CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761291Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

FDA review was conducted in conjunction with other regulatory authorities under Project ORBIS. FDA collaborated with Australia's Therapeutic Goods Administration (TGA), Brazilian Health Regulatory Agency (Agência Nacional de Vigilância Sanitária; ANVISA), Health Canada (HC), and Switzerland's Swissmedic (SMC). While the conclusions and recommendations expressed herein reflect FDA's completed review of the application, the applications may still be under review at the other regulatory agencies.

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	Original BLA
Application Number(s)	BLA 761291
Priority or Standard	Priority
Submit Date(s)	December 28, 2021
Received Date(s)	December 28, 2021
PDUFA Goal Date	November 28, 2022
Division/Office	Division of Hematologic Malignancies II/ Office of Oncologic Diseases
Review Completion Date	October 24, 2022
Established Name	Teclistamab
(Proposed) Trade Name	TECVAYLI
Pharmacologic Class	Bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager
Code Name	JNJ-64007957
Applicant	Janssen Biotech, Inc.
Formulation(s)	Injection 30 mg/3 mL (10 mg/mL) in a single-dose vial 153 mg/1.7 mL (90 mg/mL) in a single-dose vial
Dosing Regimen	The recommended dosage of TECVAYLI is step-up doses of 0.06 mg/kg and 0.3 mg/kg followed by 1.5 mg/kg once weekly.
Applicant Proposed Indication(s)/Population(s)	TECVAYLI is a bispecific B-cell maturation antigen (BCMA)-directed and CD3-directed antibody indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least (b) (4) prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an

	anti-CD38 monoclonal antibody
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	TECVAYLI is a bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

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[FDA will complete this section.]

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OPQ=Office of Pharmaceutical Quality
OBP=Office of Biotechnology Products
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE=Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRM=Division of Risk Management
DMAMES=Division of Mitigation and Medication Error Surveillance
DMPP=Division of Medical Policy Programs

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Glossary

ADA	antidrug antibody
ADC	antibody drug conjugate
ADME	absorption, distribution, metabolism, excretion
ADR	adverse drug reaction
AE	adverse event
AOM	application orientation meeting
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area under the concentration-time curve
AUC_{tau}	area under the concentration-time curve during a dosing interval
BCMA	B cell maturation antigen
BLA	Biologics License Application
BMPC	bone marrow plasma cells
bsAb	bispecific antibody
CAR	chimeric antigen receptor
C_{ave}	average plasma concentration
CD3	cluster of differentiation 3
CD38	cluster of differentiation 38
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum plasma concentration
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete response
CRS	cytokine release syndrome
CSR	clinical study report
C_{trough}	trough serum concentration
CV	coefficient of variation
CYP	cytochrome P450
DOR	duration of response
EC_{90}	90% maximal effective concentration
EC_{50}	50% maximal effective concentration
ECG	electrocardiogram
E-R	exposure-response
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 item
EQ-5D-5L	EuroQol Five Dimension Five Level Questionnaire
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
ICANS	Immune effector cell-associated neurotoxicity syndrome

ICH	International Conference on Harmonization
IgG	immunoglobulin G
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IND	Investigational New Drug
IRR	infusion-related reaction
IP	intraperitoneal(ly)
iPSP	initial Pediatric Study Plan
IRC	Independent Review Committee
ISS	International Staging System
IV	intravenous(ly)
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
MOA	mechanism of action
MRD	minimal residual disease
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Event
NDA	New Drug Application
NE	not evaluable
NSG	NOD scid gamma
OECD	Organization for Economic Co-operation and Development
ORR	overall response rate
OS	overall survival
PAA	proline, alanine, and alanine
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamic
PFS	progression-free survival
PI	proteasome inhibitor
PK	pharmacokinetic(s)
PMC	post-marketing commitment
PMR	post-marketing requirement
PPK	population pharmacokinetics
PR	partial response
PRO	patient-reported outcome
QW	every week
Q2W	every 2 weeks
Q4W	every 4 weeks
REMS	Risk Evaluation and Mitigation Strategy
RP2D	recommended Phase 2 dose
RRMM	relapsed or refractory multiple myeloma
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
sCR	stringent complete response

SET	Safety Evaluation Team
SOC	system organ class
SPR	surface plasmon resonance
TEAE	treatment-emergent adverse event
TGI	tumor growth inhibition
TK	toxicokinetic
T_{max}	maximum plasma concentration
TTR	time to response
US	United States
VGPR	very good partial response
WOE	weight of evidence

1. Executive Summary

1.1 Product Introduction

Product: Teclistamab (TECVAYLI)

Pharmacological Class: TECVAYLI is a bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager.

Proposed Indication: TECVAYLI is a bispecific B-cell maturation antigen (BCMA)-directed and CD3-directed antibody indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least (b) (4) prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

Dosing Regimen: The recommended dosage of TECVAYLI is step-up doses of 0.06 mg/kg and 0.3 mg/kg followed by 1.5 mg/kg once weekly.

1.2 Conclusions on the Substantial Evidence of Effectiveness

The FDA review team recommends accelerated approval of teclistamab for the following indication:

TECVAYLI is a bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

This recommendation is based on the observed response rate and duration of response, and the favorable benefit-risk profile in the indicated population, with risk mitigation strategies in place as described below. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

Accelerated approval of teclistamab is based on the results of the MajesTEC-1 study (Study 64007957MMY1001), an adequate and well-controlled study. The results from MajesTEC-1 are adequate for concluding substantial evidence of effectiveness to support accelerated approval of teclistamab. MajesTEC-1 is an ongoing, phase 1/2, first-in-human, single arm, multicenter trial evaluating teclistamab monotherapy in patients with relapsed or refractory multiple myeloma (RRMM). Eligible patients for phase 2 Cohort A were to have received at least 3 prior lines of therapy, including a proteasome inhibitor (PI), an immunomodulatory agent (IMiD), and an anti-CD38 monoclonal antibody (mAb). Patients treated at the recommended phase 2 dose (RP2D) in phase 1 and phase 2 received step-up doses of teclistamab 0.06 mg/kg and 0.3 mg/kg

subcutaneously (SC) followed by teclistamab 1.5 mg/kg SC once weekly thereafter, until disease progression or unacceptable toxicity. The primary efficacy endpoint was overall response rate (ORR) assessed by an Independent Review Committee (IRC).

Patients in the efficacy population (N=110) had a median age of 66 years (range 33 to 82) and received a median of 5 prior lines of therapy (range 2 to 14); 78% of patients had at least 4 prior lines of therapy, 20% had only 3 prior lines, and 1.8% had only 2 prior lines. All patients were triple-class exposed (i.e., received a prior PI, IMiD, and anti-CD38 mAb) and 76% were triple-class refractory. The ORR in the efficacy population was 61.8% (95% CI: 52.1, 70.9). At the time of the 09 Nov 2021 efficacy data cut-off, with a median follow-up of 7.4 months among responders, the median duration of response (DOR) was not reached (95% CI: 9.0, not estimable), and the estimated DOR rate was 90.6% (95% CI: 80.3, 95.7) at 6 months and 66.5% (95% CI: 38.8, 83.9) at 9 months.

The primary safety population (N=165) included all patients treated at the RP2D in phase 1 (N=40) and phase 2 Cohort A (N=125). The key safety concerns for teclistamab are cytokine release syndrome (CRS) and neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS). Other safety concerns include hepatotoxicity, infections, neutropenia, and hypersensitivity and other administration-related reactions. Recommendations are included in the Warnings and Precautions section of the teclistamab U.S. Prescribing Information (USPI) to mitigate these risks, and further mitigation strategies for CRS and neurologic toxicity, including ICANS, are discussed below.

