1)
> 10 days	9 (4.3)
Ongoing[c]	1 (0.5)
Any Grade in ≥ 5% of Subjects	
Pyrexia	194 (86.2)
Hypotension	60 (26.7)
Tachycardia	53 (23.6)
Hypoxia	35 (15.6)
Chills	34 (15.1)
Headache	19 (8.4)
Tachypnoea	16 (7.1)
C-reactive protein increased	13 (5.8)
Aspartate aminotransferase increased	12 (5.3)
Nausea	12 (5.3)
Serum ferritin increased	12 (5.3)
Number of subjects with CRS symptoms Grade 3 and above, n (%)	40 (17.8)
Grade 3 and above in ≥ 1% of Subjects	
Pyrexia	18 (8.0)
Hypoxia	9 (4.0)
Aspartate aminotransferase increased	7 (3.1)
Alanine aminotransferase increased	5 (2.2)
Febrile neutropenia	5 (2.2)
Hypotension	3 (1.3)

Note: iiNT includes immune effector cell-associated neurotoxicity syndrome reported by investigator as a neurological toxicity AE.

[a] Time to first onset of iiNT: first start date of iiNT – infusion date + 1.

[b] If the gap between two CRS records is <=1 day, these two records are considered as one event regardless the grade change, drug relationship change or seriousness change.

[c] Ongoing iiNT was excluded from calculation of duration of iiNT.

Source: ADSL, ADAESUM

The Applicant's Position:

The majority of subjects had CRS of Grade 1 or 2 maximum severity, graded according to the Lee criteria. All CRS events emerged within 30 days post-infusion. 1 subject had ongoing CRS at time of death; the cause of death was sepsis.

The FDA's Assessment:

FDA's adjudication of CRS is summarized in Table 47 below:

CRS occurred in 202/222 (91%) of the ide-cel treated subjects. Eleven subjects (5%) experienced grade 3 or higher CRS event (Table 47). There were two deaths from CRS and Grade 2 CRS was ongoing at the time of death in one subject who died from sepsis. Out of 202 subjects with CRS, 100 subjects (50%) also experienced neurologic toxicity.

The median time from ide-cel infusion to CRS onset was 1 day (Range 1-27 days). The median duration for CRS (per subject) including ongoing CRS at death or CRS as fatal AE was 4 days (Range 1-56 days).

Of the safety population (N=222), manifestations of CRS in ≥20% of subjects included fever, hypotension, and tachycardia. Grade ≥3 manifestations of CRS and that occurred in >1% of subjects include fever, hypoxia, transaminase increase, febrile neutropenia, and hypotension.

Table 47. FDA – Analysis of CRS, KarMMa-3

Worst CRS Toxicity Grade	Subjects, N=222
CRS Any Grade	202 (91%)
Grade 1	127 (57%)
Grade 2	64 (29%)
Grade 3	6 (2.7%)
Grade 4	3 (1.3%)
Grade 5	2 (0.9%)

Source: FDA , CRS Grading per Lee criteria (Lee et al. 2014).

CRS Management:

Out of the 202 subjects with CRS, 158 subjects (71%) received tocilizumab (with or without steroids) for the management of CRS and 63 subjects (28%) were treated with systemic steroids (with or without tocilizumab) for the management of CRS. Three subjects (1.4%) received siltuximab in addition to tocilizumab for the management of CRS and eight subjects (3.6%) received anakinra in addition to tocilizumab for CRS management. 61 subjects (28%) received both tocilizumab and

steroids for the management of CRS.

Dose-Toxicity Relationship for CRS:

Table 48. FDA – CRS at Different Doses

Dose Cohort	Grade 1 n(%)	Grade 2 n(%)	Grade 3 n(%)	Grade 4 n(%)	Grade 5 n(%)	Total
<300 million (N=3)	1 (33)	1 (33)	0	0	0	2 (67)
300-460 million (N=141)	84 (60)	39 (27)	1 (0.7)	2 (1.4)	1 (0.7)	127 (90)
460-510 million (N=69)	36 (52)	21 (30)	5 (7)	1 (1.4)	1 (1.4)	64 (93)
>510 (N=9)	6 (60)	3 (30)	0	0	0	9 (100)

Source: FDA

Table 49. FDA – Use of Anti-Cytokine Therapy and Steroids for CRS Management by Dose

Dose Cohort	Anti-cytokine	Corticosteroids
<300 million (N=3)	2 (66)	1 (33)
300-460 million (N=141)	94 (67)	33 (23)
460-510 million (N=69)	53 (77)	25 (36)
>510 (N=9)	9 (100)	4 (40)
Total	158 (71)	63 (28)

Source: FDA
*Includes tocilizumab, anakinra and siltuximab

Our review strategy of finding additional subjects with CRS included identifying fever or hypotension or hypoxia between treatment Day 0 and Day 30 in subjects who were not flagged as having CRS in the dataset. We additionally searched for subjects not flagged as having CRS but who received tocilizumab or vasopressors. Corticosteroid use was not used to identify additional CRS cases as it was considered a low yield strategy since corticosteroids are generally used as adjunctive to tocilizumab for CRS management and may also be used for additional indications such as NT, treatment of progressive myeloma, other AEs, hypersensitivity reactions etc.

In addition to the 194/222 subjects with CRS flag in the dataset, we identified 8 new subjects with CRS: 6 subjects with Grade 1 CRS and 2 subjects with Grade 2 CRS. In addition, CRS duration was extended in three subjects. No changes were made to the CRS grade. Refer to Tables 77 and 78 in the Appendix for details regarding readjudication of CRS.

Dose-Toxicity Relationship for CRS:

The rate of ≥ Grade 3 CRS was higher at the higher dose compared to the approved dose:10% versus 2.8%. The rate of anti-cytokine therapy use (77% versus 67%) and steroid use (36% versus 24%) was also higher at the higher dose compared to the approved dose.

In general, the CRS profile observed in the KarMMa-3 study is consistent with the known safety profile of ide-cel.

Neurologic toxicity (specific to the product class)

Data:

Table 50. Applicant - Summary of Investigator Identified Neurotoxicity - Ide-cel Arm, Safety Population in MM-003

	Ide-cel Arm (N=225)
Number of Subjects with at Least one iiNT - n (%)	34 (15.1)
Maximum Reported iiNT Grade (NCI CTCAE V4.03) - n (%)	
Grade 1	13 (5.8)
Grade 2	14 (6.2)
Grade 3	5 (2.2)
Grade 4	2 (0.9)
Grade 5	0
Time to First Onset of Any iiNT (days)[a]	
n	34
Median (Min, Max)	3.0 (1.0, 317.0[b])
Total Number of iiNT Events[c] - n	40
Time of Onset[a] - n(%)	
Within 60 Days Post ide-cel Infusion	39 (97.5)
After 60 Days Post ide-cel Infusion	1 (2.5)
Number of Events by Length of Duration (days) - n (%)	
1 - 5 days	27 (67.5)
6 - 10 days	5 (12.5)
> 10 days	3 (7.5)
Ongoing[d]	5 (12.5)
Duration of iiNT (per Event) (days)[c]	
n	35
Median (Min, Max)	2.0 (1.0, 37.0)
Number of Subjects with iiNT Symptoms Any Grade - n (%)	34 (15.1)
Any Grade in ≥ 1% of Subjects	
Confusional state	18 (8.0)
Somnolence	8 (3.6)
Depressed level of consciousness	6 (2.7)
Disturbance in attention	6 (2.7)
Dysgraphia	5 (2.2)
Encephalopathy	5 (2.2)
Memory impairment	5 (2.2)
Tremor	5 (2.2)
Aphasia	3 (1.3)
Disorientation	3 (1.3)
Headache	3 (1.3)
Lethargy	3 (1.3)
Urinary incontinence	3 (1.3)

Table 50. Applicant - Summary of Investigator Identified Neurotoxicity - Ide-cel Arm, Safety Population in MM-003

	Ide-cel Arm (N=225)
Number of Subjects with iiNT Symptoms Grade 3 and Above - n (%)	7 (3.1)
Grade 3 and Above in ≥ 1% of Subjects	
Confusional state	3 (1.3)
Depressed level of consciousness	3 (1.3)

Note: iiNT includes immune effector cell-associated neurotoxicity syndrome reported by investigator as a neurological toxicity AE.

[a] Time to first onset of iiNT: first start date of iiNT – infusion date + 1.

[b] Encephalopathy was reported in one subject 317 days after ide-cel infusion; considered by the investigator to be related to worsening pneumonia and C. difficile colitis

[c] If the gap between two iiNT records is <=1 day, these two records are considered as one event regardless the grade change, drug relationship change or seriousness change.

[d] Ongoing iiNT was excluded from calculation of duration of iiNT.

Source: ADSL, ADAESUM

The Applicant's Position:

In the ide-cel arm safety population, the majority of iiNT AEs were of Grade 1 or 2 severity. No Grade 5 iiNT events were reported. All but one iiNT events occurred within 60 days post-infusion.

The FDA's Assessment:

Among 222 subjects treated with ide-cel, 103 (46%) experienced one or more neurologic toxicity events that are considered related to ide-cel by FDA analysis. Eleven subjects (5%) experienced Grade 3 to 4 (Table 51). The following neurologic toxicity events occurred in ≥10% of subjects: headache, encephalopathy, and dizziness. The median time to onset from ide-cel infusion to the first NT event was 3 days (range 1-148 days). NT resolved in 90 out of 103 subjects (87%). Seven subjects had NT events ongoing at the time of death which includes two subjects with Grade 3 NT at the time of death from another cause (Subjects (b) (6) and (b) (6)). Median time to resolution of NT, when excluding ongoing NT events was 5 days (range: 1, 245 days). Median duration of NT was 9 days with a range of 1, 720 days in all subjects including those with ongoing neurologic events at the time of death or at data cut-off.

While not included in Table 51 below, there was one subject with Grade 5 NT in the ide-cel arm in KarMMa-3. This Grade 5 NT event reported at the time of 90-day safety update occurred on treatment day 43 in subject (b) (6) treated with 377 x10e6 CAR +T cells.

One Grade 5 NT event occurred in a subject (b) (6) initially randomized to the SOC arm who received ide-cel upon cross-over. The death occurred on treatment day 107, after receiving a dose of 521 x10e6 CAR+ T cells.

Table 51. FDA – Neurologic Toxicity in the Ide-cel Arm (N=222)

Toxicity Grade	N (%)
Any Grade	103 (46%)

Toxicity Grade	N (%)
1	54 (24%)
2	38 (17%)
3	9 (4%)
4	2 (0.9%)
5	0

Source: FDA , Grading of the neurologic toxicity was per CTCAE version 4.0.

Table 52. FDA – Ide-cel Neurotoxicity in KarMMa-3

Neurologic Events	All Grades n (%)	Grade 3 or Higher n (%)
Total	103 (46)	11 (5%)
Headache	49 (22)	0
Encephalopathy	46 (21)	6 (2.7%)
Dizziness	25 (11)	2 (0.9%)
Delirium	14 (6)	1 (0.5%)
Neuropathy	11 (5)	0
Motor dysfunction	9 (4)	1 (0.5%)
Tremor	9 (4)	0
Vision blurred	7 (3.2)	0
Aphasia	6 (2.7)	1 (0.5%)
Ataxia	5 (2.3)	2 (0.9%)
Sleep disorder	5 (2.3)	0
Urinary incontinence	4 (1.8)	0
Diplopia	3 (1.4)	0
Dysgeusia	3 (1.4)	0
Anxiety	2 (0.9)	0
Deafness unilateral	2 (0.9)	0
Decreased gait velocity	1 (0.5)	0
Dysphagia	1 (0.5)	0
Fatigue	1 (0.5)	0
Myositis	1 (0.5)	0
Nausea	1 (0.5)	0
Pupils' unequal	1 (0.5)	0
Seizure	1 (0.5)	0
Vomiting	1 (0.5)	0

Source: FDA analysis of ADAE 3 dataset.
See APPENDIX for Preferred terms and Grouped Terms used Source: ADAE 3.xpt.
Some of headaches included under NT were also considered by the investigators as symptom of CRS

Table 53. FDA – Ide-cel Neurotoxicity by Dose

Dose Cohorts	All Grades n (%)	Grade 3-4 n (%)
<300 million N=3	1 (33)	0
300-460 million N=141	66 (47)	5 (3.5)
>460-510 million N=69	27 (39)	4 (6)
>510 million N=9	9 (100)	2 (22)

Source: FDA

There was substantial difference between the Applicant's and FDA assessment of NT. The ADAE dataset included flags for investigator identified NT for 30 subjects (14%), 6 with Grade 3-4 events (2.7%). Overall, FDA identified 73 additional subjects with NT (total=103, 46%), 11 with Grade 3-4 events (5%).While the rate of overall NT was similar between the approved dose and the higher dose cohort (460-510x10e6), the higher dose cohort had a higher rate of Grade 3-4 NT (6% versus 3.5%).

The FDA has taken a broad view of NT and examined the following AEs as ide-cel related NT:

- All investigator identified NT.
- AEs under Nervous System Disorder and Psychiatric disorder SOC excluding some isolated and non-specific AEs such as insomnia or anxiety.
- Preferred terms that indicate NT but are misclassified under other system organ classes such as muscular weakness, myositis under Musculoskeletal and Connective Tissue Disorders, gait disturbance under General Disorders and vertigo under Ear and Labyrinth disorder.
- Neurological events such as headache, tremor, somnolence which investigators considered as symptoms of CRS that were indicative of NT.
- The timing of onset of the AE relative to the administration of ide-cel, the occurrence of other overlapping neurological symptoms as opposed to an isolated AE (for example: isolated dizziness versus dizziness overlapping with headache, confusion), absence of other competing causes such as concurrent illness, concomitant medications with overlapping side effects, and current understanding of CAR T cell associated NT were all considered in making assessment of attribution
- The information in the USPI is based on FDA's definition and re-adjudication of neurologic toxicity.

While there were no fatal NT in ide-cel arm at the time of the primary safety analysis, one subject (USUBJID (b) (6) died from NT on treatment day 43 The Applicant had assessed the

cause of death as unknown. This subject was a 71-year-old male with history of hydrocephalus and a ventriculo-peritoneal shunt. Subject was in very good partial response at the time of death and had not received any subsequent anti-myeloma therapy. He had Grade 2 NT from Day 1-2, Day 6-7, and Day 11-31. On Day 29, he was admitted with hypotension and agitation. According to the narrative, he had symptoms of irritability, agitation, anger, debilitation, and inability to ambulate without assistance. Brain MRI (non-contrast enhanced) showed no acute changes. CSF was not examined. He subsequently developed declining functional status and remained debilitated. According to IR # 32, Grade 2 agitation started on Day 29 and the subject was hospitalized. Steroids instituted for previous NT was stopped on same day. On Day 30, patient was recorded as being calm and on Day 38, was recorded as being hypoactive. He was discharged to hospice on Day 39 and subsequently died. The IR states that investigator had confirmed that the event of agitation was due to steroids and was not a NT event. The reviewer notes that both steroid induced delirium and CAR T associated neurotoxicity can have overlapping clinical features. Review of the narrative and IR# 32, continues to raise concern for ongoing NT with agitation followed by "hypoactive" state with ultimate transfer to hospice and death. Information about this death is included in Section 5.3, USPI.

FDA adjudicated the cause of death as NT in a subject (USUBJID (b) (6)) in the SOC arm (treatment day 107 after ide-cel infusion received upon cross-over). Applicant had stated the cause of death as unknown. Since this death had occurred in a subject randomized to the SOC arm and after receiving ide-cel as subsequent therapy upon cross-over, it is not included in the USPI.

No new neurologic toxicity concern were observed in KarMMa-3.

Serious Infections

Data:

Table 54. Applicant - Summary of Infections in ≥ 3% of Subjects in Either Treatment Arm, Safety Population in MM-003

	No. of Subjects (%)			
	Ide-cel Arm N = 225		Standard Regimens Arm N = 126	
	Adverse Event Grades			
Safety Parameters	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Infections - Overall	138 (61.3)	55 (24.4)	68 (54.0)	23 (18.3)
Upper respiratory tract infection	28 (12.4)	4 (1.8)	9 (7.1)	0
Pneumonia	23 (10.2)	15 (6.7)	9 (7.1)	5 (4.0)
Bronchitis	12 (5.3)	0	4 (3.2)	0
Urinary tract infection	12 (5.3)	1 (0.4)	5 (4.0)	0
COVID-19	11 (4.9)	2 (0.9)	6 (4.8)	1 (0.8)
Nasopharyngitis	9 (4.0)	0	4 (3.2)	0
Influenza	8 (3.6)	6 (2.7)	4 (3.2)	3 (2.4)
Sinusitis	8 (3.6)	0	6 (4.8)	0
Escherichia urinary tract infection	7 (3.1)	1 (0.4)	6 (4.8)	0

	No. of Subjects (%)			
	Ide-cel Arm N = 225		Standard Regimens Arm N = 126	
	Adverse Event Grades			
Safety Parameters	**Any Grade**	**Grade 3 or 4**	**Any Grade**	**Grade 3 or 4**
Rhinovirus infection	7 (3.1)	1 (0.4)	2 (1.6)	0
COVID-19 pneumonia	4 (1.8)	3 (1.3)	4 (3.2)	4 (3.2)

Source: ADSL, ADAESUM

The Applicant's Position:

Serious infection is a known complication of CAR T therapy and of standard AMT therapies and is a comorbidity of RRMM. The increased rates of cytopenia and hypogammaglobulinemia seen with CAR T products are additional risk factors for infection. Despite this, infection rates and types are broadly similar between the two arms. The rate of infections (all grades and Grade 3/4) in the ide-cel arm is consistent with that seen in study MM-001 (68.8% and 21.1%). Of note, Grade 3/4 COVID-19 infection rates were low and similar between the two arms.