CRS and neurologic toxicity were common, occurring in 72% and 57% of patients, respectively, treated with teclistamab at the recommended dose. CRS was Grade 1 (50%) or Grade 2 (21%) in most patients, and primarily occurred during the initial step-up dosing schedule; however, CRS was common despite consistent use of pre-medications, one patient (0.6%) had Grade 3 CRS, 2.4% of patients developed the first occurrence of CRS after completion of step-up dosing, and 33% of patients had recurrent CRS. Neurologic toxicity included headache in 25% of patients, motor dysfunction in 16%, sensory neuropathy in 15%, and encephalopathy in 13%. Grade 3 or 4 neurologic adverse events (AEs) occurred in 2.4% of patients; with longer follow-up (based on the 120-day Safety Update) there were two additional patients with serious neurologic AEs of Grade 4 seizure and fatal (Grade 5) Guillain Barré syndrome. ICANS occurred in 6% of patients. All ICANS events were Grade 1 or 2 and most occurred during the initial step-up dosing schedule; however, 2.4% of patients developed the first occurrence of ICANS after completion of step-up dosing and 1.8% of patients had recurrent ICANS. Patients in the trial were monitored closely, with hospitalization required for at least 48 hours following each dose in the initial step-up dosing schedule, and for the next dose of teclistamab following events of CRS and neurologic toxicity that met specified criteria based on severity.

The USPI will include Boxed Warnings to communicate the risks of CRS and neurologic toxicity, including ICANS, and will state that patients should be hospitalized for 48 hours after each dose

of teclistamab in the step-up doing schedule, and for the next dose of teclistamab following specified events of CRS or neurologic toxicity. In addition, a risk evaluation and mitigation strategy (REMS) with elements to assure safe use (ETASU) will be in place to ensure these risks can be adequately managed in the post-market setting. The REMS with ETASU for teclistamab will require certification of prescribers and dispensing pharmacies to verify that prescribers are certified, to ensure prescribers are educated on these risks and understand the importance of monitoring patients for signs and symptoms of CRS and neurologic toxicity, including ICANS.

A post-marketing requirement (PMR) will be issued to conduct a randomized trial in patients with RRMM to verify the clinical benefit of teclistamab. A PMR will also be issued to conduct a clinical trial to further characterize and determine the incidence of neurologic toxicities in patients receiving teclistamab. A post-marketing commitment (PMC) will be issued to obtain additional data from the MajesTEC-1 trial with longer follow-up to further assess durability of response.

1.3 Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Multiple myeloma (MM) is a plasma cell malignancy that accounts for approximately 1-2% of all cancers and approximately 17% of hematologic malignancies in the United States (1). MM is diagnosed most frequently among people aged 65-74 with a median age at diagnosis of 69 years. Despite the availability of multiple treatments, MM remains an incurable disease. Patients who have received multiple lines of therapy and treated with the major class of drugs, including a proteasome inhibitor (PI), immunomodulatory agent (IMiD) and an anti-CD38 monoclonal antibody (mAb), have poor outcomes.

Teclistamab is a first in class BCMA-directed CD3 T-cell engaging bispecific monoclonal antibody. The data to support the proposed indication is based on the MajesTEC-1 trial, a phase 1/2, single arm, multicenter, multicohort trial evaluating teclistamab monotherapy in patients with relapsed or refractory MM (RRMM). The efficacy population included 110 patients who were treated at the RP2D in Cohort A in phase 2 that enrolled patients with RRMM with at least 3 prior lines of therapy, including a PI, an IMiD, and an anti-CD38 mAb. Patients had received a median of 5 prior lines of therapy (range 2 to 14); 78% of patients had at least 4 prior lines of therapy, 20% had only 3 prior lines, and 1.8% had only 2 prior lines. The overall response rate (ORR) in the efficacy population was 61.8% (95% CI: 52.1, 70.9). At the time of the 09 Nov 2021 efficacy data cut-off, with a median follow-up of 7.4 months among responders, the median duration of response (DOR) was not reached (95% CI: 9.0, not estimable), and the estimated DOR rate was 90.6% (95% CI: 80.3, 95.7) at 6 months and 66.5% (95% CI: 38.8, 83.9) at 9 months.

The primary safety population (All-Treated Analysis Set) included patients treated at 1.5 mg/kg SC weekly (RP2D) in phase 1 (n=40) and patients treated in Cohort A in phase 2 (n=125). The key safety concerns for teclistamab are cytokine release syndrome (CRS) and neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS). CRS and neurologic toxicity were common, occurring in 72% and 57% of patients, respectively. The first occurrence of CRS occurred in 2.4% of patients after completion of the step-up dosing schedule and 33% of patients had recurrent CRS. Neurologic toxicity included headache in 25% of patients, motor dysfunction in 16%, sensory neuropathy in 15%, and encephalopathy in 13%. Grade 3 or 4 neurologic adverse events (AEs) occurred in 2.4% of patients; with longer follow-up there were two additional serious neurologic AEs of Grade 4 seizure and fatal (Grade 5) Guillain Barré syndrome (one patient each).

Benefit-Risk Summary and Assessment (Continued)

Other safety concerns include hepatotoxicity, infections, neutropenia, and hypersensitivity and other administration-related reactions. Recommendations are included in the Warnings and Precautions section of the teclistamab U.S. Prescribing Information (USPI) to mitigate these risks, and further mitigation strategies are included for CRS and neurologic toxicity, including ICANS.

The clinical efficacy of teclistamab in conjunction with a risk evaluation and mitigation strategy (REMS) with elements to assure safe use (ETASU) to mitigate the risk of CRS and neurologic toxicity, including ICANS, and the information in the USPI, including a boxed warning for CRS and neurologic toxicity, including ICANS, supports a determination of favorable benefit-risk for the approval of teclistamab for the treatment of adult patients with RRMM who have received at least 4 prior lines of therapy including a PI, an IMiD, and an anti-CD38 mAb. There were too few patients who had received 3 prior lines (n=22) to inform the benefit-risk.

A post-marketing requirement (PMR) will be issued to submit the final study report and datasets from a randomized phase 3 clinical trial to verify and describe the clinical benefit of teclistamab in patients with RRMM. The confirmatory trial is ongoing and is expected to be completed in September 2025. An additional PMR to characterize the risk of neurologic toxicity with continued administration will also be issued.

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 progression-free survival (PFS). • However, MM remains incurable, with a 5-year survival rate of 57.9%.	• RRMM is a serious and life-threatening condition.
Current Treatment Options	• Multiple drugs approved for use in MM and numerous combination regimens are considered standard of care. • Potential treatments include alkylating agents, corticosteroids, immunomodulatory agents (IMiDs), proteasome inhibitors (PIs) and monoclonal antibodies (mAbs).	• Despite the availability of multiple therapies, RRMM remains an incurable disease.
Benefit	• Assessment of the clinical benefit of teclistamab was based on the efficacy results of the MajesTEC-1 trial. The overall response rate (ORR) in the 110 patients who had received at least 3 prior lines of therapy, including a PI, an IMiD, and an anti-CD38 mAb and were treated at the RP2D was 61.8% (95% CI: 52.1, 70.9). • At the time of the 09 Nov 2021 efficacy data cut-off, with a median follow-up of 7.4 months among responders, the median duration of response (DOR) was not reached (95% CI: 9.0, not estimable), and the estimated DOR rate was 90.6% (95% CI: 80.3, 95.7) at 6 months and 66.5% (95% CI: 38.8, 83.9) at 9 months	• The ORR and durability of response represent a treatment benefit. • A post-marketing requirement (PMR) to verify and describe the clinical benefit of teclistamab in a randomized clinical trial in patients with RRMM will be issued.
Risk and Risk Management	• Safety was evaluated in 165 patients in the phase 1 and phase 2 cohorts treated at the RP2D of teclistamab. • Fatal adverse reactions (ARs) occurred in 5% of patients who received teclistamab. Serious ARs occurred in 54% of patients who received teclistamab. • The key safety concerns for teclistamab are cytokine release syndrome (CRS) and neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS). CRS and neurologic toxicity were common and occurred in 72% and 57% of patients, respectively; 33% of patients had	• Teclistamab has an acceptable safety profile in the indicated patient population. • The U.S. prescribing information (USPI) will include a boxed warning to alert the prescribers regarding the risk of CRS and neurologic toxicity, including ICANS, with teclistamab. • Patients should be hospitalized for 48

	recurrent CRS. • Grade 3 or 4 neurologic ARs occurred in 2.4% of patients; with longer follow-up there were two additional serious neurologic ARs of Grade 4 seizure and fatal (Grade 5) Guillain Barré syndrome (one patient each).	hours during the step-up dosing schedule of teclistamab. • Teclistamab will be approved with a risk evaluation and mitigation strategy (REMS) with elements to assure safe use (ETASU) A and B to ensure that the risks of teclistamab can be adequately managed in the post-market setting.