The FDA's Assessment:

In the ide-cel arm, 125 subjects (56%) had infections and 45 (20%) subjects had worst Grade ≥ 3 infections. For the SOC arm, 81 subjects (64%) had infections and 31 subjects (25%) had worse Grade ≥3 infections.

In the ide-cel arm, thirty subjects (14%) had worst Grade 3 infections and five subjects (2%) had a worst Grade 4 event. Ten subjects (4.5%) had Grade 5 infections; five patients had Grade 5 sepsis (2.3%), two patients had Grade 5 invasive fungal infections (0.9%), two patients had Grade 5 COVID 19 (0.9%)and one patient had Grade 5 pneumonia (0.5%). In the SOC arm, twenty-one subjects (17%) had worst Grade 3 infections and two subjects (2%) had a worst Grade 4 infection. Eight subjects (6%) had Grade 5 infections; two cases of COVID 19 pneumonia and six cases of bacterial sepsis. Four of the eight Grade 5 events occurred after cross-over to ide-cel arm

Details regarding infections by HLGT (high level grouped terms) and including pneumonia as an important site of infection and sepsis as clinically important syndrome are presented in Table 55.

Table 55. FDA – Infections in KarMMa-3

TEAE infections	Ide-cel Arm N=222		SOC Arm N=126	
	All Grades N(%)	Grade 3-5 N(%)	All Grades N(%)	Grade 3-5 N(%)
Infections-pathogen unspecified	78 (35)	25 (11)	50 (40)	16 (13)
Bacterial infectious disorder	32 (14)	10 (4.5)	24 (19)	14 (11)
Viral infectious disorder	40 (18)	14 (6)	35 (28)	10 (8)
Fungal infectious disorder	11 (5)	4 (1.8)	10 (8)	1 (0.8)

TEAE infections	Ide-cel Arm N=222		SOC Arm N=126	
	All Grades N(%)	Grade 3-5 N(%)	All Grades N(%)	Grade 3-5 N(%)
Pneumonia (GT)	29 (13)	20 (9)	17 (13)	15 (12)
Sepsis (GT)	14 (6)	13 (6)	13 (10)	13 (10)

Source: FDA analysis
Infections grouped under high-level grouped term by pathogen category could also be included under pneumonia or sepsis.

- The reviewer analyzed all infections that occurred in the safety population after ide-cel infusion and start of anti-myeloma therapy in the ide-cel arm and SOC arm respectively.

- For the ide-cel arm, the reviewer identified 11 additional infections in 10 subjects that were mis-classified under other SOC such as Investigations, General disorders & Administration Site Conditions and Hepatobiliary Disorders. Similarly, the reviewer identified 13 additional infections in 9 subjects in the SOC arm that were mis-classified under other SOC such as Investigations, General disorders & Administration Site Conditions, Gastrointestinal Disorders, and Respiratory, Thoracic and Mediastinal disorders. disorders. These were included under treatment emergent infections.

- The fatal infection rate with ide-cel is 5% (12/222). The fatal infection rate with SOC is 6% (8/126).

- The Applicant reported AE of febrile neutropenia in 20 subjects in the ide-cel arm and 8 subjects in the SOC arm. However, a total of 113 subjects (51%) in the ide-cel arm experienced fever that overlapped with Grade 3 or higher neutropenia in the absence of documented infection. Similarly, thirty-five subjects (28%) in the SOC arm experienced fever that overlapped with Grade 3 or higher neutropenia in the absence of documented infection. FDA adjudicated rate of febrile neutropenia is included in the USPI.

Hypogammaglobulinemia

Data:

Table 56. Applicant - Summary of Hypogammaglobulinemia, Safety Population in MM-003

	Ide-cel Arm N = 225	Standard Regimens Arm N = 126
Hypogammaglobulinemia on or after Randomization, n (%)	191 (84.9)	80 (63.5)

Based on Lab[a]	191 (84.9)	80 (63.5)
Based on Adverse Event[b]	22 (9.8)	3 (2.4)

Note: For Standard Regimens Arm, all data are included for those subjects who did not receive leukapheresis, but only data before leukapheresis are included for those subjects who planned to receive ide-cel infusion.

[a] Hypogammaglobulinemia based on lab is defined as IgG < 500mg/dl.

[b] Hypogammaglobulinemia based on AE includes the following preferred terms: Blood immunoglobulin G decreased, Hypogammaglobulinaemia, and Hypoglobulinaemia.

The Applicant's Position:

Hypogammaglobulinemia is a common secondary immunodeficiency in MM.[35] Plasma cell aplasia is an expected on-target toxicity of BCMA targeted CAR T therapies which may result in chronic hypogammaglobulinemia and the AE rate would thus be expected to be higher in the ide-cel arm than the standard regimens arm. The rate based on AE in the ide-cel arm of MM-003 is lower than that seen in MM-001 (9.8% vs 20.3% respectively).

The FDA's Assessment:

Hypogammaglobulinemia was defined as post- treatment occurrence of IgG <500 mg/dl based on laboratory assessment in ADLB dataset or on AE (defined by FDA GT) in ADAE 3 dataset.

Ide-cel arm: It was reported in 106 subjects (48%) in the ide-cel arm. Newly diagnosed hypogammaglobulinemia post ide-cel was observed in 98 subjects based on lab criteria and in 19 subjects based on AE assessment.

Hypogammaglobulinemia is a known toxicity of anti-BCMA CAR T therapy. The USPI will reflect a combination of AE and laboratory based hypogammaglobulinemia. IVIG therapy was administered in the study for subjects with serum IgG levels less than 400 mg/dl. Sixty-five subjects (29%) in the ide-cel arm received IVIG in KarMMa-3. The recommendation to administer IVIG to maintain IgG level above 400 mg/dl is included in the label as it may have reduced the overall rate of infection post ide-cel.

Cytopenia and Prolonged Cytopenia

Data:

Table 57. Applicant - Summary of Time to Recovery of Grade 3 or 4 Cytopenia - Ide-cel Arm, Safety Population in MM-003

	Ide-cel Arm (N = 225)	
Parameters	**Grade 3 or 4 Neutropenia**	**Grade 3 or 4 Thrombocytopenia**
Subject with Grade 3 or 4 cytopenia at any timepoint on/before Month 1 after ide-cel infusion N1 (%, N1/N)[a]	217 (96.4)	120 (53.3)
Recovered at Last Assessment on/before Month 1 - M (%, M/N1)[b]	128 (59.0)	36 (30.0)
Not Recovered at Last Assessment on/before Month 1 - M (%, M/N1)[b]	89 (41.0)	84 (70.0)
Recovery Status after Month 1[c]		
Censored, n (%)	7 (7.9)	13 (15.5)
Lost to follow up before recovery	1 (1.1)	2 (2.4)
Died without recovery	5 (5.6)	8 (9.5)
Ongoing as of data cutoff date	1 (1.1)	3 (3.6)
Recovered - n (%)	82 (92.1)	71 (84.5)
Time to Recovery (Months)[d]		
Median (95% CI)	1.7 (1.5, 1.9)	1.9 (1.5, 2.1)
1 Month Recovery Rate (%)	0.0	0.0
2 Months Recovery Rate (%)	69.0	60.2
3 Months Recovery Rate (%)	87.4	71.1
Time to Recovery for All Subjects (Months)[e]		
Mean (SD)	2.8 (4.29)	4.3 (6.05)
Median (Min, Max)	1.7 (0.3, 26.5)	1.9 (1.1, 28.3)
Time to Recovery for Recovered Subjects (Months)[e]		
Mean (SD)	1.9 (0.76)	2.4 (1.87)
Median (Min, Max)	1.6 (1.1, 5.6)	1.7 (1.1, 9.2)

Grade 3 or 4 neutropenia is defined as ANC < 1,000/µL. Recovery from neutropenia is achieved when ANC is ≥1,000/µL. Grade 3 or 4 thrombocytopenia is defined as platelet count < 50,000/µL. Recovery from thrombocytopenia is achieved when platelet count is ≥50,000/µL.

[a] Percentage is calculated with the Safety population as the denominator.

[b] Percentage is calculated with subjects who had Grade 3 or 4 neutropenia or thrombocytopenia at any timepoint on/before Month 1 (Day 30 plus 3 days window) after ide-cel infusion (N1) as the denominator.

[c] Percentage is calculated with subjects who did not recover from Grade 3 or 4 neutropenia or thrombocytopenia at the last assessment on or before Month 1 post infusion (M) as the denominator.

[d] Time to recovery of Grade 3 or 4 neutropenia or thrombocytopenia is defined as the time from ide-cel infusion date to the time when recovery was first met after Month 1 post infusion. The median and recovery rate are based on K-M estimate. Subjects who did not recover after Month 1 without death, including ongoing as cutoff date or lost to follow-up before recovery, are censored to last non-missing assessment date after Month 1, and subjects who died before recovery are censored to current data cutoff

[e] The summary statistics are univariate statistics without adjusting for censoring.

Source: ADSL, ADTTE

The Applicant's Position:

Cytopenias are a recognized complication of CAR T therapy. The rates of Grade 3/4 neutropenia and thrombocytopenia seen in the ide-cel arm are consistent with those seen in the MM-001 study (97.7% and 64.8% respectively).[36] Those not recovered by Month 1 are also in line with that seen in MM-001 (41.6% of subjects who had Grade 3/4 neutropenia and 74.7% of subjects who had Grade 3/4 thrombocytopenia within Month 1). Median recovery times in MM-003 and MM-001 appear comparable for both neutropenia and thrombocytopenia.

The FDA's Assessment:

Table 58 summarizes the rate of prolonged cytopenia, rate of recovery to ≤Grade 2 cytopenia and median time to recovery in the safety population, ide-cel arm. The Applicant's analysis includes the three subjects who received non-conformal ide-cel. FDA's analysis summarized below includes the 222 subjects who received conformal ide-cel.

Table 58. FDA – Prolonged Cytopenia After Treatment in the Ide-cel Arm (N=222)

Laboratory		Grade 3-4 cytopenia (n/%)	Grade 3-4 not recovered by Day 30 (n/%)	Recovered to <Grade 3 after Day 30 (n/%)	Median time to recovery in months (Range)
Neutropenia		214 (96)	87 (39)	80 (36)	1.6 (1.1, 5.6)
Thrombocytopenia		119 (54)	83 (37)	70 (32)	1.7 (1.1, 9.3)

Cytopenia and Prolonged cytopenia: Analysis is based on ADLB (laboratory dataset).
Prolonged cytopenia is defined as Grade 3 or 4 neutropenia or thrombocytopenia that is persistent for more than 1 month after receiving ide-cel. Recovery from neutropenia is achieved when ANC is ≥1000 cells/mm3. Recovery from thrombocytopenia is achieved when platelet count is ≥50,000 cells/mm3.

1. Two subjects in the ide-cel arm underwent autologous CD34+ stem cell boost on study day 136 and 163 respectively for hematopoietic reconstitution. Both had count recovery post stem cell boost.
2. Prolonged neutropenia: Seven out of 87 subjects with prolonged neutropenia did not recover at the last follow up due to death in five subjects, lost to follow up in one subject and ongoing for another subject.
3. Prolonged thrombocytopenia: Thirteen out of the 83 subjects with prolonged thrombocytopenia did not recover at the last follow up due to death in 8 subjects, lost to follow up in two subjects and ongoing thrombocytopenia in three subjects.
4. Dose-toxicity relationship: Overall, the rate of Grade 3 or 4 thrombocytopenia at any time point on or before Month 1 after ide-cel infusion was higher in the higher dose compared to the approved dose (64% versus 47%). The rate of Grade 3 or 4 neutropenia at any time point on or before Month 1 after ide-cel infusion was similar in the higher dose compared to the approved dose (94% versus 97%). A similar proportion of subjects in both the doses developed prolonged cytopenia and ultimately recovered to <Grade 3 cytopenia. The median time to recovery from prolonged thrombocytopenia and neutropenia was also similar in both the doses.

New Malignancies Including Second Primary Malignancies

Data:

Table 59. Applicant - Summary of Second Primary Malignancies - Safety Population in MM-003

SPM Categories	Ide-cel Arm	Standard Regimens Arm

Table 59. Applicant - Summary of Second Primary Malignancies - Safety Population in MM-003

SPM Subcategories Preferred Terms[a]	(N=225) n (%)	(N=126) n (%)
Subjects with at least one SPM	13 (5.8)	5 (5.4)
Invasive SPMs	9 (4.0)	3 (2.4)
Hematologic Malignancy	3 (1.3)	0
Myelodysplastic syndrome	2 (0.9)	0
Acute myeloid leukaemia	1 (0.4)	0
Solid Tumor	6 (2.7)	3 (2.4)
Sarcoma	0	1 (0.8)
Gastrointestinal stromal tumour	0	1 (0.8)
Melanoma	2 (0.9)	1 (0.8)
Malignant melanoma	2 (0.9)	0
Lentigo maligna	0	1 (0.8)
Solid Tumor of Bilateral Organ Origin	1 (0.4)	0
Breast cancer	1 (0.4)	0
Other	3 (1.3)	1 (0.8)
Breast cancer	1 (0.4)	0
Rectal adenocarcinoma	1 (0.4)	0
Small intestine adenocarcinoma	1 (0.4)	0
Bronchial carcinoma	0	1 (0.8)
Non-invasive SPMs (Non-melanoma Skin Cancer)	4 (1.8)	2 (1.6)
Basal cell carcinoma	2 (0.9)	1 (0.8)
Squamous cell carcinoma	2 (0.9)	1 (0.8)
Squamous cell carcinoma of skin	1 (0.4)	0
Bowen's disease	0	1 (0.8)

Note: For Standard Regimens Arm column, all data are included for those subjects who did not receive leukapheresis, but only data before leukapheresis are included for those subjects who planned to receive ide-cel infusion. Data on/after leukapheresis in Standard Regimens Arm are reported in a separate column.

[a] Coded using MedDRA version 24.1. A subject is counted only once for multiple events within preferred term/SPM (Sub)Category.

Source: ADSL, ADSPM

The Applicant's Position:

The percentage of subjects with second malignancies reported as of the data cutoff date was low and similar between the treatment arms. Myelodysplastic syndrome and acute myeloid leukemia, which are hematologic malignancies of interest, occurred in 2 and 1, respectively, subjects in the ide-cel arm and none in the standard regimens arm. Given differences in duration of actual time at risk (adjusted incidence was 297.82 p-y in the ide-cel arm vs 92.04 p-y in the standard regimens arm [*Source: ADSL, ADTTESMP*]), these numerical differences should be interpreted with caution. Of note, no subjects treated with ide-cel were diagnosed with T cell malignancies.

The FDA's Assessment:

The Applicant's analysis of secondary primary malignancies includes the non-conformal subjects in the ide-cel arm and separates the invasive and non-invasive malignancies. The FDA analyzed the safety population in the ide-cel arm (n=222) and combined the analysis for non-invasive and invasive malignancies to obtain an all-encompassing assessment of the secondary malignancies.

Thirteen subjects (6%) were diagnosed with a secondary malignancy in the ide-cel arm compared to five subjects (4%) in the SOC arm. This includes three subjects with myeloid malignancy in the ide-cel arm compared to none in SOC arm. At the time of the 90-day safety update report, two additional cases of MDS were reported in the ide-cel arm. One subject in the SOC arm after cross over to ide-cel developed metastatic carcinoma of unknown primary. Refer to the Appendix for a list of all secondary malignancies that developed in KarMMa-3.

1. In total, five cases of myeloid neoplasms: one case of AML and four cases of MDS (2.2%) have occurred in the ide-cel arm at a median follow up of 18.2 months. The median time to onset of myeloid neoplasm from ide-cel infusion was 332 days (Range 277-794 days). Three of these 5 patients have died following the development of myeloid neoplasm. One patient included in the safety update report had started antimyeloma therapy with an investigational CAR T therapy, three months prior to development of MDS. Bone marrow examinations for two of these five patients were negative for the CAR transgene by quantitative polymerase chain reaction. The remaining three patients were not tested for the CAR transgene. Insertion site analysis was not performed in any of the five subjects.

   No cases of MDS/AML have been reported in the SOC arm. However, the median follow up for the ide-cel recipients in the SOC arm (10.6 months) and for the SOC patients who did not cross over to ide-cel (14.9 months) at the time of the safety update is relatively short compared to the ide-cel arm (18.2 months). Notwithstanding the limitation of different follow up in the two arms, the rate of AML/MDS observed with KarMMa-3 will be included in the USPI to inform providers.

Macrophage Activation Syndrome

Data:
In the ide-cel arm safety population, 5 (2.2%) subjects had at least 1 MAS AE (); all events were reported within the first 8 weeks after ide-cel infusion. 3 of these subjects had a MAS AE of Grade 4 maximum severity. One Grade 4 event was ongoing at time of death.

The Applicant's Position:

MAS is a known risk of CAR-T therapy. No Grade 5 events due to MAS were reported in MM-003 and the rate of MAS AEs in MM-003 (2.2%) is lower than the rate in the current ide-cel label (4%).

FDA Assessment:

FDA agrees with the Applicant's assessment that HLH/MAS was observed in 5 subjects in the ide-cel arm (2%) and in one subject in the SOC arm [Grade 2 HLH/MAS after receiving ide-cel upon cross over (0.8%)].

However, FDA readjudicated the grade of HLH/MAS in one subject from Grade 4 to Grade 5 in

the ide-cel arm. Based on FDA's assessment, one subject had Grade 5, two subjects had Grade 4 and two subjects had Grade 3 HLH/MAS. The median time to onset of HLH/MAS was a median of 6 days (Range: 5-10 days). All subjects (n=5) that developed HLH/MAS had concurrent or overlapping CRS. Three subjects also had concurrent/overlapping NT.

Re-adjudicated Grade 5 HLH/MAS: One subject developed Grade 4 CRS , Grade 4 HLH/MAS (onset on treatment day 8) and Grade 4 NT. This subject developed candidemia and enterococcus faecium in the setting of profound neutropenia (onset on treatment day 2). He died on treatment day 21. An autopsy showed evidence of extensive multi-organ invasive candidiasis and the bone marrow showed histiocytes with hemophagocytosis, especially erythrophagocytosis. The Applicant has attributed the death to CRS and candida sepsis. In addition to CRS and candidiasis, FDA considers HLH/MAS as Grade 5 event given the autopsy findings. HLH/MAS could be contributory to bone marrow failure causing severe and prolonged neutropenia predisposing to invasive fungemia.

HLH/MAS is a rare but known serious safety risk of ide-cel and is included as boxed warning in the USPI. Two events (1.4%; One Grade 3 and one Grade 4 AE) occurred at the approved dose. Three events (4.3%) including the Grade 5 AE occurred at the higher dose. However, the number of events are small to derive any conclusion about dose toxicity relationship for HLH/MAS.

Autoimmune-like or Rheumatologic Disorders

Data:
In the ide-cel arm safety population, 1 (0.4%) subject had a Grade 2 autoimmune disorders AE (vasculitis) that resolved after 69 days without therapy ().

The Applicant's Position:

Autoimmune-like or rheumatologic disorders were infrequent in MM-003 and are rare events after CAR-T treatment, although immune-related late events have been reported in up to 8% of recipients.[37]

The FDA's Assessment:

The FDA does not agree with the Applicant's assessment of autoimmune toxicity. In addition to the one subject with vasculitis, the reviewer identified five additional subjects with auto-immune toxicity in the ide-cel arm. This is summarized in Table 60 below. All events were Grade 1 or 2. No subjects in the SOC arm developed autoimmune AEs.

Table 60. FDA – Ide-cel arm: Autoimmune Toxicity in KarMMa-3

Subject ID	AEDECOD	Grade	AE Start and End Day From Rx
(b) (6)	Vasculitis	2	25-93
(b) (6)	Colitis	1	44-ongoing

(b) (6)		Immune-mediated enterocolitis	2	90-254
(b) (6)		Myositis	2	106-170
(b) (6)		Colitis microscopic	1	112-370
(b) (6)		Adrenal insufficiency	2	67-ongoing

Source: FDA analysis

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:

Given ide-cel is administered as a single infusion, treatment discontinuations due to AEs in the ide-cel arm are not applicable.

One subject in the standard regimens discontinued treatment due to AEs (*Source: ADSL*).

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Dose Interruption/Reduction Due to Adverse Effects

Data:

Table 61. Applicant - AEs Leading to Dose Reduction, Interruption, or Withdrawal of LDC, Ide-cel Arm - Treated Population in MM-003

	Fludarabine	Cyclophosphamide	Fludarabine and Cyclophosphamide	Fludarabine or Cyclophosphamide
AEs Leading Dose Reduction	2 (0.8)[a]	0	0	2 (0.8)
AEs Leading Dose Interruption	1 (0.4)[b]	0	0	1 (0.4)
AEs Leading Dose Withdrawal	0	0	0	0

[a] AEs of leukopenia (n = 1) and diarrhoea (n = 1)

[b] AEs of nausea and retching (n = 1)

Source: ADSL, ADAE2

The Applicant's Position:

Given ide-cel is administered as a single infusion, dose reductions due to AEs in the ide-cel arm are not applicable. There were no dose interruptions for ide-cel infusions. As ide-cel was

administered as a single dose and follow-up continued for subjects regardless of AEs; these analyses do not permit a fair comparison to the standard regimens arm.

AEs leading to dose reduction and dose interruption of LDC were infrequently reported and there were no AEs leading to withdrawal of LDC.

In the standard regimens arm dose interruptions or reductions due to AEs were to be done per the respective approved labels.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Laboratory Findings

Data:

Table 62. Applicant - Grade 3 or 4 Laboratory Abnormalities Worsening from Baseline in at Least 10% of Patients in MM-003

Laboratory Abnormality	Ide-cel Arm	Standard Regimens Arm
Lymphocyte decreased, N n (%)	225 221 (98.2)	125 73 (58.4)
Leukocyte decreased, N n (%)	225 217 (96.4)	126 41 (32.5)
Neutrophil decreased, N n (%)	225 216 (96.0)	126 60 (47.6)
Platelet decreased, N n (%)	225 131 (58.2)	126 27 (21.4)
Hemoglobin decreased, N n (%)	225 117 (52.0)	126 24 (19.0)
Phosphate decreased, N n (%)	225 101 (44.9)	125 20 (16.0)
Triglycerides Increased, N n (%)	225 47 (20.9)	125 7 (5.6)
Alanine aminotransferase increased, N n (%)	225 30 (13.3)	126 4 (3.2)
Sodium decreased, N n (%)	225 24 (10.7)	126 2 (1.6)
Gamma Glutamyl Transferase Increased, N n (%)	225 24 (10.7)	125 5 (4.0)

NCI CTCAE version 4.03. Laboratory tests were graded according to NCI CTCAE Version 4.03 based on the numerical value only without considering the clinical evaluation. Worsening is defined as a post-baseline abnormality that is at least 1 grade higher than baseline.
Source: ADSL, ADLB

The Applicant's Position:

Overall, there were no unexpected or clinically significant changes in chemistry values over time following ide-cel infusion or treatment with standard regimens.

The FDA's Assessment:

FDA's assessment of laboratory abnormalities includes the safety population in the ide-cel and

SOC arm.

Table 63. FDA – Grade ≥3 Laboratory Abnormalities worsening from Baseline in at least 10% of Subjects

Laboratory Test	Ide-cel arm N=222 n(%)	SOC arm N=126 n(%)
Lymphopenia	218 (98)	98 (78)
Leukopenia	214 (96)	81 (64)
Neutropenia	213 (96)	91 (72)
Thrombocytopenia	130 (59)	58 (46)
Anemia	116 (52)	57 (45)
Hypophosphatemia	100 (45)	38 (30)
Hypertriglyceridemia	47 (21)	13 (10)
Hyponatremia	24 (11)	9 (7)
ALT increase	29 (13)	10 (8)
GGT increased	23 (10)	7 (6)

Source: FDA analysis AND Applicant's response to Information Request. Data cutoff April 18, 2022
Lab tests are graded according to National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE) version 4.03.
Baseline value is defined as the last non missing value before or on the date of leukapheresis for Ide-cel Arm and before or on Month 1 Day 1 for SOC arm. Worsening is defined as a postbaseline abnormality that is at least 1 grade higher than baseline.

• Laboratory data (ADLB dataset) was used to generate incidence of laboratory- based AEs since this is more accurate as opposed to using the AE dataset (ADAE dataset).
• Cytopenia of all grades were the most common laboratory abnormalities as expected and reflect toxicity of the entire investigational protocol including lymphodepleting chemotherapy.
• Hypophosphatemia was the most common grade 3-4 chemistry laboratory abnormality.

Vital Signs

The Applicant's Position:

Vital signs were monitored and recorded at the site per institutional standard of care during screening and treatment visits. These assessments were intended to be used as safety monitoring by the treating physician.

The FDA's Assessment:

The ADVS dataset included vital signs collected at scheduled visits and for only limited data points during the occurrence of AEs. During the safety review, the reviewer obtained some of the missing vital signs from the narratives to facilitate review of safety.

Electrocardiograms (ECGs)

The Applicant's Position:

No significant changes in ECG assessments (including median change from baseline) were seen for subjects in either treatment arm in MM-003 and no remarkable differences between arms were observed.

The FDA's Assessment:

FDA agrees that electrocardiogram were monitored as part of the safety assessment.

Immunogenicity

Data:

Table 64. Applicant - Summary of Anti-CAR Antibodies, Ide-cel Arm - Safety Population in MM-003

Anti-CAR-Antibodies	Ide-cel Arm (N=225) n (%)
Pre-positive [a]	5 (2.2)
Post-positive [b]	2 (0.9)
Post-negative [b]	2 (0.9)
Missing post data	1 (0.4)
Pre-negative [a]	214 (95.1)
Post-positive [b]	128 (56.9)
Post-negative [b]	84 (37.3)
Missing post data	2 (0.9)
Missing pre-data	6 (2.7)
Post-positive [b]	5 (2.2)
Post-negative [b]	1 (0.4)
Missing post data	0

By Visit

	Scheduled Visit (Post Infusion)								
Anti-CAR-Antibodies	**Baseline**	**Day 25**	**Month 2**	**Month 4**	**Month 6**	**Month 10**	**Month 19**	**Month 31**	**PFS Discontinuation**
N [c]	219	207	217	179	166	119	28	3	80
Positive, n (%)	5 (2.3)	2 (1.0)	2 (0.9)	41 (22.9)	84 (50.6)	85 (71.4)	26 (92.9)	3 (100.0)	50 (62.5)
Negative, n (%)	214 (97.7)	205 (99.0)	215 (99.1)	138 (77.1)	82 (49.4)	34 (28.6)	2 (7.1)	0	30 (37.5)

[a] Pre-positive is defined as the last value before or on ide-cel infusion date is positive; Pre-negative is defined as the last value before or on ide-cel infusion date is negative.
[b] Post-positive is defined as at least one positive value post ide-cel infusion; post-negative is defined as all negative values post ide-cel infusion.
[c]: N is number of subjects with anti-CAR antibody data record, which is used as the denominator of percentage calculation for each visit.
Source: ADSL, ADIS

The Applicant's Position:

The impact of pre-existing and post-infusion ADA on cellular expansion appeared to be limited. The limited impact of post-infusion ADA formation on cellular expansion kinetics of ide-cel was

in line with the observation that 99% of subjects were ADA negative in the first month after ide-cel infusion. No apparent difference was observed in the transgene levels between subjects who were ADA positive and ADA negative through Month 1 post-infusion, while the median transgene level of the ADA positive subjects was considerably lower than that of the ADA negative subjects after Month 5 Day 1 post-infusion. There was no apparent effect of anti-CAR antibody on the safety of ide-cel.

The FDA's Assessment:

FDA agrees with the Applicant's assessment that ide-cel induced anti- CAR antibodies. The presence of anti-CAR antibodies at baseline was not associated with hypersensitivity reaction with ide-cel.

8.2.4 Analysis of Submission-Specific Safety Issues

The Applicant's Position:

No submission-specific safety issues have been identified beyond the ide-cel/Abecma known/established Adverse Reactions and AESIs.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

8.2.5 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:

Not applicable.

The FDA's Assessment:

FDA agrees with the Applicant's assessment that COA does not inform the safety/tolerability for ide-cel.

8.2.6 Safety Analyses by Demographic Subgroups

Data:

Table 65. Applicant - Any Grade Adverse Events ≥ 20% of the Treated Population by Age, Sex, Race, and Region in MM-003

	Ide-cel Arm, N = 250			Standard Regimens Arm, n = 132		
Age Category	**< 65, N = 148**	**65 - 74, N = 90**	**75 - 84, N = 12**	**< 65, N = 72**	**65 - 74, N = 45**	**75 - 84, N = 9**
Total	**147 (99.3)**	**89 (98.9)**	**12 (100.0)**	**70 (97.2)**	**44 (97.8)**	**9 (100.0)**
CRS	115 (77.7)	73 (81.1)	9 (75.0)	0	0	0
Neutropenia	115 (77.7)	71 (78.9)	9 (75.0)	31 (43.1)	21 (46.7)	3 (33.3)
Anaemia	104 (70.3)	52 (57.8)	9 (75.0)	23 (31.9)	17 (37.8)	5 (55.6)
Thrombocytopenia	88 (59.5)	42 (46.7)	6 (50.0)	16 (22.2)	17 (37.8)	3 (33.3)
Nausea	63 (42.6)	42 (46.7)	7 (58.3)	16 (22.2)	16 (35.6)	2 (22.2)
Diarrhoea	46 (31.1)	33 (36.7)	6 (50.0)	15 (20.8)	12 (26.7)	3 (33.3)
Hypokalaemia	42 (28.4)	32 (35.6)	4 (33.3)	7 (9.7)	6 (13.3)	1 (11.1)
Hypophosphataemia	46 (31.1)	28 (31.1)	4 (33.3)	7 (9.7)	2 (4.4)	1 (11.1)
Lymphopenia	45 (30.4)	24 (26.7)	4 (33.3)	12 (16.7)	11 (24.4)	2 (22.2)
Leukopenia	47 (31.8)	20 (22.2)	5 (41.7)	10 (13.9)	4 (8.9)	1 (11.1)
Fatigue	42 (28.4)	24 (26.7)	3 (25.0)	21 (29.2)	20 (44.4)	3 (33.3)
Pyrexia	38 (25.7)	26 (28.9)	5 (41.7)	10 (13.9)	9 (20.0)	3 (33.3)
Hypomagnesaemia	35 (23.6)	13 (14.4)	4 (33.3)	2 (2.8)	2 (4.4)	2 (22.2)
Vomiting	34 (23.0)	15 (16.7)	2 (16.7)	8 (11.1)	2 (4.4)	1 (11.1)
Dyspnoea	28 (18.9)	15 (16.7)	1 (8.3)	12 (16.7)	13 (28.9)	2 (22.2)
Sex	**Male, N = 155**		**Female, N = 95**	**Male, N = 75**		**Female, N = 51**
Total	**154 (99.4)**		**94 (98.9)**	**73 (97.3)**		**50 (98.0)**
CRS	117 (75.5)		80 (84.2)	0		0
Neutropenia	119 (76.8)		76 (80.0)	31 (41.3)		24 (47.1)
Anaemia	92 (59.4)		73 (76.8)	27 (36.0)		18 (35.3)
Thrombocytopenia	76 (49.0)		60 (63.2)	24 (32.0)		12 (23.5)
Nausea	71 (45.8)		41 (43.2)	18 (24.0)		16 (31.4)
Diarrhoea	45 (29.0)		40 (42.1)	18 (24.0)		12 (23.5)
Hypokalaemia	41 (26.5)		37 (38.9)	6 (8.0)		8 (15.7)
Hypophosphataemia	48 (31.0)		30 (31.6)	6 (8.0)		4 (7.8)
Lymphopenia	49 (31.6)		24 (25.3)	15 (20.0)		10 (19.6)
Leukopenia	49 (31.6)		23 (24.2)	10 (13.3)		5 (9.8)
Fatigue	45 (29.0)		24 (25.3)	23 (30.7)		21 (41.2)
Pyrexia	43 (27.7)		26 (27.4)	14 (18.7)		8 (15.7)
Hypomagnesaemia	26 (16.8)		26 (27.4)	3 (4.0)		3 (5.9)
Vomiting	30 (19.4)		21 (22.1)	6 (8.0)		5 (9.8)

Table 65. Applicant - Any Grade Adverse Events ≥ 20% of the Treated Population by Age, Sex, Race, and Region in MM-003

	Ide-cel Arm, N = 250			Standard Regimens Arm, n = 132		
Dyspnoea	22 (14.2)		22 (23.2)	15 (20.0)		12 (23.5)
Race	**White, N = 171**	**African American, N = 18**	**Other/Not Reported,[a] N = 61**	**White, N = 75**	**African American, N = 17**	**Other/Not Reported,[a] N = 34**
Total	**170 (99.4)**	**17 (94.4)**	**49 (80.3)**	**74 (98.7)**	**17 (100.0)**	**32 (94.1)**
CRS	134 (78.4)	14 (77.8)	49 (80.3)	0	0	0
Neutropenia	140 (81.9)	12 (66.7)	43 (70.5)	34 (45.3)	6 (35.3)	15 (44.1)
Anaemia	114 (66.7)	7 (38.9)	44 (72.1)	33 (44.0)	4 (23.5)	8 (23.5)
Thrombocytopenia	99 (57.9)	6 (33.3)	31 (50.8)	24 (32.0)	4 (23.5)	8 (23.5)
Nausea	82 (48.0)	7 (38.9)	23 (37.7)	22 (29.3)	7 (41.2)	5 (14.7)
Diarrhoea	68 (39.8)	5 (27.8)	12 (19.7)	20 (26.7)	3 (17.6)	7 (20.6)
Hypokalaemia	63 (36.8)	5 (27.8)	10 (16.4)	8 (10.7)	3 (17.6)	3 (8.8)
Hypophosphataemia	61 (35.7)	9 (50.0)	8 (13.1)	5 (6.7)	3 (17.6)	2 (5.9)
Lymphopenia	54 (31.6)	1 (5.6)	18 (29.5)	17 (22.7)	4 (23.5)	4 (11.8)
Leukopenia	49 (28.7)	2 (11.1)	12 (19.7)	7 (9.3)	4 (23.5)	4 (11.8)
Fatigue	53 (31.0)	6 (33.3)	10 (16.4)	28 (37.3)	8 (47.1)	8 (23.5)
Pyrexia	55 (32.2)	4 (22.2)	10 (16.4)	18 (24.0)	2 (11.8)	2 (5.9)
Hypomagnesaemia	41 (24.0)	5 (27.8)	6 (9.8)	5 (6.7)	0	1 (2.9)
Vomiting	36 (21.1)	2 (11.1)	18 (29.5)	7 (9.3)	3 (17.6)	1 (2.9)
Dyspnoea	33 (19.3)	2 (11.1)	9 (14.8)	15 (20.0)	4 (23.5)	8 (23.5)
Region	**North America, N = 143**	**Europe, N = 103**	**Japan, N = 4**	**North America, N = 78**	**Europe, N = 43**	**Japan, N = 5**
Total	**141 (98.6)**	**103 (100.0)**	**4 (100.0)**	**77 (98.7)**	**42 (97.7)**	**4 (80.0)**
CRS	110 (76.9)	83 (80.6)	4 (100.0)	0	0	0
Neutropenia	109 (76.2)	83 (80.6)	3 (75.0)	30 (38.5)	23 (53.5)	2 (40.0)
Anaemia	83 (58.0)	78 (75.7)	4 (100.0)	26 (33.3)	19 (44.2)	0
Thrombocytopenia	70 (49.0)	63 (61.2)	3 (75.0)	20 (25.6)	16 (37.2)	0
Nausea	69 (48.3)	42 (40.8)	1 (25.0)	26 (33.3)	8 (18.6)	0
Diarrhoea	53 (37.1)	32 (31.1)	0	23 (29.5)	7 (16.3)	0
Hypokalaemia	54 (37.8)	24 (23.3)	0	10 (12.8)	4 (9.3)	0
Hypophosphataemia	62 (43.4)	16 (15.5)	0	10 (12.8)	0	0
Lymphopenia	38 (26.6)	31 (30.1)	4 (100.0)	17 (21.8)	8 (18.6)	0
Leukopenia	39 (27.3)	30 (29.1)	3 (75.0)	9 (11.5)	6 (14.0)	0
Fatigue	53 (37.1)	16 (15.5)	0	32 (41.0)	12 (27.9)	0
Pyrexia	43 (30.1)	26 (25.2)	0	14 (17.9)	8 (18.6)	0
Hypomagnesaemia	36 (25.2)	16 (15.5)	0	6 (7.7)	0	0
Vomiting	30 (21.0)	19 (18.4)	2 (50.0)	8 (10.3)	3 (7.0)	0
Dyspnoea	31 (21.7)	13 (12.6)	0	17 (21.8)	9 (20.9)	1 (20.0)