1.4 Patient Experience Data

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

□	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
	■ Clinical outcome assessment (COA) data, such as	
	■ Patient reported outcome (PRO)	8.1.2 and 8.2.6
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that was not submitted in the application but was considered in this review.	

X

Cross-Disciplinary Team Leader

2. Therapeutic Context

2.1 Analysis of Condition

The Applicant's Position:

Multiple myeloma is characterized by the proliferation of neoplastic clones of plasma cells derived from B lymphocytes. These neoplastic clones grow in the bone marrow, frequently invade the adjacent bone, disrupt both bone homeostasis and hematopoiesis, and cause multifocal destructive lesions throughout the skeleton that result in bone pain and fracture (Chung 2017). Common clinical presentations of multiple myeloma are hypercalcemia, renal insufficiency, anemia, bony lesions, bacterial infections, hyperviscosity, and secondary amyloidosis (Orlowski 2013).

With the introduction of new treatments, patient survival with multiple myeloma is lengthening, largely in developed countries. In the US, 6-year relative survival increased from 31% to 56% in those diagnosed with multiple myeloma from 2006 to 2010 (Kumar 2017). In the US, multiple myeloma accounts for approximately 1.8% of all cancers and 18% of hematologic malignancies (American Cancer Society 2021). There were an estimated 32,270 new cases of multiple myeloma annually from 2013 to 2017 and 12,830 deaths from 2014 to 2018 in the US (SEER 2020). An estimated 140,779 people were living with multiple myeloma in the US in 2017, giving an approximate prevalence proportion of 43 per 100,000 (SEER 2020).

Despite multiple therapeutic options, the disease most often recurs and remains incurable. With each successive relapse, symptoms return, quality of life worsens, and the chance and duration of response typically decreases. Therefore, there remains critical unmet need for new therapeutic options with alternative mechanisms of action that can better control the disease; provide deeper, more sustained responses; and yield better long-term outcomes, including maintenance of health-related quality of life (Usmani 2016). In recent years, newer agents with novel mechanisms of action have received FDA approval for the treatment of heavily pretreated multiple myeloma.

The FDA's Assessment:

FDA generally agrees with the Applicant's analysis of condition.

2.2 Analysis of Current Treatment Options

Data:

Until 2000, standard therapies for multiple myeloma were melphalan- or doxorubicin-based regimens with corticosteroids (Chung 2017). Since then, the introduction of PIs (eg, bortezomib, carfilzomib, and ixazomib); histone deacetylase inhibitors (eg, panobinostat); IMiDs (eg, thalidomide, lenalidomide, and pomalidomide); and monoclonal antibodies (daratumumab and isatuximab [anti-CD38] and elotuzumab [anti-CS1/SLAMF7]) have provided numerous therapeutic avenues for patients with multiple myeloma. Currently, the 3 most used classes of therapy for the treatment of multiple myeloma are IMiDs, PIs, and antiCD38 monoclonal

antibodies. Patients who progress after receiving IMiD, PI, and anti-CD38 monoclonal antibody therapies have limited therapeutic options.

A recent prospective observational study evaluated the outcomes of 246 subjects with relapsed or refractory multiple myeloma who were triple-class exposed (Moreau 2021). The study enrolled subjects from 10 countries; these subjects had to have received at least 3 prior lines of therapy or be considered double-refractory to a PI and an IMiD. All subjects were triple-class exposed, 75% were triple-class refractory, and 93% were refractory to the last line of therapy. The ORR was 28%. With a median duration of follow-up of 7.8 months, the median DOR was 5.1 months, the median PFS was 4.4 months, and the median OS was 12.4 months.

Similar to the prospective study, an earlier retrospective medical record review of 275 subjects from 14 academic institutions in the US found that those who were refractory to anti-CD38 monoclonal antibodies had a dismal prognosis. The median OS for the entire cohort was 8.6 months (95% CI:7.5, 9.9; Gandhi 2019). Subjects who became refractory to anti-CD38 therapy and received ≥1 subsequent treatment had ORR of 31%, with a median PFS and median OS of 3.4 months and 9.3 months, respectively. The median OS for subjects who received no further treatment was 1.3 months.

Approved regimens for the treatment of patients with multiple myeloma who are triple-class exposed (IMiDs, PIs, and anti-CD38 monoclonal antibodies) include selinexor, belantamab mafodotin, and idecabtagene vicleucel (Table 1). ORR are <31% for the off-the-shelf options and higher for CAR-T therapy.

Table 1: Applicant - Summary of Approved Treatments (as of 31 December 2021) for Patients with Relapsed and Refractory Multiple Myeloma Who are Triple-class Exposed

Product (s) Name	Relevant Indication	Year of Initial Approval/ Current Type of Approval*	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
FDA Approved Treatments					
Selinexor/ Dexamethasone	Selinexor in combination with dexamethasone is indicated for the treatment of adult patients with relapsed/refractory multiple myeloma who have received at least 4 prior therapies and whose disease is refractory to at least 2 PIs, at least 2 IMiDs, and an anti-CD38 monoclonal antibody.	2020/Full Approval.	Selinexor 80 mg taken orally on Days 1 and 3 of each week until disease progression or unacceptable toxicity in combination with dexamethasone 20 mg taken orally with each dose of selinexor on Days 1 and 3 of each week.	Open-label, single-arm study STORM (Chari 2019) ORR: 26.2% Median PFS: 3.7 months Median DOR: 4.4 months Median OS: 8.6 months.	Selinexor can cause: • Life-threatening thrombocytopenia, potentially leading to hemorrhage • Life-threatening neutropenia, potentially increasing the risk of infection • Severe gastrointestinal toxicities (nausea/vomiting, diarrhea, anorexia/weight loss), severe or life-threatening hyponatremia, serious and fatal infections, and life-threatening neurological toxicities • Fetal harm in a pregnant woman • New onset or exacerbation of cataract.
Belantamab mafodotin	Belantamab mafodotin is indicated for the treatment of adults with RRMM who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an IMiD.	2020/ Accelerated Approval.	Belantamab mafodotin 2.5 mg/kg of actual body weight given as an IV infusion over approximately 30 minutes once every 3 weeks until disease progression or unacceptable toxicity.	Open-label, randomized study DREAMM-2 (Lonial 2020) ORR: 31% Median PFS: 2.9 months Median DOR: 11.0 months.	Belantamab mafodotin can cause: • Changes in the corneal epithelium resulting in changes in vision, including severe vision loss and corneal ulcer, and symptoms, such as blurred vision and dry eyes • Thrombocytopenia and infusion-related reactions • Fetal harm in a pregnant woman because it contains a genotoxic compound (the microtubule inhibitor, MMAF) and it targets actively dividing cells.

Table 1: Applicant - Summary of Approved Treatments (as of 31 December 2021) for Patients with Relapsed and Refractory Multiple Myeloma Who are Triple-class Exposed

Product (s) Name	Relevant Indication	Year of Initial Approval/ Current Type of Approval*	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Idecabtagene vicleucel	Idecabtagene vicleucel is indicated for the treatment of adult patients with RRMM after 4 or more prior lines of therapy, including an IMiD, a PI, and an anti-CD38 monoclonal antibody.	2021/ Full Approval	After lymphodepletion (cyclophosphamide 300 mg/m^2+ fludarabine 30 mg/m^2 x 3), patients received 150–450 × 10^6 CAR+ T cells (target dose range).	Single-arm study KarMMa (Munshi 2021) ORR (all enrolled): 67%[a]; ORR (all treated): 73% Median PFS: 8.8[b] months Median DOR: 10.7[b] months.	Patients who received Ide-cel reported: • Neutropenia (91%), CRS (84%), anemia (70%), and thrombocytopenia (63%) • Neurotoxicity developed in 18% patients Four treatment related deaths (bronchopulmonary aspergillosis, gastrointestinal hemorrhage, CRS, and cytomegaloviral pneumonia).

Keys: ARDS=Acute Respiratory Distress Syndrome; CAR=chimeric antigen receptor; CRS=cytokine release syndrome; DOR=duration of response; HUS= hemolytic uremic syndrome; IMiD=immunomodulatory drug; IV=intravenous; MM=multiple myeloma; MMAF=monomethyl auristatin F; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PI=proteasome inhibitor; PML=progressive multifocal leukoencephalopathy; PRES=posterior reversible encephalopathy syndrome; RBC=red blood cell; TLS=tumor lysis syndrome; TTP=thrombotic thrombocytopenic purpura.

[a] Includes 128 subjects treated and an additional 12 subjects who underwent leukapheresis, but never received idecabtagene vicleucel.
[b] 150 × 10^6 to 450 × 10^6 CAR+ T cells.

The Applicant's Position:

There is an unmet need for new treatment options beyond the current classes of anti-myeloma therapies for the treatment of adult subjects with relapsed or refractory multiple myeloma, whose prior regimens included a PI, an IMiD, and an anti-CD38 monoclonal antibody and who had disease progression on or after the last regimen. Beyond the therapies in Table 1, the therapeutic options for heavily pretreated patients are either entry into a clinical study or retreatment with a prior treatment regimen (if toxicity profile permits). But often, if no other treatment options remain, they are provided with palliative care to ameliorate disease-related symptoms only.

Teclistamab is an off-the-shelf product that targets the CD3 receptor expressed on the surface of T cells and BCMA, which is expressed on the surface of malignant multiple myeloma B-lineage cells, as well as late-stage B cells and plasma cells. Teclistamab is proposed to be indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least (b) (4) prior therapies, including a PI, an IMiD, and an anti-CD38 monoclonal antibody. The Applicant will demonstrate in the sections below that teclistamab has a positive benefit/risk profile in the treatment of patients who have received 3 or more prior lines of therapy and are triple-class exposed.

The FDA's Assessment:

FDA generally agrees with the Applicant's analysis of current treatment options for patients with RRMM who have received a previous PI, IMiD, and anti-CD38 mAb. However, the FDA notes additional regimens are approved for patients with RRMM who have received 3 prior lines of therapy, such as elotuzumab + lenalidomide + dexamethasone (ERd), elotuzumab + pomalidomide + dexamethasone (EPd), daratumumab + carfilzomib + dexamethasone (DKd), isatuximab + carfilzomib + dexamethasone (Isa-Kd), and isatuximab + pomalidomide + dexamethasone (Isa-Pd). Patients who have been exposed to a PI, an IMiD, and an anti-CD38 mAb may respond to another agent in the same class.

Additionally, a second CAR T-cell therapy, ciltacabtagene autoleucel, has been granted FDA approval for patients with RRMM and at least 4 prior lines of therapy including a PI, IMiD, and anti-CD38 mAb. We also note that the histone deacetylase inhibitor, panobinostat, is no longer an available therapy for patients with MM.

3. Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Teclistamab is currently under development and is not authorized anywhere in the world. This BLA supports teclistamab treatment of adult patients with relapsed or refractory multiple myeloma who have previously received at least (b) (4) prior therapies, including a PI, an IMiD, and an anti-CD38 monoclonal antibody.

The FDA's Assessment:

The FDA generally agrees with the Applicant's statement. However, the indication for teclistamab supported by the BLA will be for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

3.2 Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

The Applicant submitted IND 131272 to the Agency on 16 February 2017 to support the investigation of teclistamab in the treatment of subjects with relapsed or refractory multiple myeloma. The notification that the study was safe to proceed was provided on 17 March 2017. The clinical development program was designed after consultation with global health authorities. Key FDA interactions are summarized below in Table 2.

Table 2: Key US FDA Interactions Relevant to Teclistamab BLA

Event	Date	Description
Type C meeting	26 February 2020	Waiver request for additional toxicology studies to support the BLA of teclistamab WRO Feedback
Type B End-of-Phase 1 meeting	21 September 2020	Obtain the Agency's review and agreement on Part 3/Phase 2 of Study 64007957MMY1001
n/a	24 November 2020	Orphan Drug Designation Granted for the treatment of multiple myeloma (DRU-2020-7829)
Type B End-of-Phase 2 meeting	04 May 2021	Discuss key aspects of the design and elements of the proposed Study 64007957MMY3001
n/a	26 May 2021	Breakthrough Designation Granted
Type B BLA Format and Content	26 May 2021	Obtain the Agency's feedback on the format and content of the planned BLA (WRO feedback)
n/a	26 July 2021	Agreed iPSP – Agreement Letter received from FDA
n/a	29 July 2021	MajesTEC-1 Statistical Analysis Plan (Amendment 1) submitted to FDA
Type B Pre-BLA Meeting	19 November 2021	To present topline data to the Agency and receive feedback on the planned BLA

The FDA's Assessment:

FDA agrees with the outline of relevant pre-submission activity presented by the Applicant in Table 2. Regarding the Type B BLA Format and Content Meeting scheduled for 26 May 2021, FDA conveyed preliminary comments regarding concerns with the Sponsor's proposal to seek accelerated approval based on a single arm trial and the need to ensure the primary efficacy population includes patients with a minimum of 6 months of follow-up from the time of response to allow for adequate assessment of durability of response. The Sponsor cancelled the meeting teleconference after receipt of FDA's preliminary comments. At the Type B Pre-BLA Meeting on 19 Nov 2021, FDA reiterated the significant concerns with the Sponsor's proposal to submit a BLA for teclistamab for accelerated approval based on the results of a single arm trial, reiterated concerns with the limited duration of follow-up proposed, and stated that if the Sponsor chooses to submit a marketing application based on the results of the single arm trial, the submission should include all available data with adequate duration of follow-up at the time of the initial submission, and that the confirmatory trial should be ongoing at the time a marketing application is submitted.

FDA also notes the following relevant submission-related activities/interactions:

- 28 Dec 2021: Applicant submitted BLA 761291 for teclistamab (based on 07 September 2021 data cut-off)
- 04 Feb 2022: Application Orientation Meeting (AOM) for BLA 761291
- 25 Jan 2022: Applicant submitted updated efficacy data (based on 09 November 2021 data cut-off) and updated USPI
- 28 April 2022: Mid-cycle Communication Teleconference: FDA conveyed concerns regarding the risks of CRS and neurologic toxicity and strong consideration of the need for a REMS and potential need for observation after initial administration of teclistamab, concerns with the lack of data to support the use of tocilizumab for management of CRS, and concerns regarding the need for the confirmatory phase 3 trial to be well underway.
- 09 July 2022: Applicant submitted proposed REMS program documents (Major Amendment – PDUFA date revised from August 28, 2022 to November 28, 2022)
- 19 July 2022: Late-Cycle Teleconference: FDA reiterated concerns regarding the risks of CRS and neurologic toxicity and the need for a REMS with ETASU and addition of a boxed warning for neurologic toxicity; conveyed that hospitalization requirements in the USPI should be consistent with the protocol recommendations and that management of CRS in the USPI should be based on standard guidelines.
- June – Sept 2022: Multiple teleconferences to discuss need for a REMS program and specific components of the REMS

FDA also notes interactions related to the ongoing phase 3 confirmatory trial, MMY3001, including the End-of-Phase 2 Meeting on 04 May 2021 as noted in Table 2 (above). MMY3001 is an ongoing, phase 3, randomized study evaluating teclistamab in combination with daratumumab (Tec-Dara) vs. investigator's choice of daratumumab with pomalidomide and dexamethasone (DPd) or daratumumab with bortezomib and dexamethasone (DVd) in patients with RRMM with 1 to 3 prior line(s) of therapy including a PI and lenalidomide. The primary endpoint is PFS. The expectation that the confirmatory trial should be ongoing at the time of

submission of the BLA was conveyed to the Sponsor at the Pre-BLA Meeting on 19 Nov 2021. At the AOM on 04 Feb 2022, the Applicant stated that 24/560 patients had been randomized. FDA's concerns regarding the need for the confirmatory trial to be well underway were reiterated at the Mid-Cycle Communication Teleconference on 28 Apr 2022. During PMR/PMC negotiations, the Applicant provided an update that enrollment was 294/560 (52%) and there were 13 PFS events as of 01 Sept 2022. The Applicant also stated that they anticipated 100% enrollment by the first quarter of 2023.