[a] Other/Not Reported includes American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, Other, and Not Collected or Reported

Table 66. Applicant - AESIs by Age, Sex, Race, and Region, Ide-cel Arm, Safety Population in MM-003

	Ide-cel Arm, N = 225		
Age Category	**< 65 N = 128**	**65 - 74 N = 85**	**75 - 84 N = 12**
Total	**128 (100.0)**	**85 (100.0)**	**12 (100.0)**
CRS	115 (89.8)	73 (85.9)	9 (75.0)
NT - Broad[a]	66 (51.6)	52 (61.2)	10 (83.3)
NT - Focused[b]	32 (25.0)	35 (41.2)	7 (58.3)
Infections - Overall	67 (52.3)	45 (52.9)	9 (75.0)
Cytopenia - Overall	117 (91.4)	76 (89.4)	10 (83.3)
Cytopenia - Neutropenia	109 (85.2)	68 (80.0)	9 (75.0)
Cytopenia - Thrombocytopenia	74 (57.8)	40 (47.1)	5 (41.7)
New Malignancies	6 (4.7)	7 (8.2)	2 (16.7)
MAS	2 (1.6)	2 (2.4)	1 (8.3)
Autoimmune Disorders	1 (0.8)	0	0
Sex	**Male N = 141**		**Female N = 84**
Total	**141 (100.0)**		**84 (100.0)**
CRS	117 (83.0)		80 (95.2)
NT - Broad[a]	78 (55.3)		50 (59.5)
NT - Focused[b]	49 (34.8)		25 (29.8)
Infections - Overall	77 (54.6)		44 (52.4)
Cytopenia - Overall	123 (87.2)		80 (95.2)
Cytopenia - Neutropenia	113 (80.1)		73 (86.9)
Cytopenia - Thrombocytopenia	69 (48.9)		50 (59.5)
New Malignancies	6 (4.3)		9 (10.7)
MAS	5 (3.5)		0
Autoimmune Disorders	1 (0.7)		0
Race	**White N = 155**	**African American N = 17**	**Other/Not Reported[a] N = 53**
Total	155 (100.0)	17 (100.0)	53 (100.0)
CRS	134 (86.5)	14 (82.4)	49 (92.5)
NT - Broad[b]	104 (67.1)	6 (35.3)	28 (52.8)
NT - Focused[c]	61 (39.4)	3 (17.6)	12 (22.6)
Infections - Overall	81 (52.3)	10 (58.8)	31 (58.5)
Cytopenia - Overall	140 (90.3)	14 (82.4)	50 (94.3)
Cytopenia - Neutropenia	131 (84.5)	12 (70.6)	46 (86.8)
Cytopenia - Thrombocytopenia	86 (55.5)	5 (29.4)	30 (56.6)
New Malignancies	11 (7.1)	1 (5.9)	3 (5.7)
MAS	3 (1.9)	0	2 (3.8)
Autoimmune Disorders	1 (0.6)	0	0
Region	**North America N = 131**	**Europe N = 90**	**Japan N = 4**
Total	**131 (100)**	**90 (100.0)**	**4 (100.0)**
CRS	110 (84.0)	83 (92.2)	4 (100.0)
NT - Broad[a]	88 (67.2)	38 (42.2)	2 (50.0)
NT - Focused[b]	59 (45.0)	13 (14.4)	2 (50.0)
Infections - Overall	63 (48.1)	57 (63.3)	1 (25.0)
Cytopenia - Overall	114 (87.0)	85 (94.4)	4 (100.0)

Table 66. Applicant - AESIs by Age, Sex, Race, and Region, Ide-cel Arm, Safety Population in MM-003

	Ide-cel Arm, N = 225		
Cytopenia - Neutropenia	103 (78.6)	79 (87.8)	4 (100.0)
Cytopenia - Thrombocytopenia	61 (46.6)	55 (61.1)	3 (75.0)
New Malignancies	9 (6.9)	6 (6.7)	0
MAS	3 (2.3)	2 (2.2)	0
Autoimmune Disorders	0	1 (1.1)	0

[a] Other/Not Reported includes American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, Other, and Not Collected or Reported

[b] All PTs within the primary or secondary SOCs of nervous system disorder and psychiatric disorder

[c] Selected PTs of NT events as determined by Sponsor with consideration of biological/pharmacological plausibility for a drug-event relationship, known neurologic toxicities reported with this class of drug and consistent with published guidelines for CAR T encephalopathy, and clinical judgement.

Source: ADSL, ADAE2

The Applicant's Position:

No clinically meaningful differences in AE or AESIs by age or sex were observed; however, results in the 75 - 84 years age subgroup should be interpreted with caution due to the small number of subjects.

Results by race should be interpreted with caution due to the small number of African American subjects (N = 17), but AEs/AESIs are generally consistent across racial subgroups.

Subgroup analyses for ethnicity were not performed as the majority of subjects in the safety population identified as not Hispanic or Latino (74.9%) and the next largest group (20.7%) had ethnicity as not reported (19.7%), mainly due to restrictions in the collection of data in several participating countries.

The FDA's Assessment:

Ide-cel arm: FDA conducted a subgroup analysis for safety in subjects ≥65 years of age compared with <65 years of age for ≥ Grade 3 AESIs. There were insufficient subjects in the ≥75 years subgroup (n=12) to analyze safety for comparison with other subgroups. Out of the 222 subjects in the safety analysis population, 96 (43%) subjects were ≥65 years of age and 126 subjects (57%) were <65 years of age. Compared with subjects who were < 65 years old, subjects who were ≥ 65 years old had similar rates of Grade ≥3 NT, Grade ≥3 CRS, and any grade cytopenia. Rate of ≥Grade 3 infections were numerically higher in ≥65 years age subgroup compared to <65 years (28% versus 14%).The rate of any secondary malignancies was also higher in the ≥65 years subgroup compared to <65 years (9% versus 3.1%).

There are insufficient data to evaluate safety according to race

Given the relatively small sample size in the different age cohorts, small absolute differences and the post hoc nature of these analyses, the reviewer does not recommend including this information in the Section 8.5, "Geriatric Use" of the USPI.

8.2.7 Specific Safety Studies/Clinical Trials

The Applicant's Position:

Not applicable.

The FDA's Assessment:

No specific studies were conducted to evaluate safety concerns.

8.2.8 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

There have been no confirmed T-cell, or other hematologic, vector-mediated malignancies reported/identified, to date.

The FDA's Assessment:

Refer to Section 8.2.1, New Malignancies including Second Primary Malignancies.

Human Reproduction and Pregnancy

The Applicant's Position:

Pregnant or lactating females were excluded from clinical studies based on potential risk to fetus or breastfeeding newborns.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

MM does not occur in pediatric populations. Studies were only conducted in adult subjects, aged 18 years or older.

The FDA's Assessment:

[FDA agrees with the Applicant's assessment.

8.2.9 Safety Data Pooled Across Studies

Data:

Table 67. Applicant - Overall Summary of Safety - Individual and Pooled Studies

Safety Parameter	CRB-401 150 - 450 x 10^6 CAR+ T cells (N = 56)	MM-001 (N = 127)	MM-001 Japan (N = 8)	MM-002 Cohort 1 (N = 68)	MM-002 Cohort 2 (N = 97)	MM-004 (N = 12)	Pooled Data from CRB-401, MM-001, MM-001 Japan, MM-002 Cohort 1 (N = 259)	MM-003 Arm A (N = 222)
Overall number of deaths, n (%)	17 (30.4)	33 (26.0)	2 (25.0)	18 (26.5)	9 (9.3)	1 (8.3)	70 (27.0)	54 (24.3)
Death from malignant disease under study, or complication due to malignant disease under study	13 (23.2)	23 (18.1)	1 (12.5)	11 (16.2)	5 (5.2)	1 (8.3)	48 (18.5)	29 (13.1)
Death from other cause	1 (1.8)	4 (3.1)	1 (12.5)	2 (2.9)	2 (2.1)	0	8 (3.1)	12 (5.4)
Death from adverse event (not otherwise specified)	3 (5.4)	6 (4.7)	0	2 (2.9)	2 (2.1)	0	11 (4.2)	11 (5.0)
Death from second primary malignant disease, or complication due to second primary malignant disease	0	0	0	1 (1.5)	0	0	1 (0.4)	2 (0.9)
Missing	0	0	0	2 (2.9)	0	0	2 (0.8)	0
All-causality, n (%)								
SAEs	42 (75.0)	85 (66.9)	4 (50.0)	33 (48.5)	33 (34.0)	1 (8.3)	164 (63.3)	95 (42.8)
AEs	56 (100)	127 (100)	8 (100)	68 (100)	97 (100)	11 (91.7)	259 (100)	222 (100)
Grade 3-4 AEs	55 (98.2)	126 (99.2)	8 (100)	67 (98.5)	93 (95.9)	10(83.3)	256 (98.8)	206 (92.8)
Treatment-related, n (%)								
SAEs	18 (32.1)	46 (36.2)	2 (25.0)	14 (20.6)	8 (8.2)	1 (8.3)	80 (30.9)	37 (16.7)
AEs	50 (89.3)	124 (97.6)	8 (100)	68 (100)	93 (95.9)	10 (83.3)	250 (96.5)	214 (96.4)
Grade 3-4 AEs	35 (62.5)	87 (68.5)	8 (100)	61 (89.7)	65 (67.0)	7 (58.3)	191 (73.7)	153 (68.9)
AESI (Number of subjects with at least one AESI/Selected AEs), n (%)	56 (100)	127 (100)	8 (100)	68 (100)	97 (100)	11 (91.7)	259 (100)	222 (100)
CRS	42 (75.0)	108 (85.0)	8 (100)	64 (94.1)	74 (76.3)	8 (66.7)	222 (85.7)	194 (87.4)
NT - Focused	49 (87.5)	96 (75.6)	2 (25.0)	43 (63.2)	62 (63.9)	7 (58.3)	190 (73.4)	128 (57.7)
Infections - Overall	42 (75.0)	88 (69.3)	5 (62.5)	39 (57.4)	54 (55.7)	2 (16.7)	174 (67.2)	119 (53.6)

Table 67. Applicant - Overall Summary of Safety - Individual and Pooled Studies

Safety Parameter	CRB-401 150 - 450 x 10^6 CAR+ T cells (N = 56)	MM-001 (N = 127)	MM-001 Japan (N = 8)	MM-002 Cohort 1 (N = 68)	MM-002 Cohort 2 (N = 97)	MM-004 (N = 12)	Pooled Data from CRB-401, MM-001, MM-001 Japan, MM-002 Cohort 1 (N = 259)	MM-003 Arm A (N = 222)
Cytopenia - Overall	52 (92.9)	123 (96.9)	8 (100)	67 (98.5)	91 (93.8)	11 (91.7)	250 (96.5)	200 (90.1)
Neutropenia	52 (92.9)	120 (94.5)	8 (100)	63 (92.6)	88 (90.7)	9 (75.0)	243 (93.8)	183 (82.4)
Thrombocytopenia	42 (75.0)	83 (65.4)	6 (75.0)	43 (63.2)	43 (44.3)	3 (25.0)	174 (67.2)	118 (53.2)
New Malignancies	7 (12.5)	8 (6.3)	0	3 (4.4)	2 (2.1)	1 (8.3)	18 (6.9)	14 (6.3)
MAS	0	4 (3.1)	1 (12.5)	1 (1.5)	0	0	6 (2.3)	5 (2.3)
Autoimmune Disorders	0	0	0	0	0	0	0	1 (0.5)

Coded using MedDRA version 24.1. Graded using CTCAE version 4.03. All deaths after initial ide-cel infusion including deaths after retreatment and maintenance therapy are reported. Primary cause category selected from case report form except for CRB-401 death category was determined by clinical review.
For subjects in studies CRB-401, MM-001, and MM-002 Cohort 1 who received retreatment, only the AEs started before retreatment lymphodepleting chemotherapy are included. For subjects who received maintenance therapy, only the AEs started before maintenance therapy are included.
A subject is counted only once for multiple events within each AESI/Selected AEs category. The PT under AE categories are selected using the protocol specified AESIs, SMQ definitions or MedDRA SOC and PT definitions, and medical judgment. A preferred term may be seen in multiple AESI/Selected AEs categories.
Source: ADSL, ADAE

Table 68. Applicant - Summary of Safety by No. of Prior Antimyeloma Lines of Treatment - Pooled Studies - Safety Population

	Pooled Data from CRB-401, MM-001, MM-001 Japan, MM-002 Cohort 1, and MM-003 Arm A		
	2 and 3 (N = 193)	≥ 4 (N = 288)	Total (N = 481)
All Causality, n (%)			
SAEs	81 (42.0)	178 (61.8)	259 (53.8)
AEs	193 (100)	288 (100)	481 (100)
Grade 3-4 AEs	180 (93.3)	282 (97.9)	462 (96.0)
AESIs (Number of subjects with ≥ 1 AESI/selected AE), n (%)	193 (100)	288 (100)	481 (100)
CRS	165 (85.5)	251 (87.2)	416 (86.5)
NT - Focused	115 (59.6)	203 (70.5)	318 (66.1)
Infections - Overall	102 (52.8)	191 (66.3)	293 (60.9)

	Pooled Data from CRB-401, MM-001, MM-001 Japan, MM-002 Cohort 1, and MM-003 Arm A		
	2 and 3 (N = 193)	≥ 4 (N = 288)	Total (N = 481)
Cytopenia - Overall	176 (91.2)	274 (95.1)	450 (93.6)
Neutropenia	166 (86.0)	260 (90.3)	426 (88.6)
Thrombocytopenia	108 (56.0)	184 (63.9)	292 (60.7)
New Malignancies	7 (3.6)	25 (8.7)	32 (6.7)
MAS	6 (3.1)	5 (1.7)	11 (2.3)
Autoimmune Disorders	1 (0.5)	0	1 (0.2)

Coded using MedDRA version 24.1. Graded using CTCAE version 4.03.
Note: For subjects in studies CRB-401, MM-001, and MM-002 Cohort 1 who received retreatment, only the AEs started before retreatment lymphodepleting chemotherapy are included. For subjects who received maintenance therapy, only the AEs started before maintenance therapy are included.
Source: ADSL, ADAE

Table 69. Applicant - Summary of Safety by Actual Ide-cel Dose Administered - Pooled Studies

	Pooled Data from MM-001, MM-002 Cohort 1, and MM-003 Arm A			
	300 - 460 (x 10^6 CAR+ T Cells) (N = 283)		> 460 - 510 (x 10^6 CAR+ T Cells) (N = 92)	
	Grade 3/4	Grade 5	Grade 3/4	Grade 5
All Causality, n (%)	272 (96.1)	41 (14.5)	85 (92.4)	10 (10.9)
AESIs (Number of subjects with ≥ 1 AESI/selected AE) , n (%)	265 (93.6)	14 (4.9)	84 (91.3)	5 (5.4)
CRS	14 (4.9)	2 (0.7)	7 (7.6)	1 (1.1)
NT - Focused	29 (10.2)	0	9 (9.8)	0
Infections - Overall	61 (21.6)	11 (3.9)	18 (19.6)	4 (4.3)
Cytopenia - Overall	259 (91.5)	0	82 (89.1)	0
Neutropenia	199 (70.3)	0	65 (70.7)	0
Thrombocytopenia	131 (46.3)	0	43 (46.7)	0
New Malignancies	5 (1.8)	0	3 (3.3)	1 (1.1)
MAS	4 (1.4)	0	3 (3.3)	0
Autoimmune Disorders	0	0	0	0

Note: Subjects who received non-conforming ide-cel product are excluded from analysis. For subjects in studies MM-001 and MM-002 Cohort 1 who received retreatment, only the AEs started before retreatment lymphodepleting chemotherapy are included. For subjects who received maintenance therapy, only the AEs started before maintenance therapy are included.
AESI/Selected AEs categories used either MedDRA version 24.1 SMQ or sub-SMQ or SOC or high level term or list of PTs. A subject is counted only once for multiple events within each AESI/Selected AEs category.
Source: ADSL, ADAE

The Applicant's Position:
Pre-planned safety analyses are as follows:

- Individual side-by-side presentation for MM-003 and the 5 studies listed in Table 67 and pooled data from CRB-401, MM-001, MM-001 Japan, and MM-002 Cohort 1

- For selected subgroup analyses, pooled data from the ide-cel arm in MM-003, CRB-401, MM-001, MM-001 Japan, and MM-002 Cohort 1 are presented.