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

4.1 Office of Scientific Investigations (OSI)

OSI conducted inspections at 2 domestic clinical sites (Site US-10004 and Site US-10005) in support of BLA 761291. Site US-10004 in Philadelphia, PA (Investigator: Alfred Garfall, M.D.) enrolled 17 patients and Site US-10005 in Duarte, CA (Investigator: Amrita Krishnan, M.D.) enrolled 14 patients. The sites were selected for inspection based on their high enrollment and calculated risk scores from the OSI Clinical Investigator Site Selection Tool. Although no Form FDA 483 was issued, it was noted that 2 subjects at Site US-10005 had adverse events (nausea and mild diarrhea) that were not captured in the eCRF. While it was noted that they should have been captured, they were considered isolated and unlikely to have significant impact on the overall safety profile of teclistamab. OSI concluded that the study data derived from the two clinical investigator sites are considered reliable and the study data submitted to the Agency for assessment appeared acceptable in support of the proposed indication.

4.2 Product Quality

Refer to the Office of Product Quality review for specific recommendations regarding the product quality. The FDA Product Quality review team recommended approval.

4.3 Clinical Microbiology

Refer to the Office of Microbiology review for specific recommendations regarding the drug substance and drug product microbiology. The FDA Microbiology review team recommended approval.

4.4 Devices and Companion Diagnostic Issues

Not applicable.

5. Nonclinical Pharmacology/Toxicology

5.1 Executive Summary

Teclistamab (also referred to as JNJ-64007957 or BCMB72) is an IgG4-based bispecific antibody (bsAb) construct directed against B-cell maturation antigen (BCMA) and CD3. BCMA is expressed on the surface of multiple myeloma (MM) cells and some healthy B-lineage cells and the CD3 receptor complex is expressed on the surface of T-cells. The Applicant developed teclistamab to promote the T-cell dependent elimination of BCMA-expressing MM cells.

In in vitro studies, teclistamab bound human T-cells endogenously expressing CD3 (K_D=28.03 nM) and purified human BCMA antigen (K_D=0.18 nM). Lower affinity binding was observed for cynomolgus monkey T-cells (K_D=38.48 nM), purified cynomolgus monkey BCMA antigen (K_D=6.5 nM), and murine BCMA antigen (K_D=72.4 nM). The parental CD3 monoclonal antibody did not bind rodent CD3, and teclistamab is not expected to bind rabbit CD3 or BCMA due to low sequence similarity; thus, the cynomolgus monkey was determined to be a pharmacologically relevant species for toxicology studies. Studies evaluating the concomitant binding affinity of CD3 and BCMA were not submitted. Teclistamab bound to BCMA-expressing MM cell lines, and binding intensity correlated with the cell surface BCMA expression level.

The functional activity of teclistamab was evaluated in T-cell redirected lysis assays with human T-cells as effector cells and MM cell lines as target cells. Teclistamab caused the concentration-dependent lysis of the target cell lines (EC_{50}=0.07-0.70 nM), T-cell activation (EC_{50}=0.15-0.50 nM), and release of various cytokines. No activity was observed in the absence of target cells, or with control bsAbs that singly targeted CD3 or BCMA. Teclistamab was not an agonist of BCMA receptor signaling. Teclistamab is IgG4-based and has proline, alanine, and alanine (PAA) (b) (4)

The in vivo antitumor activity of teclistamab was evaluated in two xenograft mouse models of MM; the prevention of tumorigenesis was evaluated in a prophylactic model, while the tumor growth inhibition (TGI) of palpable tumors was evaluated in the established tumor model. In the prophylactic model, NOD scid gamma (NSG) mice were implanted with human peripheral blood mononuclear cells (PBMCs) before implantation of a MM cell line, after which treatment with teclistamab was initiated (0.1, 0.5, or 1 µg/dose, intravenously [IV], on study Days 1, 4, 6, 8, and 11). In the established tumor model, NSG mice were implanted with a MM cell line and tumors were allowed to establish (tumor volume of 75-100 mm^3) before implantation of human effector cells and treatment with teclistamab was initiated (1, 10, or 50 µg/dose, intraperitoneally [IP], on study Days 8, 11, 13, 15, 18, and 25). Teclistamab conferred dose-dependent antitumor activity in both xenograft mouse models of MM. Comparably higher dose levels of teclistamab were necessary to achieve antitumor activity in the established tumor model.

The toxicity and toxicokinetics (TK) of teclistamab were evaluated in a 5-week repeat-dose toxicity study in cynomolgus monkeys. Teclistamab binds BCMA in cynomolgus monkeys with

~36-fold lower affinity than in humans; despite this difference, the cynomolgus monkey is the most pharmacologically-relevant nonclinical species to evaluate the toxicology of teclistamab. Monkeys were administered teclistamab (0 [control], 1, 10, or 30 mg/kg/dose, IV) once weekly for five total doses followed by an 8-week recovery period. Teclistamab was administered at dose levels expected to be pharmacologically active, but there was no evidence of pharmacodynamic (PD) activity or teclistamab-related adverse effects. Antidrug antibodies (ADAs) were detected in 21/30 teclistamab-treated animals, and seven of these animals exhibited lower teclistamab exposure after dosing on Day 22 or Day 29. Lack of teclistamab PD activity may be attributed to the lower binding affinity of teclistamab to cynomolgus monkey BCMA, the paucity of BCMA-expressing target cells in healthy cynomolgus monkeys, and the decreased teclistamab systemic exposure in animals affected by neutralizing ADAs. Teclistamab group mean systemic exposure (C_{max}, AUC) increased in a dose-proportional manner, there were no apparent sex-related differences, and minimal accumulation was observed. This study evaluated the IV route of administration, whereas the clinical route of administration is subcutaneous (SC). The potential impact of target-mediated drug disposition on teclistamab TK was not assessed due to the low frequency of BCMA-expressing target cells in healthy cynomolgus monkeys and the low amount of soluble BCMA.

A local tolerance study was conducted in New Zealand White rabbits to support the clinical transition from the IV to SC route of administration. The purpose of this study was to evaluate the local tolerance of the formulation only, as rabbits are not a pharmacologically-relevant nonclinical species to evaluate the on-target effects of teclistamab. The teclistamab formulation evaluated in the local tolerance study was the same as the formulation evaluated in the repeat-dose toxicity study in cynomolgus monkeys. Rabbits were administered a single dose of teclistamab (20 mg, SC); there were no teclistamab-related gross or microscopic findings in the injection sites or draining lymph nodes. TK was not evaluated in this study.

In a tissue cross-reactivity study with normal human tissues, biotinylated teclistamab stained mononuclear leukocytes in the peripheral blood smears, lymphoid tissues, ovary, prostate, and skin. It is unclear if the staining was due to cross-reactivity with CD3 and/or BCMA. No unanticipated cross-reactivity was observed.

Teclistamab is expected to cause cytokine release due to the mechanism of action (MOA). In an in vitro cytokine release assay, increases in IL-8, IFN-γ, TNF-α, IL-2, and IL-1β were observed; EC_{50} values were not provided for any cytokine. This assay was conducted in the soluble format.

Toxicology studies were not conducted in rodents due to the lack of teclistamab binding in these species. Given the dearth of findings and the induction of neutralizing ADAs in the 5-week repeat-dose toxicity study in cynomolgus monkeys, a 13-week repeat-dose toxicity study would not provide meaningful information and is not warranted to support a BLA. Similarly, reproductive and developmental toxicity studies would not provide meaningful information and are not warranted to support a BLA. The Applicant provided a weight of evidence (WOE)-based approach for the assessment of potential reproductive and developmental toxicity. Teclistamab is a T-cell redirecting bsAb; risks associated with T-cell activation include cytokine release and

associated inflammatory effects, which may adversely affect a pregnant woman or the developing fetus. Teclistamab may cross the placenta to the developing fetus. Due to the potential for teclistamab to cause fetal harm, the use of effective contraception is recommended for female patients of reproductive potential while receiving teclistamab and for 5 months after the last dose. The recommendation for the duration of contraception use is based on the FDA guidance "Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations".

There are no data on the presence of teclistamab in human milk, the effects on the breastfed child, or on milk production. Teclistamab is an IgG4-based bsAb construct, and maternal IgG is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed child are unknown. Because of the potential for serious adverse events in the breastfed child, the product label for teclistamab recommends women to avoid breastfeeding during treatment with teclistamab and for 5 months after the last dose. The recommendation for the duration to avoid breastfeeding is based on five-times the plasma $t_{1/2}$ of teclistamab, rounded up to 5 months.

Teclistamab binds BCMA and CD3 and promotes the T-cell dependent elimination of BCMA-expressing cells; the Established Pharmacologic Class of teclistamab is “bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager”.

The teclistamab container closure system was evaluated in an extractables and leachables study, and the Applicant submitted a toxicological safety assessment for compounds identified in the study; we agree with the conclusions of the toxicological safety assessment.

The nonclinical pharmacology, TK, and toxicology data submitted to BLA 761291 are adequate to support the approval of teclistamab for the proposed indication.

5.2 Pharmacology

Primary pharmacology

The binding affinity of teclistamab to CD3 expressed endogenously on human and cynomolgus monkey T-cells was determined by flow cytometry; teclistamab bound human T-cells (average K_D=28.03 nM) with slightly greater affinity than cynomolgus monkey T-cells (average K_D=38.48 nM). No appreciable binding of the parental CD3 monoclonal antibody to rodent CD3 was observed under the conditions tested. Surface plasmon resonance (SPR) studies demonstrated teclistamab bound purified human BCMA antigen (average K_D=0.18 nM) with ~36-fold greater affinity than purified cynomolgus monkey BCMA antigen (average K_D=6.5 nM); the relative binding affinity of teclistamab to murine BCMA antigen was much lower (average K_D=72.4 nM).

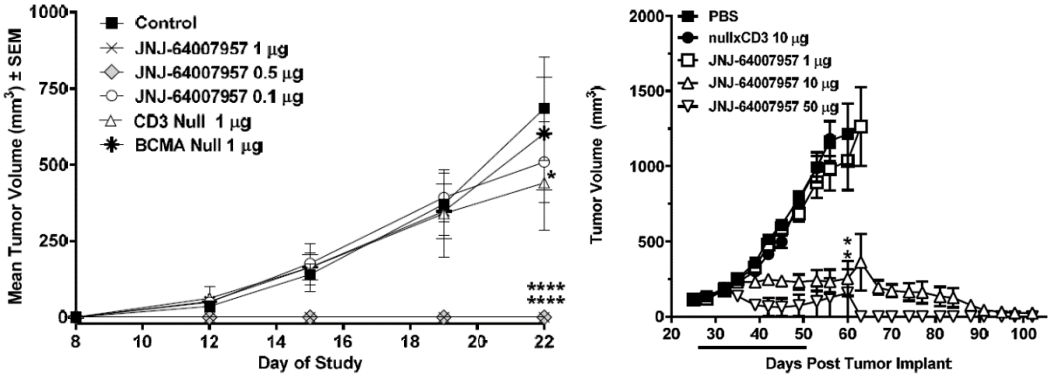
A commercially-available anti-BCMA antibody was used to detect BCMA protein on the surface of various B-cell and MM cell lines, and on $CD138^+$ cells isolated from healthy human donors and patients with MM. Flow cytometry studies demonstrated teclistamab bound MM cell lines that

are known to express BCMA. Peak binding for the H929, MM.1R, and RPMI 8226 cell lines was observed at ~60 nM, and the binding intensity correlated with the cell surface BCMA expression level. A similar binding pattern was observed for a control bsAb that binds BCMA but not CD3 (BCMAxnull); however, a control bsAb that binds CD3 but not BCMA (nullxCD3) did not specifically bind any of the cell lines under the conditions tested. Teclistamab did not bind the AML cell line MV4-11 that does not express BCMA. Teclistamab was not an agonist of BCMA receptor signaling in a BCMA signaling assay that measured p38 phosphorylation.

The pharmacologic activity of teclistamab was evaluated in a T-cell redirected lysis assay with the aforementioned cell lines as target cells and human T-cells as effector cells; this assay measured target cell lysis, T-cell activation, and cytokine release. Lysis of the BCMA-expressing target cell lines (EC_{50}=0.07-0.70 nM; maximum lysis=81-92%) was observed, but there was no lysis of the negative control target cell line MV4-11. Target cell lysis correlated with the induction of the T-cell activation marker CD25 (EC_{50}=0.15-0.50 nM; maximum activation=67-82%). The presence of cytokines was assessed in the assays with the H929 and RPMI8226 target cells only; IFNγ, TNFα, IL-2, IL-6, IL-8, and IL-10 were detected in these assay supernatants. Teclistamab did not activate T-cells in the absence of target cells. The BCMAxnull and nullxCD3 control bsAbs did not demonstrate any lytic activity, the potential to activate T-cells, or induce cytokine release under the conditions tested.

The in vivo antitumor activity of teclistamab was evaluated in human MM xenograft mouse studies. Both prophylactic and established tumor models were evaluated. In the prophylactic model, NSG mice were first intravenously implanted with human PBMCs, and 7 days later the mice were subcutaneously implanted with H929 human MM cells (study day 1); mice were then intravenously administered teclistamab (0.1, 0.5, or 1 µg) or control bsAbs on study days 1, 4, 6, 8, and 11. In the established tumor model, NSG mice were first subcutaneously implanted with RPMI-8226 human MM cells, and 18 days later the mice were intravenously implanted with human PBMCs (study day 1); mice were then intravenously administered teclistamab (0.1 or 1 µg) or control bsAbs on study Days 8, 11, 13, 15, 18, and 25. In the prophylactic model, teclistamab prevented tumorigenesis at doses ≥0.5 µg (see **FDA Figure 1**, left). In the established tumor model, modest antitumor activity was observed at 0.1 µg, but no antitumor activity was observed at 1 µg (data not shown). The established tumor model study was repeated under similar overall conditions, but with human pan T-cells intraperitoneally implanted in place of human PBMCs, and higher doses of teclistamab (1, 10, or 50 µg, IP) or nullxCD3 control bsAb administered on study Days 26, 29, 33, 36, 40, 43, 47, and 50. In the repeated established tumor model study, teclistamab demonstrated significant antitumor activity at doses ≥10 µg (see **FDA Figure 1**, right).

FDA Figure 1: Antitumor activity observed in prophylactic and established MM tumor models
(Figure excerpted from Applicant's submission)



Left: Prevention of tumorigenesis in H929 prophylactic model; right: TGI activity in RPMI-8226 established model

Secondary Pharmacology

The Applicant's Position:
No secondary pharmacology studies have been conducted.

The FDA's Assessment:
We agree that no secondary pharmacology studies were conducted or are needed to support the approval of BLA 761291.

Safety Pharmacology

The Applicant's Position:
The cynomolgus monkey was selected as the only pharmacologically relevant species for the nonclinical PK and toxicology assessments of teclistamab based on cross-species comparisons of sequence homology, relative target-binding affinities, and functional activity in cell-based assays.

Separate safety pharmacology studies were not conducted with teclistamab; however, the 5-week GLP study in cynomolgus monkey incorporated cardiovascular, respiratory as well as observational CNS assessments (body temperature and clinical signs).

There were no teclistamab-related effects on examined cardiovascular, respiratory, or CNS parameters associated with IV administration up to 30 mg/kg/week in cynomolgus monkey.

The FDA's Assessment:
We agree the cynomolgus monkey is a pharmacologically-relevant nonclinical species to assess the safety pharmacology of teclistamab, and we agree there were no teclistamab-related effects on safety pharmacology parameters in the 5-week repeat-dose toxicity study. We note that CNS endpoints in the 5-week study were evaluated by clinical observations only.

5.3 Referenced NDAs, BLAs, DMFs

The Applicant's Position:
There are no referenced NDAs, BLA, or Drug Master Files related to nonclinical pharmacology or toxicology for teclistamab.

The FDA's Assessment:
We agree that no other applications are being referenced to support the approval of BLA 761291.

5.4 ADME/PK

The Applicant's Position:
The nonclinical PK program characterized the linearity, dose proportionality, and immunogenicity of teclistamab in cynomolgus monkeys, the pharmacologically relevant species (see Section 5.3).