The side-by-side presentation aims to provide comprehensive safety profiles from a broad range of studies, when pooling is not clinically justified due to clinically meaningful differences in subject populations (ie, RRMM and NDMM), various dose levels of ide-cel administered, and different AE data collection schedules in those studies.

To be consistent with the analyses performed in the original BLA, only CRB-401 subjects from the ide-cel target dose range of 150 to 450 x 10^6 CAR+ T cells were included. All ide-cel treated subjects from MM-001, MM-001-Japan, MM-002 Cohort 1 and 2, and MM-004, were included with the following exceptions. Subjects who received non-conforming CAR+ T cell product (ie, not meeting the pre-established product release quality specifications) were excluded from all analyses. For subjects who received ide-cel retreatment (eg, CRB-401, MM-001, and MM-002 Cohort 1), only safety data prior to retreatment were included. For subjects who received maintenance therapy (ie, MM-002 Cohort 2c and MM-004), only safety data prior to maintenance initiation were included. Safety data in long-term follow-up studies LTF-305 and GC-LTFU-001 were incorporated into corresponding parent study for the purposes of these analyses.

Based on the type, frequency, and severity of AEs reported, the safety profile of ide-cel was similar between the ide-cel arm in MM-003 and the pooled studies ().

In the subgroup analyses, based on the assessment of the type, frequency, and severity of AEs reported in pooled studies, the safety profile of ide-cel is similar in the pre-planned analyses across the number of prior antimyeloma lines of treatment received (Table 68), and across the 2 ide-cel dose ranges of 300 to 460 × 10^6 CAR+ T cells and > 460 to 540 × 10^6 CAR+ T cells.

To support the dose range expansion proposal, relevant safety data from Study MM-001 and MM-002 Cohort 1 along with MM-003 ide-cel arm are presented pooled and side-by-side across 2 dose ranges: the current USPI dose range (300 to 460 × 106 CAR+ T cells) and the requested expansion dose group (> 460 to 510 × 106 CAR+ T cells). Based on the assessment of the type, frequency, and severity of AEs reported in pooled studies, the safety profile of ide-cel is similar across ide-cel doses (Table 69). Additional analyses by the 10 x 106 CAR+ T cell dose increments were conducted, and overall, no clear pattern of CRS or iiNT incidence or severity was identified in the ide-cel arm of MM-003 or the pooled studies (Source: ADSL, ADAE).
The experience at the upper end of the dose range for the pooled population supports a proposed upper dose of 510 × 10^6 CAR+ T cells. This is the highest dose administered to a sufficient number of subjects in the pooled population to enable reliable assessment of efficacy (Section 1.4) and safety.

8.2.10 Safety in the Post-market Setting

Safety Concerns Identified Through Post-market Experience

The Applicant's Position:

Routine Pharmacovigilance activities including periodic comprehensive and detailed reviews, as well as ongoing safety surveillance of all safety data/information received, to date, have not identified a significant safety concern that negatively impacted the current benefit-risk balance of ide-cel in currently approved indications.

The identified and potential risks of ide-cel are adequately addressed in the current product labeling, and no additional risk-minimization measures are considered necessary at this time.

The FDA's Assessment:

No new safety issues were identified upon review of the most recent Periodic Safety Update Report.

Expectations on Safety in the Post market Setting

The Applicant's Position:

Based on the safety data reported in the ide-cel arm of MM-003, the safety of ide-cel in the post-marketing setting would be expected to remain consistent with the known safety experience of ide-cel, to date.

The FDA's Assessment:

REMS with Elements to Assure Safe Use (ETASU) will be implemented to ensure safe use in the post marketing setting.

8.2.11 Integrated Assessment of Safety

The Applicant's Position:

In MM-003, ide-cel presented a manageable safety profile consistent with the mechanism of action for CAR T therapy and previous clinical experience. CRS and neurotoxicity were manageable with established guidelines and acceptable in the context of the observed clinical activity. No new clinically important events were identified.

Overall, the safety data reported in the ide-cel arm of MM-003 were consistent with that reported in the original BLA. The safety profile of ide-cel is manageable with no new identified safety concerns. Similar proportions of AESIs, events known to be associated with the therapeutic class of CAR T-cell therapies, including CRS and iiNT, were observed in the RRMM population of MM-003, consistent with the original BLA. Additionally, based on the type, frequency, and severity of AEs reported, the safety profile of ide-cel was similar between the ide-cel arm in MM-003 and pooled studies.

The FDA's Assessment:

[FDA will complete this section.]

The safety analysis set for the ide-cel arm included 222 subjects who received the conformal product and 126 subjects in the SOC arm who received any standard of care therapy. This includes 69 subjects that crossed over and underwent leukapheresis and 60 subjects that received ide-cel upon cross over (including 2 subjects that received non-conformal ide-cel).

Ide-cel arm:

The most common non-laboratory adverse reactions for the ide-cel arm was (incidence ≥20%) included CRS, pyrexia, any infection, febrile neutropenia, hypogammaglobulinemia, musculoskeletal pain, hypotension, fatigue, tachycardia, diarrhea, nausea, headache, encephalopathy, dyspnea, and edema. The most common non-laboratory adverse reactions for the SOC arm (incidence ≥20%) included infection, pyrexia, musculoskeletal pain , fatigue, nausea, CRS, diarrhea, dyspnea, headache, motor dysfunction, edema, febrile neutropenia, hypogammaglobulinemia, sleep disorder, tachycardia, neuropathy, hypertension, encephalopathy, decreased appetite and cough.

The most common (≥ 10%) Grade 3 or 4 non-laboratory adverse reactions for ide-cel arm and SOC arm were febrile neutropenia and infections. The most common (≥10%) Grade 3 or 4 laboratory abnormalities in the ide-cel arm included lymphopenia, leukopenia, neutropenia, thrombocytopenia, anemia, hypophosphatemia, elevated triglycerides , alanine aminotransaminase increased, hyponatremia, and increased GGT. For the SOC arm, the most common (≥10%) Grade 3 or 4 laboratory abnormalities included lymphopenia, leukopenia, neutropenia, thrombocytopenia, anemia , hypophosphatemia, and elevated triglycerides.

Serious adverse events (SAEs) occurred in 95 subjects (43%) in the ide-cel arm and in 71 subjects (56%) in the SOC arm. The most common serious adverse reactions (≥ 5%) included pneumonia, encephalopathy, pyrexia, and sepsis in the ide-cel arm ; in the SOC arm it was pneumonia, sepsis, viral infection, musculoskeletal pain, and general physical deterioration.

Twenty-one subjects (9%) had fatal adverse reaction in the ide-cel arm; causes included CRS, HLH/MAS, infection, sudden cardiac death, myeloid neoplasms, COVID-19, stroke, brain hemorrhage, hemothorax, pancreatic adenocarcinoma and respiratory failure. Ten subjects (8%) had fatal adverse reaction; causes included infection, NT and respiratory failure.

In terms of the AESIs in the ide-cel arm, any grade of CRS occurred in 202 (91%) subjects, and neurologic toxicity occurred in 103 (46%) subjects. Most common Grade 3 or higher AEs of special interest (AESI) included: prolonged neutropenia (87 subjects; 39%), prolonged thrombocytopenia (83 subjects, 37%) infections (45 subjects; 20%), neurologic toxicities (NT) (11 subjects; 5%), and CRS (11 subjects; 5%).

Visual inspection of the Kaplan Meier plot for OS indicated that there were more early deaths occurring in the ide-cel arm compared to the SOC arm. OS in the Kapan-Meier (KM) curve in the first 15 months after randomization was lower in the ide-cel arm with crossing of the OS curves at approximately 15 months. (OS analysis from April 18, 2022 and April 28, 2023 data cut off).

FDA's analysis of deaths that occurred in the first 15 months in the study demonstrated a higher rate of death in the ide-cel arm in the first 9 months post randomization. The death rate in the first 9 months post randomization in the ide-cel arm (45/254; 18%) compared to the SOC arm (15/132; 11%) in the ITT population (N=386). This includes a higher rate of death from

disease progression, any AEs, and unknown causes. Analysis of deaths that occurred within the first 9 months demonstrated that 8% of the patients (20 patients) randomized to the ide-cel arm died without receiving the intended CAR T cell infusion compared to none such patients in the SOC arm. The most common cause of death was disease progression followed by AEs and unknown causes. These deaths were mainly due to disease progression in subjects who were awaiting ide-cel. An inadequately characterized bridging therapy (BT) for the study population, manufacture failures, delays resulting in patient ineligibility, subject withdrawal, and physician decision to not administer ide-cel , all contributed to the patient attrition from randomization to ide-cel infusion. No prognostic factor was associated with a higher early mortality with ide-cel arm since the higher early mortality was observed across multiple prognostic subgroups and was observed even in the absence of poor prognostic factors. The higher rate of early death observed in ide-cel appears to be a frontloaded inherent risk of this therapy.

In the safety analysis population, the rate of deaths from AEs that occurred within 90 days from starting treatment was 2.7% in the ide-cel arm and 1.6 % in the SOC arm. This includes death from CRS, HLH, neurologic toxicity, infections, and stroke in the ide-cel arm.

This risk of higher rate of early death in KarMMa-3 will be included in the Warning and Precautions section of the label which already includes the risk of CRS, NT, HLH/MAS, infections, prolonged cytopenia, secondary malignancies. and hypogammaglobulinemia.

The risk of T cell malignancies has been added to the boxed warning in addition to the risks of CRS, NT, HLH/MAS and prolonged cytopenia. There were no cases of T cell lymphoma in KarMMa-3, however post-marketing cases of T cell neoplasms have been reported with other anti-BCMA and anti-CD19 CAR T products.

During conduct of the KarMMa-3, risk of life-threatening and fatal adverse reactions attributed to ide-cel was mitigated by mandated site and investigator training, careful site selection and monitoring, and instructions for early detection and management of the most serious complications. The life-threatening and fatal adverse reactions warrant warnings, including a boxed warning for CRS and NT, and a REMS with ETASU. The focus of the REMS ETASU is site preparation, patient education, and risk mitigation strategies with emphasis on early recognition and treatment of CRS and NT.

There are inherent limitations with pooling of safety data across studies due to potential differences in patients, disease, and treatment characteristics, differences in sample size and thus the precision of the estimates. These limitations extend to pooling of rates of AESIs, as done in the Warnings and Precautions section of the USPI to inform CRS rates, NT rates, infection rates, and other outcomes. For example, the dose of CAR-T cells, which correlates with the rate and severity of CRS and NT, was generally lower in the KarMMa (median of 315x10e6 CAR+ T cells) compared to KarMMa-3 (median of 445 x10e6 CAR+T cells). Nevertheless, when rates of AESIs are comparable across studies, pooling is helpful for characterizing the general tolerability of the regimen.

Because the most common toxicities were similar between Studies KarMMa (the study that was the basis for approval of ide-cel in RRMM after four or more prior lines of therapy in triple-class exposed population) and KarMMa-3, (the study supporting the current sBLA), the most common adverse reactions (non-laboratory and laboratory) will be presented, in the label, combined for the two studies.

Long-term safety after treatment with ide-cel, particularly from the risk of insertional mutagenesis related secondary malignancies remains a concern due to the limited follow-up duration. The ide-cel study which fulfills the KarMMa PMR (post-marketing requirement study) had the accrual goal of 1,500 RRMM patients. The sample size of the PMR study has been expanded to accrue an additional 200 patients for the expanded indication and/or the expanded dose range for a total of 1700 patients. The ongoing follow up for 15 years will inform about the long-term toxicities in this population.

ISS datasets were not updated to reflect FDA's adjudication of CRS, NT, infections, and the grouped terms for KarMMa. Therefore, ISS datasets were not used to generate the AESI that will be reflected in the label. Instead, the original datasets and the clinical review memo for KarMMa were used to generate the incidence of AEs and added to AEs from KarMMa-3; ide-cel arm to summarize incidence of most frequent AEs in the Highlights Sections and incidence of AESI in Section 5 of the USPI.

The incidence of TEAEs that occurred in ≥20% of the safety population for all subjects KarMMa (n=127) and KarMMa-3; ide-cel arm (n=222) combined are listed below in Table 70.

Table 70. FDA – Most Common AEs in KarMMa and KarMMa-3 Occurring in ≥20% of Safety Population (N=349)

TEAEs	KarMMa N=127	KarMMa-3 N=222	KarMMa, KarMMa-3 N=349
	All Grades n(%)	All Grades n(%)	All Grades n(%)
CRS	108 (85)	202 (91)	310 (89)
Fever	114 (90)	203 (91)	317 (91)
Hypotension	55 (43)	79 (36)	134 (38)
Encephalopathy	33 (26)	49 (22)	82 (23)
Tachycardia	49 (39)	71 (32)	120 (34)
Fatigue	57 (45)	74 (33)	131 (38)
Headache	41 (32)	54 (24)	95 (27)
Febrile neutropenia	29 (23)	113 (51)	142 (41)
Nausea	47 (37)	60 (27)	107 (31)
Infections with pathogen unspecified	65 (51)	78 (35)	143 (41)
Chills	48 (38)	42 (19)	90 (26)
Diarrhea	50 (39)	65 (29)	115 (33)
Musculoskeletal pain	57 (45)	81 (36)	138 (40)
Upper respiratory tract infection	43 (34)	42 (19)	85 (24)
Edema	32 (25)	44 (20)	76 (22)
Dyspnea	16 (13)	46 (21)	62 (18)
Viral infection	34 (27)	40 (18)	74 (21)
Hypogammaglobulinemia	52 (41)	106 (48)	158 (45)

Source: FDA Analysis

Adverse Events of Special Interest:
Incidences of CRS and neurologic toxicity AEs for KarMMa (N=127) and KarMMa-3 (N=222) combined are listed in Table 71. Table 71 also includes the most common symptoms of CRS and NT occurring in ≥10% of patients combined in KarMMa and KarMMa-3 . This information is included in Sections 5.2 and 5.3 of the USPI.
Table 74 includes Grade ≥3 infections, prolonged cytopenia, and hypogammaglobulinemia.

Table 71. FDA – Most Common AESIs for KarMMa and KarMMa-3 (CRS,NT & HLH/MAS)

TEAEs	KarMMa N=127		KarMMa-3 N=222		KarMMa and KarMMa 3 N=349	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Subjects with CRS, n(%)	108 (85)	12 (9)	202 (91)	11 (5)	310 (89)	23 (7)
CRS symptoms, n(%)						
Fever	106 (98)	37 (34)	199 (90)	18 (8)	305 (87)	55 (16)
Hypotension	44 (41)	7 (6)	61 (27)	3 (1)	105 (30)	10 (2.9)
Tachycardia	38 (35)	2 (1.8)	52 (23)	0	90 (26)	2 (0.6)
Chills	33 (31)	0	34 (15)	1 (0.5)	67 (19)	1 (0.3)
Hypoxia	22 (20)	6 (6)	35 (16)	9 (4)	57 (16)	15 (4.3)
Fatigue	13 (12)	0	9 (4)	0	22 (6)	0
Headache	11 (10	0	19 (9)	0	30 (9)	0
Subjects with any NT, n(%)	36 (28)	5 (3.9)	103 (46)	11 (5)	139 (40)	16 (4.6)
NT symptoms, %						
Encephalopathy (GT)	26 (20)	5 (4)	46 (21)	6 (2.7)	72 (21)	11 (3.2)
Headache (GT)	4 (3)	0	49 (22)	0	53 (15)	0
Tremor	12 (9)	0	9 (4)	0	21 (6)	0
Dizziness (GT)	2 (1.6)	0	25 (11)	2 (0.9)	27 (8)	2 (0.6)
Aphasia (GT)	9 (7)	1 (0.8)	6 (2.7)	1 (0.5)	15 (4.3)	2 (0.6)
Delirium (GT)	7 (6)	0	14 (0.6)	1 (0.5)	21 (6)	1 (0.3)
Motor dysfunction (GT)	4 (3)	0	9 (4)	1 (0.5)	13 (3.7)	1 (0.3)
Neuropathy (GT)	0	0	11 (5)	0	11 (3.1)	0
Subjects HLH/MAS, n(%)	5 (4)	2 (1.6)	5 (2)	5 (2)	10 (2.9)	7 (2)

Source: FDA

Table 72. FDA – Onset and Duration of CRS in KarMMa and KarMMa-3

Parameter	KarMMa N=127	KarMMa-3 N=222	KarMMa, KarMMa-3 N=349
Time to onset of CRS Median (Days) Min, Max	 1.0 1, 23	 1.0 1, 27	 1.0 1, 27
Duration of CRS (Including ongoing CRS) Median (Days) Min, Max	108 6.5 1, 63	202 4.0 1, 56	310 5.0 1, 63

Source: FDA analyses and Applicant IR
Duration of CRS = Latest CRS end date - earliest CRS start date + 1.
For fatal CRS events, the end date is the death date.

Table 73. FDA – Onset and Duration of NT in KarMMa and KarMMa-3

Parameter	KarMMa N=127	KarMMa-3 N=222	KarMMa, KarMMa-3 N=349
Time to onset of NT Median (Days) Min, Max	 2.0 1, 42	 3.0 1, 148	 2.0 1, 148
Duration of NT (Including ongoing NT) Median (Days) Min, Max	36 6.0 1, 578	103 9.0 1, 720	310 8.0 1, 720
Time to resolution (Excludes ongoing NT) Median (Days) Min, Max	33 5.0 1, 61	90 5.0 1, 245	123 5.0 1, 245

Source: FDA analyses and Applicant IR
Duration of NT = Latest NT end date - earliest NT start date + 1.
For ongoing NT, end date is imputed with death date for dead subjects and imputed with data cutoff for alive subjects

Table 74. FDA – Most Common AESIs for KarMMa and KarMMa-3 (Infections, Prolonged cytopenia and Hypogammaglobulinemia)

TEAE	KarMMa N=127		KarMMa-3 N=222		KarMMa and KarMMa 3 N=349	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Infections, n(%)	89 (70)	29 (23))	125 (56)	45 (20)	214 (61)	74 (21)
Infections - pathogen unspecified, n(%)	65 (51)	19 (15)	78 (35)	25 (11)	143 (41)	44 (13)
Bacterial infections, n(%)	19 (15)	5 (4)	33 (15)	11 (5)	52 (15)	16 (4.6)
Viral infections, n(%)	34 (27)	12 (9)	40 (18)	14 (6)	74 (21)	26 (7)
Fungal infections, n(%)	10 (8)	1 (0.8)	11 (5)	4 (1.8)	21 (6)	5 (1.4)
Febrile neutropenia, n(%)	20 (16)	20 (16)	113 (51)	113 (51)	133(38)	133(38)
Prolonged cytopenia by lab analysis, n(%)						
Neutropenia, n(%)		52 (41)		87 (39)		139 (40)
Recovered, n(%)		43 (83)		80 (92)		123 (89)
Median time to recovery (range)		1.9 (1.2, 5.6)		1.6 (1.1, 5.6)		1.9 (1.1, 5.6)
Thrombocytopenia%		62 (49)		83 (37)		145 (42)
Recovered, n(%)		40 (65)		70 (84)		110 (76)
Median time to recovery (range)		2.1 (1.2, 9.5)		1.7 (1.1, 9,2)		1.9 (1.1, 9.5)
Hypogammaglobulinemia, n (%)	52 (41)			106 (48)		158 (45)
Based on Lab, n (%)	32 (25)	N/A		98 (44)	N/A	130 (37)
Based on AE, n (%)	27 (21)	1 (0.8)		19 (9)	0	46 (13)

Source: FDA, Prolonged cytopenia is Grade 3-4 neutropenia or thrombocytopenia not resolved by Month 1 following ide-cel infusion

1.Because the most common toxicities are similar in KarMMa and KarMMa -03 , these will be presented combined under the Highlights section and Warning and precautions section of the label.

2. Overall rate of CRS was similar across KarMMa and KarMMa-3 (85% and 91%). The rate of ≥Grade 3 CRS was also similar in KarMMa 3 compared to KarMMa (9% and 5%).

3.Overall rate of all grade NT (28% and 46%) was lower in KarMMa -3 compared to KarMMa. However, the rate of ≥Grade 3 NT was similar across the two studies (4% and 4.9%). This difference in the overall rate of NT may be related to the differences in the study population. In addition, in adjudicating NT in KarMMa, FDA considered the events that occurred in first 60 days from treatment start. Since our understanding of NT has

evolved, we considered neurological events that occurred within 60 days and also considered events that occurred beyond 60 days post-treatment for KarMMa-3.

4.Prolonged cytopenia for the KarMMa and KarMMa-3 are based on analysis of the ADLB dataset. The rate of prolonged thrombocytopenia was lower in KarMMa-3 compared to KarMMa (37% versus 49%) with a higher rate of recovery (84% versus 65%).This difference may be related to the less heavily pre-treated nature of the study population enrolled in KarMMa-3 compared to KarMMa.

5. The overall rate of hypogammaglobulinemia was similar across the two studies

Table 75. FDA –Grade 3 and 4 Laboratory Abnormalities in ≥50% of Safety Population: KarMMa and KarMMa-3

Laboratory Test	Grade 3-4 N=349 n (%)
Leukocyte decreased	336 (96)
Neutrophils decreased	334 (96)
Lymphocytes decreased	333 (95)
Hemoglobin decreased	189 (54)
Platelets decreased	206 (59)
Phosphorus decreased	156 (45)

For the purpose of pooled analyses, the baseline is the last non-missing value prior to LDC
Worsening is defined as a post-baseline abnormality that is at least 1 grade higher than baseline.

The most common Grade 3 and 4 laboratory abnormalities for KarMMa and KarMMa-3 combined will be presented in the highlights section of the USPI. These are included in Table 75 above.

For the dose-toxicity relationship for Grade ≥3 CRS, ≥ Grade 3 NT and Grade 3-4 thrombocytopenia (Refer To FDA section on Adverse Events of Special Interest: CRS, neurologic toxicity and Cytopenia & Prolonged Cytopenia, Section 8.2.3), the pooled analysis from KarMMa and KarMMa-3 is presented in the USPI.

CRS: In the pooled studies, the rate of ≥ Grade 3 CRS was 10% (7/71) for patients treated in dose range of 460 to 510 x 10^6 CAR-positive T cells and 5.4% (13/241) for patients treated in dose range of 300 to 460 x 10^6 CAR-positive T cells. For patients treated in dose range of 460 to 510 x 10^6 CAR-positive T cells, 76% (54/71) of patients received tocilizumab and 35% (25/71) received at least 1 dose of corticosteroids for treatment of CRS. For patients treated in dose range of 300 to 460 x 10^6 CAR-positive T cells, 63% (152/241) of patients received tocilizumab and 20% (49/241) received at least 1 dose of corticosteroid for treatment of CRS.

Neurologic Toxicity: The rate of Grade 3 or 4 CAR T cell-associated neurotoxicity was 5.6% (4/71) and 3.7% (9/241) for patients treated in dose range of 460 to 510 x 10^6 CAR-positive T cells and 300 to 460 x 10^6 CAR-positive T cells, respectively.

Cytopenia: The rate of Grade 3 or 4 thrombocytopenia was 62% (44/71) and 56% (135/241) for

patients treated in dose range of 460 to 510 x 10^6 CAR-positive T cells and 300 to 460 x 10^6 CAR-positive T cells, respectively.

9 SUMMARY AND CONCLUSIONS

9.1Statistical Issues

The FDA's Assessment:

1. Impact of cross-over on overall survival:

   Despite the statistically significant improvement in PFS and ORR, the ide-cel arm did not show improvement over SOC in OS. Based on the most recent updated OS analysis with a cutoff date of April 28, 2023, the two KM OS curves crossed at around 15 months after randomization, with the ide-cel arm having lower survival probability compared with SOC in the first 15 months. There was heavy censoring after the OS crossing point. At the time of the OS analysis , 56% of the subjects in the SOC arm have crossed over to ide-cel arm. The OS results were confounded by the treatment crossover from the SOC to ide-cel upon disease progression.

According to the Statistical Analysis Plan, the primary analysis of OS was the ITT analysis. Two models accounting for treatment crossover were specified as sensitivity analyses, the rank preserving structural failure time (RPSFT) model and the 2-stage accelerated failure time (AFT) model Another post-hoc analysis using the Inverse Probability of Censoring Weighting (IPCW) method was also performed by the Applicant at the request of other regulatory authorities. The RPSFT model assumes common treatment effect, that is, the treatment effect of ide-cel on OS is the same when administered after disease progression on the SOC arm as when administered after initial randomization. This raised a critical question regarding the impact of the treatment on OS when administered after disease progression on SOC arm versus upfront after randomization. Patients who crossed over and received ide-cel cannot be assumed to be similar to the "as randomized" population. They are likely a selected subgroup of patients who met the eligibility criteria to receive ide-cel after disease progression on the SOC arm. Because potential differences in underlying patient and disease characteristics could influence the prognosis of these patients, the "common treatment effect" assumption may not hold, thus limiting the reliability of RPSFT analysis results. The AFT and IPCW approaches both assume that there are no unmeasured confounders at the time of treatment cross-over, in other words, any systematic differences between subjects who cross over and those who do not can be explained by model covariates.

Overall, all three sensitivity analyses demonstrated an estimated HR below 1 but these are based on unverifiable and questionable model assumptions, limiting their interpretability (Refer to the Statistical Review Memo, Dr. Xue Lin, March 26, 2024). Additionally, although each point estimate was less than one after adjusting for treatment crossover, it is notable that the crossing hazards pattern persisted after adjusting for crossover. As a result, the average HRs are not interpretable . There is also considerable uncertainty around the point estimates, reflected by the wide CIs.

2.Duration of the period of increased risk of early mortality in the ide-cel arm compared to the SOC arm:

Kaplan Meier plot for OS represents a crossing of the curves which indicates that the treatment effect constancy assumption cannot be made (i.e., there is none proportional hazards). In this scenario, average HR is an unreliable summary statistic to quantify the treatment effect. Piecewise Hazard ratio assessment can aid in estimating treatment effect at set time intervals in the setting of non-proportional hazards. Based on this assessment, and on a numeric assessment of death rate by time: 3-month intervals, there appears to be an increased risk of death extending to at least 9 months in KarMMa 3. (Refer to the Appendix for Piecewise Hazard Ratio Assessment, ITT population and Deaths by Time Intervals from Randomization, ITT population.

In summary, the statistical review team did not recommend approval given the early OS detriment and confounded interpretation of OS analysis.

9.2 Conclusions and Recommendations

The FDA's Assessment:

The benefit-risk assessment for ide-cel in the indicated population is primarily based on the results of KarMMa-3, a Phase 3, randomized (2:1), open-label, multicenter study. A total of 386 patients with relapsed and refractory MM after two to four prior lines of therapy including a PI , an IMiD and anti-CD38 monoclonal antibody and refractory to the last line of therapy were enrolled. The primary efficacy endpoint is progression free survival (PFS) as determined by a blinded (IRC) using the international myeloma working group (IMWG) 2016 criteria. Key secondary efficacy outcome measures in hierarchical testing order are overall response rate (ORR) and overall survival (OS).

KarMMa-3 demonstrated a statistically significant and clinically meaningful improvement in PFS for ide-cel compared to standard of care (SOC) (Hazard ratio (HR) was 0.495 [95% confidence interval (CI): 0.379, 0.647]; p-value <0.0001). Median PFS was 13.3 months in the ide-cel arm (95% CI: 11.8, 16.1), and was 4.4 months (95% CI: 3.4, 5.9) in the SOC arm. The IRC-assessed ORR rate was statistically significant; 71% (95% CI: 66, 77) in the ide-cel arm compared to 42% (95% CI: 33, 50) in the SOC arm. Similarly, the overall complete response rate (sCR +CR rate)

was higher at 39% (95% CI:33, 45) in the ide-cel cel arm compared to 5% (95% CI: 1.5, 9.1) in the SOC arm. At the time of the primary analysis of PFS, OS was immature (information fraction of 49%); FDA considered ide-cel's effects on OS as part of the safety assessment. Results from the second interim OS analysis (74% IF) done at the time of the final PFS analysis with more mature OS data and an additional one year of follow-up were consistent with the first interim OS analysis with persistent OS detriment for approximately 15 months after randomization (April 28, 2023 data cut off).

Sixty-nine subjects (31%) in the ide-cel treated population received a dose of >460 -510 x10e6 CAR+ T cells which is the dose expansion requested in the sBLA. The median PFS and ORR per IRC assessment in this dose cohort was similar to the that of the approved ide-cel dose cohort of 300-460 x10e6 CAR+ T cells and to the overall ide-cel arm. Overall, the extension of the dose range has been assessed to be acceptable for approval given the variability in manufacturing of a biological product and data to support efficacy.

The rate of adverse reactions of ide-cel was similar to prior studies, including the rate of the serious risks such as CRS, NT,HLH/macrophage activation syndrome (MAS), prolonged cytopenia and infections. However, in KarMMa-3, a signal of increased early deaths was observed in patients randomized to ide-cel compared to patients randomized to SOC arm. Specifically, a higher proportion of patient randomized to ide-cel compared to SOC experienced death in with first 9 months following randomization (n=45/254;18% vs. n=15/132;11%). The higher early mortality with ide-cel was observed across multiple prognostic subgroups and was observed even in the absence of individual poor prognostic factors. In the safety analysis population, there was also a higher rate of fatal adverse reaction that occurred within 90 days from starting treatment with ide-cel arm compared to the SOC arm (2.7% versus 1.6%).

No new safety signals were identified in this submission. The safety of ide-cel was consistent with its established safety profile. All patients in the ide-cell arm experienced at least one treatment emergent adverse event (TEAE). The rate of Grade 3 and Grade 4 AEs was 18% and 64% in the ide-cel arm. The most common (≥5%) Grade 3-4 TEAEs in the ide-cel arm were febrile neutropenia (51%), infection (16%), fever (9%), hypertension (7%), hypoxia (6%), and renal failure (5%). Any grade of CRS occurred in 202 (91%) subjects, and neurologic toxicity occurred in 103 (46%) subjects. Most common Grade 3 or higher adverse events of special interest (AESI) included: prolonged neutropenia (87 subjects; 39%), prolonged thrombocytopenia (83 subjects, 37%) infections (45 subjects; 20%), neurologic toxicities (NT) (11 subjects; 5%), and CRS (11 subjects; 5%).The rate of death from AEs was 9% in the ide-cel arm compared to 8% in the SOC arm.

Due to the lack of long-term safety data in the sBLA, a post-marketing long-term follow-up registry study to fulfil the KarMMa-3 post-marketing requirement of 1500 RRMM patients is ongoing. The Applicant has voluntarily expanded the study to enroll an additional 200 patients

to encompass the expanded indication and/or dose range for a total of 1700 patients. Follow up of patients for 15 years in this study will provide long-term safety data.

The following measures have been implemented for risk mitigation:

- Early mortality observed with KarMMa-3 has been added to Section 5.1, Warning and Precautions.
- The product label includes a boxed warning for CRS and NT, and the warnings and precautions section conveys the treatment algorithm for CRS and NT management.
- Daily monitoring following ide-cel infusion for 7 days (Section 2.2, Administration, USPI).
- REMS with ETASU to assure the safe use of ide-cel.

In conclusion, KarMMa-3 provides substantial evidence of the effectiveness of ide-cel for patients with RRMM after two to four prior lines of therapy, including a PI, an immunomodulatory agent (IMiD) and anti-CD38 monoclonal antibody and refractory to last line of therapy. KarMMa-3 demonstrates clinical benefit through clinically meaningful improvements in PFS, ORR , CR rate and the potential for durable duration of response in the proposed patient population with a single administration without the need for continuous therapy. The most common serious risks of ide-cel have been characterized and are mitigated through product labeling and a Risk Evaluation and Mitigation Strategies (REMS). The observed higher rate of early death observed in KarMMa-3 does not have a clear etiology but as discussed in the ODAC, may represent the risks associated with the treatment and its administration. KarMMa-3 was not designed to provide definitive information on how this risk can be mitigated. Treatment with ide-cel may require careful consideration of individual patient characteristics, disease characteristics, the therapeutic context among other factors. The risk of increased early mortality with ide-cel will be included under Warning and Precautions section of the USPI. The ODAC members assessed the risks acceptable in the indicated population.

The clinical review team recommends traditional approval of ide-cel for the treatment of adult patients with RRMM who have received at least two prior lines of therapy, including a PI, an IMiD, and an anti-CD 38 monoclonal antibody. The clinical review team recommends approval of the proposed dose range of 300-510 x 10e6 CAR+ T cells. The recommendation for approval is based on demonstration of substantial evidence of effectiveness based on data from the Phase 3 KarMMa-3 study, in the context of an acceptable risk profile.

X X

Primary Clinical Reviewer Clinical Team Leader

10 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

FDA convened a meeting of the Oncologic Drugs Advisory Committee (ODAC) to discuss the benefits and risks of treatment with ABEMCA in the indicated population. In particular, FDA was interested in the Committee's opinion regarding the higher rate of early deaths in the ide-cel arm, in the context of a statistically significant PFS benefit in the KarMMa-3 trial.

On March 15, 2023, the ODAC considered the results of KarMMa-3 and discussed the following questions:

The main discussion questions for the ODAC were as follows:

- Issue #1: Discuss whether the results of KarMMa-3 are sufficient to support a positive risk-benefit assessment of ide-cel for the proposed indication.
- Issue #2: Is the risk of early death associated with ide-cel treatment acceptable in the context of the PFS benefit?

The results of the voting questions are as follows:

- Voting Question: Is the risk-benefit assessment for ide-cel for the proposed indication, favorable?
  Yes -8. No-3.
  The committee vote affirmed that ide-cel has a favorable risk-benefit assessment in the intended population.
  Bridging Therapy: The discussion highlighted some of the concerns regarding BT which may have not been well characterized for the study population. Therefore, the inadequacy of BT and breaks built into the ide-cel arm given the apheresis and manufacture resulting in treatment-free period may have contributed to disease progression and early deaths. However, the committee recognized that despite these speculations, the exact cause of the early OS detriment observed in KarMMa-3 is not well understood. The committee identified the need for optimization of BT for CAR T

cell therapy. Some of panel members stated that BT was constrained in KarMMa-3 and it could be individualized based on the clinical context in the real-world setting.

PFS benefit: The committee determined that the treatment-free PFS benefit with a single infusion of ide-cel without maintenance or continuous therapy was of clinical benefit for the triple class exposed MM population. The committee noted that the PFS curves separate but the benefit with ide-cel is not durable as there is no plateau in the ide-cel arm.