- In repeat-dose IV toxicity studies dosed for up to 5 weeks, most cynomolgus monkeys administered teclistamab weekly demonstrated continuous exposure at concentrations expected to be pharmacologic based on in vitro assays.
- At doses >0.1 mg/kg/week, systemic exposure increased in a dose-proportional manner, with no apparent sex-related differences and minimal accumulation (approximately 2-fold) in the study.
- Among the 30 cynomolgus monkeys dosed with teclistamab in the IV 5-week study, 21 tested positive for the presence of ADA. Seven of the 21 ADA-positive animals had lower exposure compared with other animals in the same group. The total of 7 animals includes 1, 2, and 2 animals in the 1, 10, and 30 mg/kg/week groups, respectively, during the Day 22 dosing period and 1 animal each in the 1 and 10 mg/kg/week groups on Day 29.
- Conventional distribution, metabolism, and excretion studies were not conducted for teclistamab since it is an IgG-based bispecific antibody with a molecular weight of approximately 146,000 kD.

The FDA's Assessment:
Teclistamab TK parameters from the 5-week repeat-dose toxicology study in cynomolgus monkeys are described in **FDA Table 1**; this study evaluated the IV route of administration, whereas the clinical route of administration is SC. The local tolerance study in New Zealand White rabbits did not evaluate teclistamab TK parameters.

TK data from general toxicology studies

JNJ-64007957 (BCMAxCD3): A 5-Week, Intravenous Repeat-dose GLP Toxicity Study in Cynomolgus Monkeys with a 8-Week Recovery Period / T-2016-030

FDA Table 1: 5-week repeat-dose toxicology study in cynomolgus monkeys, summary of mean teclistamab TK parameters

Dose of teclistamab (mg/kg/dose)	Sex	Following Dose on Day 1		Following Dose on Day 22			Following Dose on Day 29	ADA^
		C_{max} (µg/mL)	AUC_{Day1-8} (µg*day/mL)	C_{max} (µg/mL)	$AUC_{Day22-29}$ (µg*day/mL)	R	$t_{1/2}$ (day)	
1	M	25.99	63.28	39.75	151.63	2.41	NR	4/5
	F	27.56	63.44	37.41	106.23	1.67	10.64	4/5
10	M	288.78	704.67	415.93	1220.97	1.77	NR	4/5
	F	311.82	735.04	419.57	1141.47	1.54	NR	4/5
30	M	793.59	2020.05	1054.61	2813.04	1.41	10.27	3/5
	F	777.30	2044.64	1113.40	4285.33	2.09	NR	2/5

R: accumulation ratio calculated from $AUC_{Day22-29}$ and AUC_{Day1-8}; NR: not recorded; ^ incidence of animals with ADAs present on ≥1 occasion (animals with ADAs were excluded from the calculation of $t_{1/2}$ following dose on Day 29)

5.5 Toxicology

The nonclinical program for teclistamab was conducted in accordance with the ICH guidelines S9 and S6(R1), as well as S7A, S2(R1), M3(R2), S3A, and S5(R3). All nonclinical studies were conducted in accordance with best scientific principles. Pivotal nonclinical studies were conducted in conformance with GLP, 21 CFR, Part 58 and/or the principles of OECD-GLP in countries that are part of the OECD Mutual Acceptance of Data process and include the appropriate documentation. The cynomolgus monkey is considered the pharmacologically relevant species for the toxicology program of teclistamab (see Section 5.3).

5.5.1. General Toxicology

The Applicant's Position:

Teclistamab was well tolerated in cynomolgus monkey when administered IV for weekly doses up to 30 mg/kg for 5 weeks in GLP and non-GLP studies. The lack of pharmacodynamic (eg, cytokine release or transient lymphocyte decreases) or toxicological response to teclistamab was attributed to a combination of BCMA-expressing plasma cells (and consequently low expression of BCMA) in a healthy cynomolgus monkey relative to a patient and limited cross

reactivity of teclistamab to cynomolgus monkey relative to humans. The no-observed-effect level for 5 weekly IV doses of teclistamab-treated monkeys was 30 mg/kg , the highest dose tested, with corresponding $AUC_{Day22-29}$ and Day 22 C_{max} mean values of 3549 µg·day/mL and 1084 µg/mL, respectively. All doses were expected to be pharmacologically active, as mean serum concentrations of teclistamab throughout the treatment periods were higher than the EC_{50} (0.09 to 0.48 ug/mL) for cytotoxicity with cynomolgus monkey T cells against cBCMA-expressing target cells.

No evidence of immunotoxicity in cynomolgus monkeys was observed following IV weekly dosing in any of the above toxicity studies. While ADAs were detected in a number of animals in the toxicology studies, the relationship between immunogenicity in animals and human is not well established, and results in animals are not expected to be predictive of the human immunogenic response (Bugelski 2004).

A 3-month toxicity study in cynomolgus monkeys was not conducted due to the absence of pharmacologic or toxicologic effects, the high incidence of ADAs in the 5-week study that impacted exposure in some animals, and the restricted expression of BCMA to the B cell lineage that limits the potential for toxicity on other normal cells and tissues. In accordance with the above, the FDA provided feedback via written responses only and agreed a 3-month animal toxicology study is not warranted.

A SC local tolerance GLP study demonstrated teclistamab was well tolerated at injection sites in New Zealand rabbits administered a single dose of 20 mg (2.0 mL dose volume) in formulation buffer. Because rabbits are not a pharmacologically relevant species, this study only tested the local tolerance of the formulation at an antibody protein concentration of 10 mg/mL. The formulation buffer contains the same components as the drug product. Additionally, there were no adverse injection site findings following repeat-dose IV administration in cynomolgus monkeys administered doses of 1, 10, or 30 mg/kg/week.

The FDA's Assessment:

We agree with the Applicant's assessment of the 5-week repeat-dose toxicity study in cynomolgus monkeys; a detailed review of this study is provided below. Lack of PD activity or teclistamab-related adverse effects at dose levels expected to be pharmacologically active may be attributed to the relatively low binding affinity of teclistamab to cynomolgus monkey BCMA, the paucity of BCMA-expressing target cells, and the decreased teclistamab systemic exposure in animals affected by ADAs. A longer-duration repeat-dose toxicity study would not provide meaningful information and is not warranted. The cynomolgus monkey is a pharmacologically-relevant nonclinical species to assess the toxicology of teclistamab and general toxicology studies in other species are not warranted.

We agree with the Applicant's assessment of the local tolerance study in New Zealand White rabbits.

Study title / Study number: JNJ-64007957 (BCMAxCD3): A 5-Week, Intravenous Repeat-dose GLP

Toxicity Study in Cynomolgus Monkeys with a 8-Week Recovery Period / T-2016-030

Key Study Findings

- JNJ-64007957 was well tolerated with no test article-related observations.
- ADAs were detected at least once in 21/30 test article-treated animals; seven of these animals exhibited lower JNJ-64007957 exposure after dosing on Day 22 or Day 29.

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0 (control), 1, 10, or 30 mg/kg/dose Once weekly for 5 total doses (Days 1, 8, 15, 22, and 29) An 8-week recovery period was included at the end of the 5th dosing cycle
Route of administration:	IV injection (slow bolus)
Formulation/Vehicle:	(b) (4) Acetate, (b) (4) (w/v) Sucrose, (b) (4) (w/v) PS20, (b) (4) µg/mL (b) (4), at pH (b) (4)
Species/Strain:	Cynomolgus monkey
Number/Sex/Group:	Main study: 3 animals/sex/group Recovery period: 2 animals/sex/group
Age:	2.7 to 4.3 years old
Satellite groups/ unique design:	No
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	None
Clinical Signs	Unremarkable
Body Weights	Unremarkable
Ophthalmoscopy	Unremarkable
ECG	Unremarkable
Body Temperature	Unremarkable
Respiration Rate	Unremarkable
Blood Pressure	Unremarkable
Heart Rate	Unremarkable
Hematology and Coagulation	Unremarkable
Clinical Chemistry	Unremarkable
Immunophenotyping	Unremarkable
Cytokines	Unremarkable
Gross Pathology	Unremarkable
Organ Weights	Unremarkable
Histopathology	Unremarkable
Anti-Drug Antibodies	Incidence of animals with ADAs on ≥1 occasion: LD: 4/5 (M); 4/5 (F) MD: 4/5 (M); 4/5 (F) HD: 3/5 (M); 2/5 (F)

LD, low dose; MD, mid dose; HD, high dose

5.5.2. Genetic Toxicology

The Applicant's Position:
Genotoxicity studies were not conducted with teclistamab. As indicated in the ICH S6(R1) guidance, genotoxicity studies routinely conducted for pharmaceuticals, are not appropriate for biotechnology-derived pharmaceuticals such as monoclonal antibodies.