OS data: The committee noted that despite the PFS improvement, no OS advantage was observed with earlier treatment with ide-cel. The committee highlighted the possibility that crossing over of the OS curves could be due to a higher rate of early deaths in the SOC arm upon cross-over to ide-cel arm similar to the early OS detriment observed in the ide-cel arm. The committee stated that cross-over of 56% of the SOC arm subjects to the ide-cel arm confounded the interpretation of the OS data. However, a cross-over study design in an unmet need MM population is a patient-centric study design. The early OS detriment represents the upfront risk associated with ide-cel. The committee also opined that the median OS survival for both the arms appears to be improved compared to the historical data for a triple class exposed population after 2-4 prior lines of therapy.

11 Pediatrics

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Pediatric subjects have not been included in any study of ide-cel. In addition, ide-cel was granted Orphan Drug Designation (ODD) on May 11, 2016 for the treatment of MM. Since this is an sBLA, FDARA Title V which eliminates orphan exemption for pediatric studies for NME directed at relevant molecular targets does not apply. Therefore, submission of a pediatric assessment is not required for this submission.

12 Labeling Recommendations

Data:

Table 76. FDA – Summary of Significant Labeling Changes (High Level Changes and Not Direct Quotations)

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
1. Indications and Usage	ABECMA is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody	ABECMA is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma after two or more prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody
2. Dosage and Administration	Revised the recommended dose range from 300 - 460 x 10^6 to 300 - 510 x 10^6 CAR-positive T cells.	FDA agrees with the recommended dose of 300-510x10e6 CAR+ T cells supported by safety and efficacy data from KarMMa-3
5. Warnings and Precautions	Revised sections 5.1, 5.2, 5.3, 5.6, 5.7, and 5.8 to add MM-003 clinical data.	Added risk of early mortality associated with ide-cel observed in KarMMa-3 under Section 5.1. 5.10 was updated to include safety-related labeling change language for the serious risk of T-cell malignancies with serious outcomes. Section 14 (OS KM curves) is cross-referenced to Section 5.1
6.1 Clinical Trial Experience		This section includes ADRs, and laboratory abnormalities observed in KarMMa-3 based on FDA's adjudication of AEs, and FDA's grouped terms. Section 14 (OS KM curves) is cross-referenced to Section 6.0
14.2 Clinical Studies		This section is updated to include efficacy data from KarMMa-3
Medication Guide		Updated to include risk of early mortality associated with ide-cel observed in KarMMa-3 . OS KM curves are included. PRO data and MRD data from KarMMa-3 has not been included in the USPI.
Boxed Warning		Updated to include the safety related labeling change language for T-cell malignancies with Abecma

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
6.2 Post marketing section		Section is added to inform prescribers that T cell malignancies have been reported with anti-BCMA and anti-CD19 CAR T products in the post-marketing section

The Applicant's Position:

The clinical data provided in this s BLA demonstrate the clinical benefit and safety of the use of ide-cel for the treatment of adult patients with relapsed or refractory multiple myeloma who have received an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.

The FDA's Assessment:

Labeling negotiations are ongoing at the time of the completion of the Assessment Aid. Key changes to the USPI are summarized below:

1. Revised Indication: The Applicant has sought a broad indication statement for the treatment of patients with RRMM who have received an IMiD, a PI , an anti-CD38 monoclonal antibody which is not reflective of the population evaluated in KarMMa-3. The indication statement is updated to reflect the population in which the benefit-risk was evaluated and is favorable in KarMMa-3; adult patients with RRMM after two or more prior lines of therapy including an immunomodulatory agent, a PI, and an anti-CD38 monoclonal antibody.

2. Addition of Early Mortality to Section 5.1 of the USPI: The risk of early death with ide-cel is incorporated under Section 5.1, Warning and Precautions, Section 17; Patient Counseling Information and the Medication Guide.

3. Update to CAR T cell therapy class SLC under 125736/218:

   The applicant agreed to implement the CAR –T cell therapy class safety labeling change to include the language "T cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T cell immunotherapies, including ABECMA" as a Boxed Warning and in Section 5 Warnings and Precautions. The ABECMA USPI was updated to include new safety information on the serious risk of T cell malignancies in the following sections: Boxed Warning, Warnings and Precautions (5.8), Post-marketing Experience (6.3), Patient Counseling Information (17), and Medication Guide.

13 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

Negotiations between the OBPV review team and the Applicant are ongoing at the time of this review. Refer to OBPV review for details of the major REMS modification submissions.

ABECMA REMS modification to minimize burden on the health care delivery system:

In accordance with section 505-1(g)(4)(B) of the Federal Food, Drug, and Cosmetic Act, FDA made the determination that the approved REMS for the BCMA- or CD19-directed genetically modified autologous T cell immunotherapies product class, including ABECMA, must be modified to minimize the burden on the healthcare delivery system of complying with the REMS. As part of the above CAR-T cell therapy class REMS modification, the REMS goal of "Ensuring that those who prescribe, dispense, or administer [product] are aware of how to manage the risks of CRS and neurologic toxicities" was removed from the ABECMA REMS. Please see the OBPV Risk Evaluation and Mitigation Strategies (REMS) Modification Memorandum under 125736/218 (dated February 23, 2024) for the rationale for this decision.

14 Post-marketing Requirements and Commitment

The ide-cel registry protocol MM-005 titled "Registry study of patients with multiple myeloma (MM) treated with ide-cel (ide-cel, bb2121)" was originally submitted to Biologics License Application 125736 to fulfill the KarMMa PMR requirement.
The primary objective of the study is to characterize the incidence and severity of selected AEs including secondary malignancy, Grade ≥3 CRS and NT, prolonged cytopenia, pregnancy outcome in patients treated with ide-cel and to monitor for additional clinically important events that have not yet been identified as part of ide-cel safety profile. The secondary objective is to assess survival in patients treated with ide-cel. Patients with RRMM who are treated in the PMR setting with ide-cel within the approved indication and dose range per the US prescribing information are eligible for the study. In addition, patients enrolled in the ide-cel interventional clinical trials and treated with ide-cel within the approved indication and dose range per the USPI are eligible for enrollment.
Study participants will be followed for 15 years. The original accrual goal of 1,500 RRMM patients for this study has been amended to add 200 additional subjects who receive ide-cel as an earlier line treatment under the current expanded indication and/or the expanded dose range. The planned final study report submission is by June 30, 2042.

15 Chief, Clinical Hematology Branch

X

16 Oncology Center of Excellence (OCE)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

17 Division Director (DCEPT)

X

18 Appendices

Table 77. FDA – FDA Adjudicated New Subjects with CRS in ide-cel Arm

USUBJID	CRS Duration:	CRS Symptoms	CRS Grade	Oxygen Y/N	Vasopressors Y/N	Concurrent end organ dysfunction Y/N
(b) (6)	Day 1-2	Fever	1	No	No	No
	Day 2-7	Fever, hypotension	2	No	No	No
	Day 3-4	Fever	1	No	No	No
	Day 1-2	Fever, chills	1	No	No	No
	Day 27-28	Fever	2	Yes Fio2=28%	No	No
	Day 1-2	Fever	1	No	No	No
	Day 3-7	Fever	1	No	No	No
	Day 1-4	Fever	1	No	No	No

Source: FDA analysis

Table 78. FDA – FDA Adjudicated CRS Duration in ide-cel Arm

USUBJID	Applicant's assessment	Re-adjudicated duration/grade Treatment day	Grade on re-adjudicated days	Reason
(b) (6)	Gd 1 Day 1-2 Gd 2 Day 2-5 Duration 1-5	Gd 2 Day 6	Grade 2	Oxygen use 1-2L/mt. on day 6 per ADCM. Overall duration increased to Day 1-6
(b) (6)	Gd 1 Day 1-2	Gd 1 Day 3	Grade 1	Tocilizumab given on Day 3. Duration increased to Day 1-3.
(b) (6)	Gd 1 Day 1 Gd 2 Day 2- 4 Gd 3 Day 5	Gd 2 Day 6-8	Grade 2	Oxygen use of 2-3 L/mt. on Day 6-8.

Source: FDA analysis

Table 79. FDA – Second Primary Malignancies in Ide-cel Arm, KarMMa 3

Malignancy	N=222
Acute myeloid leukemia	1
Myelodysplastic syndrome	4
Breast cancer	2
Malignant melanoma	2

Malignancy	N=222
Rectal adenocarcinoma	1
Pancreatic adenocarcinoma	1
Basal cell carcinoma*	2
Squamous cell carcinoma of skin*	1
Squamous cell carcinoma of thoracic wall	1
Squamous cell carcinoma of skin in situ	1
Total	15

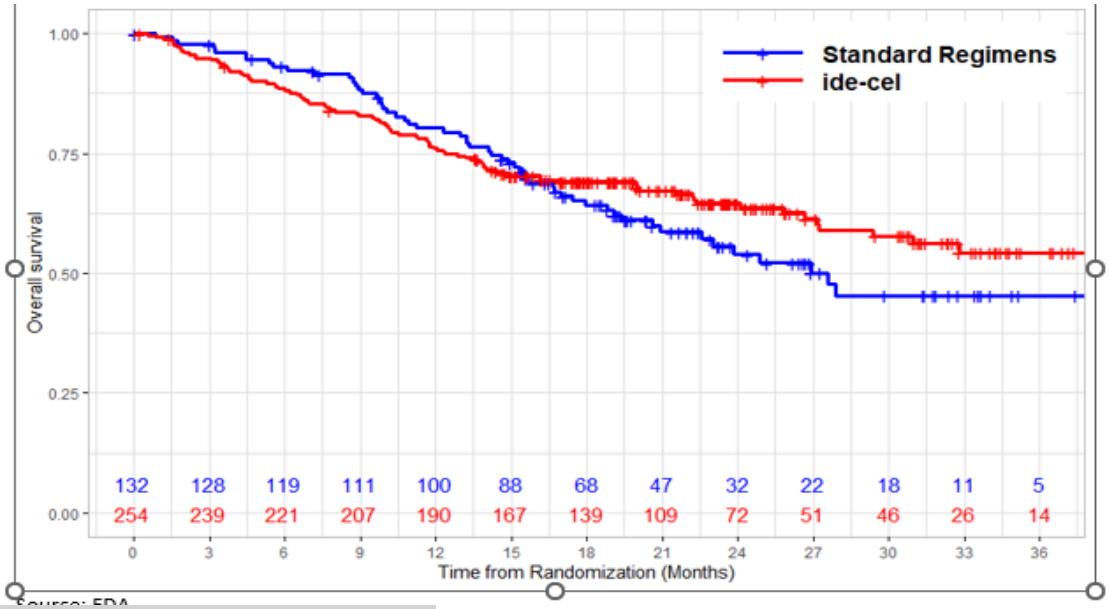
Source: FDA analysis
Data cutoff October 3, 2022 (safety update)
*One subject developed both squamous cell carcinoma and basal cell carcinoma is included under both categories
The table does not include one subject who received nonconformal ide-cel and developed renal cell carcinoma

Table 80. FDA – Second Primary Malignancies in SOC Arm, KarMMa 3

Malignancy	N=126
Developed prior to ide-cel	
Metastatic bronchial carcinoma	1
Lentigo maligna	1
GI stromal tumor	1
Developed after ide-cel infusion	
Metastatic squamous cell carcinoma skin (ear)	1
Squamous cell carcinoma of skin	1
Metastatic carcinoma of unknown primary	1
Total	6

Source: FDA analysis
Data cutoff October 3, 2022.(Safety update)

Figure 13. FDA – Overall Survival, ITT Population, Post-hoc Analysis



Source: FDA analysis; Data cutoff=October 3, 2022

Table 81. FDA – Exploratory Analyses for Early Mortality, Prognostic Factors

Prognostic Factor	ide-cel (N=254) %	SOC (N=132) %
Extramedullary plasmacytoma		
Present	7	3.8
Absent	10	8
Revised ISS Stage		
Stage III	4.7	1.5
Stage I/II	13	9
Cytogenetics		
High-risk	11	5
Absent high-risk	6	3.8
Age (years)		
>/=65	7	3.8
<65	11	8
ECOG performance status		
>/=1	12	8
0	6	3
Lines of therapy		
2	3.9	4.5
3-4	14	7
Triple-class refractory		

Prognostic Factor	ide-cel (N=254) %	SOC (N=132) %
Yes	15	9.8
No	2.4	1.5

Source: FDA analyses

Table 82. FDA – Fatal Adverse Reactions in ide-cel Arm at Final PFS Analysis

USUBJID	Dose (10e6 CAR +cells)	Fatal AR	Therapy Day of Death	PD	AMT
(b) (6)	422	Cytokine release syndrome	6	No	No
	498.6	Candidiasis, CRS, HLH/MAS	21	No	No
	459	Sepsis	39	No	No
	377	Neurotoxicity	43	No	No
	505	Pneumogenic sepsis	62	No	No
	431	Stroke in the setting of atrial fibrillation	64	No	No
	407	Sudden death	97	PD	No
	184	Hypoxic respiratory failure	135	Yes	Yes
	395	Sepsis	187	No	No
	421	Sepsis	192	No	No
	441	Sepsis	218	Yes	Yes
	406	COVID 19 infection	245	No	No
	476	COVID 19 infection	275	No	No
	462	Respiratory failure, Serratia marcescens bacteremia	280	Yes	Yes
	391	Heart failure from coronary artery dissection	296	Yes	Yes
	418	Multifocal pneumonia	301	No	No
	467	Acute myeloid leukemia, pulmonary abscess	325	No	No
	501	Sepsis	328	Yes	No
	480	Brain hemorrhage s/p allogeneic SCT, grade 3 thrombocytopenia	372	Yes	Yes
	395	Right hemothorax with active hemorrhage	386	Yes	Yes
	525	Bronchopulmonary aspergillosis in setting of MDS on azacytidine	432	No	No
	378	Refractory shock	625	Yes	Yes
	494	Septic shock	734	Yes	Yes
	454	Pancreatic adenocarcinoma	906	No	No

Source: FDA, Deaths that were not reported at the primary PFS analysis but at the Final PFS analysis are highlighted in red. PD: disease progression
AMT: subsequent anti-myeloma therapy

Table 83. FDA – Fatal Adverse Reactions in SOC Arm, Final PFS Analysis

USUBJID	Cause of Death	Therapy Day of Death from Rx start	PD	AMT	Ide-cel on cross-over
(b) (6)	E coli Sepsis	23	No	Yes	No
	Respiratory failure	46	No	No	No
	Sepsis	131	Yes	Yes	No
	Multiple organ failure (pseudomonal sepsis)	180	Yes	No	No
	Neurotoxicity	215	Yes	Yes	Yes
	COVID 19	266	Yes	Yes	No
	Neutropenic sepsis	383	No	No	No
	Sepsis	398	Yes	Yes	Yes
	Sepsis	429	Yes	Yes	Yes
	COVID 19	438	No	No	No
	Poorly differentiated carcinoma of unknown primary	505	Yes	Yes	Yes
	Acute respiratory failure	751	No	No	No

Source: FDA, Deaths that were not reported at the primary PFS analysis but at the Final PFS analysis are highlighted in red

Table 84. FDA – Deaths from Fatal Adverse Reactions in SOC arm after cross over and ide-cel (Primary PFS Analysis)

USUBJID	Dose of CAR +T cells 10e6	Cause of Death	Therapy Day of Death after Ide-cel	PD after ide-cel *	AMT after ide-cel
(b) (6)	521	Neurotoxicity	61	No	No
	461	Sepsis	130	Yes	No
	524	Sepsis	133	Yes	Yes
	430	Poorly differentiated carcinoma unknown primary	307	Yes	Yes

Source: FDA, Deaths that were not reported at the primary PFS analysis but at the Final PFS analysis are highlighted in red

Table 85. FDA – Table of Events: Treatment Arm: ide-cel

Table 3: Table of Events: Treatment Arm A (Continued)

	Screening Period			Treatment Period		PFS Follow-up Period (28-day month)								Follow-up Period	
	Screening	Leukapheresis[a]	Baseline[b]	LD Chemotherapy[c]	bb2121 infusion[d]	M1			M2-M6	M7-M12	M13-M24	≥ M25 every 3 months	PFS discon[e] ≤7 days from PD or discon decision	28 days after PFS Discon	SFU every 3 months
	-28 to randomization			D-5 D-4 D-3	D1	D2-8	D9-15	D18 D22 D25	D1	D1	D1	D1			
Visit Window (Days)					+7			±1	±2	±3	±3	±3		+3	±14
Prior/concomitant medication and procedures evaluation	X (-28 days from screening)	Continuously for minimum of 6 months post bb2121 infusion (through M6)								Concomitant medications associated with Grade ≥ 3 AEs, all SAEs and all AESIs will be collected continuously from M7 until 28 days after PFS Discontinuation Visit					X[ff]
SAFETY ASSESSMENTS															
AE (including AESI) evaluation[f]	All AEs will be collected continuously from informed consent signature (for AESI from bb2121 infusion) for minimum of 6 months post bb2121 infusion (through M6)									Grade ≥ 3 AEs, all SAEs and all AESI will be collected from M7 until 28 days after PFS Discontinuation Visit					X[ff]
Monitoring for SPMs	-	-	-	-	Continuous from bb2121 infusion										X[ff]
Tumor biopsy	-	-	-	-	Will be requested if subject develops a SPM while enrolled in this study, the Sponsor may request a sample of the neoplastic tissue for safety and efficacy analysis of the bb2121 cells										X[ff]
Physical examination	X	X	X	-	Daily			D22	X M2D15[gg] M3D15[gg]	X	X	X	X	-	X[ff]
Routine neurologic examination	X	X	X	-	Daily			D22	X	X	X	X	X	-	-
Vital signs[g]	X	X	X	-	Daily[h]			D22	X	X	X	X	X	X	-
Height	X	-	-	-	-			-	-	-	-	-	-	-	-

Table 3: Table of Events: Treatment Arm A (Continued)

	Screening Period			Treatment Period		PFS Follow-up Period (28-day month)								Follow-up Period	
	Screening	Leukapheresis[a]	Baseline[b]	LD Chemotherapy[c]	bb2121 infusion[d]	M1			M2-M6	M7-M12	M13-M24	≥ M25 every 3 months	PFS discon[e] ≤7 days from PD or discon decision	28 days after PFS Discon	SFU every 3 months
	-28 to randomization			D-5 D-4 D-3	D1	D2-8	D9-15	D18 D22 D25	D1	D1	D1	D1			
Visit Window (Days)					+7			±1	±2	±3	±3	±3		+3	±14
Weight	X	X	X	-	Daily			X	X	X	X	X	X	X	-
MMSE	-	-	X	-	-	Every other day[i]		X	M2 M4	-	-	-	-	-	-
Hematology	X	X	X	-	Daily[k]			X[k]	X M2D15[gg] M3D15[gg]	X	X	X	X	X	X[ff]
Chemistry	X	X	X	-	Daily[k]			X[k]	X M2D15[gg] M3D15[gg]	X	X	X	X	X	X[ff]
Coagulation parameters	X	-	X	-	Daily[k]			X[k]	X	X	X	X	X	-	-
CRS[j]	-	-	X	-	Daily[k]			X[k]	M2	-	-	-	-	-	-
Renal function (CrCl)	X	X	X	-	Daily[k]			X[k]	X	X	X	X	X	X	-
Temperature monitoring	-	-	-	-	Daily every 6-8 hrs			Daily every 6-8 hrs[j]	-	-	-	-	-	-	-
Lymphocyte subset panel[m]	-	X	X	-	X[m]	-	-	-	X	M7	-	-	-	-	-

Table 3: Table of Events: Treatment Arm A (Continued)

	Screening Period			Treatment Period		PFS Follow-up Period (28-day month)								Follow-up Period	
	Screening	Leukapheresis[a]	Baseline[b]	LD Chemotherapy[c]	bb2121 infusion[d]	M1			M2-M6	M7-M12	M13-M24	≥ M25 every 3 months	PFS discon[e] ≤7 days from PD or discon decision	28 days after PFS Discon	SFU every 3 months
	-28 to randomization			D-5 D-4 D-3	D1	D2-8	D9-15	D18 D22 D25	D1	D1	D1	D1			
Visit Window (Days)					+7			±1	±2	±3	±3	±3		+3	±14
Assessment of response (IMWG Uniform Response Criteria)[g]	-	-	X	-	-	-	-	-	X	X	X	X	X	-	-
Serum and urine protein electrophoresis	X	X	X	-	-	-	-	-	X	X	X	X	X	-	-
Serum and urine immunofixation	X	X	X	-	-	-	-	-	X	X	X	X	X	-	-
Serum free light chains assay	X	X	X	-	-	-	-	-	X	X	X	X	X	-	-
Quantitative serum immunoglobulin	X	X	X	-	-	-	-	-	X	X	X	X	X	-	-
Beta-2 microglobulin	X	X	X	-	-	-	-	-	X	X	X	X	X	-	-
EMP clinical assessment	X	X	X	-	-	-	-	-	X	X	X	X	X	-	-
EMP radiological assessment (only required if history of or clinical indication of EMPs only assessable radiographically)[f]	X	-	X[w]	-	-	-	-	-	Day 1 starting at M3, then every 3 months thereafter					-	-

Table 3: Table of Events: Treatment Arm A (Continued)

	Screening Period			Treatment Period		PFS Follow-up Period (28-day month)								Follow-up Period	
	Screening	Leukapheresis[a]	Baseline[b]	LD Chemotherapy[c]	bb2121 infusion[d]	M1			M2-M6	M7-M12	M13-M24	≥ M25 every 3 months	PFS discon[e] ≤7 days from PD or discon decision	28 days after PFS Discon	SFU every 3 months
	-28 to randomization			D-5 D-4 D-3	D1	D2-8	D9-15	D18 D22 D25	D1	D1	D1	D1			
Visit Window (Days)					+7			±1	±2	±3	±3	±3		+3	±14
BNP	-	-	X	-	-	-	-	-	-	-	-	-	-	-	-
ECHO/MUGA	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
12-lead ECG	X	-	X	-	-	-	-	-	M6	-	-	-	X	-	-
Hepatitis and HIV testing[n]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HBV DNA/HCV RNA testing[o]	-	-	-	-	-	-	-	-	-	M7	M13 M19	M25	X	-	-
Urinalysis	X	If clinically indicated											X	-	-
Pregnancy test (minimum sensitivity 25 mIU/mL) for FCBP[hh]	-10 to -14 days	-	X[p]	-	-	-	-	D25	M4	-	M13	-	-	-	-
Pregnancy counseling[ii]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
EFFICACY AND OTHER ASSESSMENTS															
ECOG Performance status	X	X	X	-	X	D8	D15	D22	X	X	X	X	X	-	-

Source: Clinical Protocol, BLA 124736/218

Table 86 FDA – Table of Events: Treatment Arm :SOC

Table 4: Table of Events: Treatment Arm B (DPd, IRd, Kd or EPd) (Continued)

	Screening Period	Treatment Period						Follow-up Period				
		M1-2		M3-6	M7-24	≥ M25 every 3 months	EOT (≤ 7 days from trt discon decision)	28 days after EOT[b]	PFS FU every month[c]	PFS FU discon	28 days after PFS FU discon	SFU every 3 months
	-28 to Random-ization	D1[a]	D8, D15, D22	D1, D15	D1	D1						
Visit Window (Days)		±3	±3	±3	±3	±3		+3	±3	±3	+3	±14
Monitoring for SPMs	-	Continuous from the start of study treatment to the end of trial (5 years after last subject has been randomized)										
Physical examination	X	X	M1	D1	X	X	X	-	X	X	-	-
Routine neurologic examination	X	X	M1	D1	X	X	X	-	-	-	-	-
MMSE	-	M1 M2	M1	M4 D1	-	-	-	-	-	-	-	-
Vital signs[f]	X	X	X	X	X	X	X	X	X	X	X	
Height	X	-	-	-	-	-	-	-	-	-	-	-
Weight	X	X	X	X	X	X	X	X	X	X	X	-
ECHO/MUGA	X	-	-	-	-	-	-	-	-	-	-	-
12-lead ECG	X	M1[aa]	-	M6 D1[aa]	-	-	X[aa]	-	-	-	-	-
Hepatitis and HIV testing[g]	X	-	-	-	-	-	-	-	-	-	-	-
Hematology	X	X	X	X	X	X	X	X	X	X	X	-
Coagulation parameters	X	X	D15	D1	X	X	X	-	-	-	-	-
Chemistry	X	X	X	X	X	X	X	X	X	X	X	-
CRS[h]	-	X	M1	-	-	-	-	-	-	-	-	-
Renal Function (CrCl)	X	X	X	X	X	X	X	X	X	X	X	-

Table 4: Table of Events: Treatment Arm B (DPd, IRd, Kd or EPd) (Continued)

	Screening Period	Treatment Period						Follow-up Period				
		M1-2		M3-6	M7-24	≥ M25 every 3 months	EOT (≤ 7 days from trt discon decision)	28 days after EOT[b]	PFS FU every month[c]	PFS FU discon	28 days after PFS FU discon	SFU every 3 months
	-28 to Random-ization	D1[a]	D8, D15, D22	D1, D15	D1	D1						
Visit Window (Days)		±3	±3	±3	±3	±3		+3	±3	±3	+3	±14
Urinalysis	X	If clinically indicated					X	-	-	-	-	-
Pregnancy test (minimum sensitivity 25 mIU/mL) for FCBP with regular or no menstrual cycles	-10 to -14 days and -24 hours prior to first dose weekly for 28 days after first dose, then every 28 days						X	X[w]	X[w]	-		-
Pregnancy test (minimum sensitivity 25 mIU/mL) for FCBP with irregular menstrual cycles	-10 to -14 days and -24 hours prior to first dose weekly for 28 days after first dose, then every 14 days						X	X[w]	X[w]	-		-
Pregnancy counseling	X	X	-	D1	X	Every month	X	-	-	-		-
Antiviral prophylaxis	-	Initiate within 1 week of starting DARA and continue until 90 days after the last dose of DARA or 28 days after EOT Visit, whichever is later										-
TE prophylaxis for all subjects on POM or LEN as part of study treatment	-	Continuous during POM or LEN treatment					-	-	-	-	-	-
EFFICACY AND OTHER ASSESSMENTS												
ECOG Performance status	X	X	M1	D1	X	X	X	-	X	X	-	-
Assessment of response (IMWG Uniform Response Criteria)[i]	-	M2	-	D1	X	X	X	-	X	X	-	-

Table 4: Table of Events: Treatment Arm B (DPd, IRd, Kd or EPd) (Continued)

	Screening Period	Treatment Period						Follow-up Period				
		M1-2		M3-6	M7-24	≥ M25 every 3 months	EOT (≤ 7 days from trt discon decision)	28 days after EOT[b]	PFS FU every month[c]	PFS FU discon	28 days after PFS FU discon	SFU every 3 months
	-28 to Random-ization	D1[a]	D8, D15, D22	D1, D15	D1	D1						
Visit Window (Days)		±3	±3	±3	±3	±3		+3	±3	±3	+3	±14
Serum and urine protein electrophoresis	X	X	-	D1	X	X	X	-	X	X	-	-
Serum and urine immunofixation	X	X	-	D1	X	X	X	-	X	X	-	-
Serum free light chains assay	X	X	-	D1	X	X	X	-	X	X	-	-
Quantitative serum immunoglobulin	X	X	-	D1	X	X	X	-	X	X	-	-
Beta-2-microglobulin	X	X	-	D1	X	X	X	-	-	-	-	-
EMP clinical assessment	X	X	-	D1	X	X	X	-	X	X	-	-
EMP radiological assessment (only required if history of or clinical indication of EMPs only assessable radiographically)[j]	X	Day 1 starting at M3, then every 3 months thereafter						-	Every 3 months		-	-
Skeletal Survey for bone lesions[k]	X (within 60 days prior to randomizati on is acceptable)	Repeated during treatment if clinically indicated to confirm PD						-	If indicated to confirm PD		-	-

Source: Clinical Protocol, BLA 124736/218

Table 87: FDA – Table of Grouped Terms

FDA Grouped Term	AEDECOD Preferred Term
Abdominal pain	abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, dyspepsia
Aphasia	aphasia, dysarthria, slow speech, speech disorder
Ataxia	Ataxia, balance disorder, dysmetria, gait disturbance
Cardiac arrhythmia	arrhythmia, atrial fibrillation, atrial flutter, atrial tachycardia, atrioventricular block first degree, conduction disorder, electrocardiogram qt prolonged, sinus arrest, supraventricular tachycardia, tachyarrhythmia, ventricular extrasystoles, ventricular tachycardia
Cardiac failure	congestive cardiomyopathy, cardiac failure, cardiac failure congestive, ejection failure decreased, left ventricular dysfunction
Coagulopathy	aPTT prolonged, blood fibrinogen decreased, coagulopathy, disseminated intravascular coagulation, hypofibrinogenemia, INR increased, PT prolonged
Cough	cough, productive cough, upper-airway cough syndrome
Delirium	agitation, delirium, disorientation, hallucination, hallucination auditory, hallucination visual, restlessness
Diarrhea	colitis, colitis microscopic, enterocolitis, diarrhea
Dizziness	dizziness, presyncope, syncope, vertigo, vertigo positional, vestibular disorder
Dyspnea	dyspnea, dyspnea exertional, dyspnea paroxysmal nocturnal, tachypnoea

FDA Grouped Term	AEDECOD Preferred Term
Abdominal pain	abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, dyspepsia
Aphasia	aphasia, dysarthria, slow speech, speech disorder
Ataxia	Ataxia, balance disorder, dysmetria, gait disturbance
Edema	eyelid oedema, face oedema, fluid retention, generalized oedema, hypervolemia, localized oedema, mouth swelling, oedema, oedema peripheral, periorbital oedema, periorbital swelling, peripheral swelling, swelling, swelling face
Encephalopathy	amnesia, cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, dysgraphia, encephalopathy, immune effector cell-associated neurotoxicity syndrome, incoherent, lethargy, memory impairment, mental status changes, metabolic encephalopathy, somnolence, stupor, toxic encephalopathy
Fatigue	asthenia, fatigue, malaise, muscle fatigue
Febrile neutropenia	febrile neutropenia, febrile bone marrow aplasia,
Gastroenteritis	bacterial diarrhea, enterocolitis infectious, gastroenteritis, gastroenteritis E coli, gastroenteritis norovirus, gastroenteritis rotavirus, gastroenteritis salmonella, gastrointestinal viral infection
Headache	head discomfort, headache
Hypotension	hemodynamic instability, hypotension, orthostatic hypotension
Hypoxia	hypoxia, oxygen saturation decreased
Motor dysfunction	akathisia, dyskinesia, dysphonia, hypertonia, muscle spasms, muscle twitching, muscular weakness, restless legs syndrome
Musculoskeletal pain	arthralgia, back pain, bone pain, joint stiffness, muscle strain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, noncardiac chest pain
Neuropathy	carpal tunnel syndrome, dysaesthesia, hyperaesthesia, hypoaesthesia, hypoaesthesia oral, mononeuropathy, neuralgia, neuritis, neuropathy peripheral, paraesthesia, paraesthesia oral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, peroneal nerve palsy, radicular pain, radiculopathy, sacral radiculopathy, sciatica, sensory loss, toxic neuropathy
Neutropenia	neutropenia, neutrophil count decreased
Pneumonia	bronchopulmonary aspergillosis, coronavirus pneumonia, covid-19 pneumonia, organizing pneumonia, pneumonia, pneumonia Escherichia, pneumonia adenoviral,

FDA Grouped Term	AEDECOD Preferred Term
Abdominal pain	abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, dyspepsia
Aphasia	aphasia, dysarthria, slow speech, speech disorder
Ataxia	Ataxia, balance disorder, dysmetria, gait disturbance
	pneumonia aspiration, pneumonia bacterial, pneumonia fungal, pneumonia influenzas, pneumonia legionella, pneumonia parainfluenza viral, pneumonia pseudomonal, pneumonia streptococcal, pneumonia viral, pulmonary nocardiosis
Pulmonary edema	pulmonary congestion, pulmonary edema
Rash	acne, catheter site dermatitis, catheter site rash, dermatitis, dermatitis contact, drug eruption, eczema, erythema, papulopustular rosacea, photosensitivity reaction, rash, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic, skin irritation, skin lesion, urticaria
Renal failure	acute kidney injury, blood creatinine increased, chronic kidney disease, creatinine renal clearance decreased, glomerular filtration rate decreased, nephropathy toxic, oliguria, renal failure, renal impairment, urine output decreased

FDA Grouped Term	AEDECOD Preferred Term
Abdominal pain	abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, dyspepsia
Aphasia	aphasia, dysarthria, slow speech, speech disorder
Ataxia	Ataxia, balance disorder, dysmetria, gait disturbance
Sepsis	bacteremia, bacterial sepsis, candida sepsis, Escherichia bacteremia, clostridial sepsis, device related bacteremia, enterococcal sepsis, Escherichia bacteremia, Escherichia sepsis, klebsiella bacteremia, klebsiella sepsis, multiple organ dysfunction syndrome, neutropenic sepsis, pulmonary sepsis, sepsis, septic shock, staphylococcal bacteremia, streptococcal bacteremia, streptococcal sepsis
Sleep disorder	hypersomnia, insomnia, sleep disorder
Tachycardia	heart rate increased, sinus tachycardia, tachycardia
Thrombocytopenia	platelet count decreased, thrombocytopenia
Thrombosis	deep vein thrombosis, device related thrombosis, embolism, pulmonary embolism, thrombosis, thrombosis in device
Transaminase elevation	
Tremor	head titubation, intention tremor, resting tremor , tremor
Vomiting	retching, vomiting
Upper respiratory tract infection	acute sinusitis, epiglottitis, laryngitis, HCoV-OC43 infection, upper respiratory tract infection, sinusitis, nasopharyngitis, respiratory tract congestion, rhinovirus infection, rhinitis, pharyngitis, pharyngeal inflammation, pharyngeal erythema, pharyngitis, pharyngitis streptococcal, respiratory tract infection, upper respiratory tract infection bacterial, viral respiratory tract infection, rhinitis

Source: FDA

18.1 References

The Applicant's References: Section

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18.2 Financial Disclosure

The Applicant's Position:

A list of all investigators in MM-003 will be provided and will include a financial disclosure package which provides the details of the process followed for collecting financial disclosures, table of investigators with disclosable interests reported by investigators, and if applicable, a table with due diligence efforts for the collection of missing financial disclosures. If/when an investigator reported disclosable financial interest, an assessment of the potential bias will be included.

The FDA's Assessment:

The Applicant employed appropriate risk-reduction strategies to minimize bias and adequately investigated individuals who did not provide financial disclosure information. Neither the disclosed significant payments nor the missing disclosures are likely to have negatively impacted the integrity of KarMma-3 conduct or findings. See Table for Covered Clinical Study below for details

Covered Clinical Study (Name and/or Number):* **MM-003**

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1097		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 11		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 11 Significant payments of other sorts: 11		

Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 2 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 4		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

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