The FDA's Assessment:
We agree that genotoxicity studies are not needed to support the approval of BLA 761261.

5.5.3. Carcinogenicity

The Applicant's Position:
Carcinogenicity studies were not conducted with teclistamab. As indicated in the ICH S9 guidance, carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer.

The FDA's Assessment:
We agree that carcinogenicity studies are not needed to support the approval of BLA 761261.

5.5.4. Reproductive and Developmental Toxicology

The Applicant's Position:
No reproductive and developmental toxicity studies were conducted for teclistamab. In accordance with ICH S5(R3) and S6(R1) and the US FDA Guidance for Oncology, a weight of evidence based on the intended patient population, BCMA target biology including data from genetically modified mice that lack BCMA, the mechanism of action of teclistamab and published data on trafficking of antibodies has been provided in Module 2.4 "Reproductive and Developmental Studies" to provide information on pregnancy risk. Teclistamab is not expected to be teratogenic based on the restricted expression of BCMA on plasma cell lineage compared with other normal cells and tissues and the on-target specificity of teclistamab.

The FDA's Assessment:
We agree with the Applicant's WOE-based approach for the assessment of reproductive and developmental toxicity. There is no BCMA gene or protein expression in human reproductive organs; therefore, the risk of on-target/off-tumor toxicity in these tissues is relatively low. In the 5-week repeat-dose toxicity study in cynomolgus monkeys, there were no findings in reproductive tissues. Mice deficient in BCMA developed normally.

In the tissue cross-reactivity study with normal human tissues (see 5.5.5. Other Toxicology Studies), teclistamab stained mononuclear leukocytes in the ovary and prostate. Teclistamab is a T-cell redirecting bsAb; risks associated with T-cell activation include cytokine release and associated inflammatory effects. The occurrence of inflammatory AEs in the mother may adversely affect the pregnancy or the developing fetus. Teclistamab may cross the placenta to the developing fetus similarly as an endogenous IgG antibody. It is unknown if the level of BCMA

expression in the developing fetus could trigger inflammatory effects.

The approval of BLA 761291 does not rely on product-specific published literature.

5.5.5. Other Toxicology Studies

The Applicant's Position:
In the in vitro tissue cross reactivity studies (non-GLP: monkey and human; GLP: human), teclistamab staining of mononuclear cells occurred very rarely to occasionally in most tissues. Teclistamab was compatible with human blood and serum at concentrations up to 10 mg/mL. In addition, in an in vitro assay using whole human blood, the cytokine release profile demonstrated teclistamab induced statistically significant but low-level release of IL-8, IFN-α, and TNF-α at concentrations ≥82 ng/mL compared with negative control.

The FDA's Assessment:
We agree with the Applicant's assessment of the GLP human tissue cross reactivity study, hemolytic potential and serum compatibility studies, and in vitro cytokine release assay.

In the tissue cross-reactivity study, teclistamab stained mononuclear leukocytes in the peripheral blood smears, lymphoid tissues, and select non-lymphoid tissues (ovary, prostate, and skin). Teclistamab is expected to bind mononuclear leukocytes; no unanticipated cross-reactivity was observed.

The in vitro cytokine release assay was conducted in the soluble format only. In addition to statistically significant increases in IL-8, IFN-γ, and TNF-α, lower level increases in IL-2 and IL-1β were observed. EC_{50} values were not provided for any cytokine.

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Michael Manning, PhD
Primary Reviewer

Brenda Gehrke, PhD
Supervisor

6. Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:
Teclistamab is a humanized IgG4 bispecific antibody directed against the B-cell maturation antigen (BCMA) and CD3 receptors. The proposed recommended dosage regimen consists of a step-up dosing regimen [0.06 mg/kg subcutaneously (SC), followed 2 to 4 days later by 0.3 mg/kg SC, followed 2 to 4 days later by 1.5 mg/kg SC] followed by weekly administration at 1.5 mg/kg SC thereafter.

BLA 761291 includes clinical data from one clinical study. Study 64007957MMY1001 (MajesTEC-1) is an ongoing, first-in-human, Phase 1/2, dose escalation and expansion study of teclistamab administered either intravenously (IV) or SC in adult patients with relapsed or refractory multiple myeloma. A total of 340 patients had received at least one dose of teclistamab by the data cut-off date (7 Sep 2021) including 165 patients at the proposed recommended SC dosage regimen. Important safety events include cytokine release syndrome (CRS) and neurologic adverse events including immune effector cell-associated neurotoxicity syndrome (ICANS). The step-up dosing regimen and SC route of administration are intended to reduce the rate and severity of CRS.

A population PK (PPK) and exposure-response (E-R) report was submitted based on a data cut-off date of 14 Jun 2021. The PPK model includes data from 308 patients treated with teclistamab (n=83 IV + n=225 SC) and evaluated covariates including age, sex, race, ethnicity, body weight, renal function, hepatic function, disease characteristics, and prior treatments. The E-R analyses include evaluation of potential relationships between teclistamab exposure and overall response rate (ORR), progression-free survival (PFS), duration of response (DOR), overall survival (OS), and selected treatment-emergent adverse events of interest (Grade ≥3 anemia, neutropenia, lymphopenia, thrombocytopenia, and infection).

Recommendations: The Office of Clinical Pharmacology has reviewed the information submitted in BLA 761291. This BLA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below in ***FDA Table 2***.

FDA Table 2: Key FDA Clinical Pharmacology Review Issues

Review Issue	Recommendations and Comments
Pivotal and Supportive evidence of effectiveness	The primary evidence of effectiveness is the overall response rate (ORR) observed in MajesTEC-1 (see **Section 8.1.2 – Study Results**). The Applicant's proposed SC dosing regimen is supported by the ORR observed in 110 patients with relapsed or refractory multiple myeloma treated with the recommended SC dosing regimen.
General dosing instructions	The recommended SC dosing regimen (step-up dosing schedule of 0.06 mg/kg on Day 1, 0.3 mg/kg on Day 4, and 1.5 mg/kg on Day 7, followed by 1.5 mg/kg once weekly thereafter) is acceptable for approval in the general patient population.

Review Issue	Recommendations and Comments
	• The recommended SC dosing regimen demonstrated clinically meaningful ORR and an acceptable safety profile (with appropriate monitoring and adverse event management) in patients enrolled in MajesTEC-1. • MajesTEC-1 allowed flexibility in the timing of administration for the step-up dosing schedule (2-4 days between each of the first three doses with longer interval if needed to allow for resolution of toxicities). A 3-day interval between each of the first 3 doses is described in the labeling to reduce confusion. Based on the observed dosing intervals in MajesTEC-1, allowance to administer the first 3 doses with 2-4 days between each dose and up to 7 days if needed to allow for resolution of toxicities is described in footnotes.
Dosing in patient subgroups	No therapeutic individualization of teclistamab is needed based on age, sex, race, ethnicity, mild or moderate renal impairment, or mild hepatic impairment. Limited data are available in patients with severe renal impairment and no data are available in patients with moderate or severe hepatic impairment. Dedicated studies in patients with severe renal impairment or moderate or severe hepatic impairment are not required given that teclistamab is a large biologic that is not expected to have substantial renal or hepatic clearance.
Drug-drug interactions	No clinical drug interaction studies were conducted with teclistamab. Teclistamab causes release of cytokines (including IL-6 and IL-10) that may suppress activity of cytochrome P450 (CYP) enzymes, resulting in increased exposure of CYP substrates. The highest risk of drug-drug interaction is expected to occur from initiation of the step-up dosing schedule up to 7 days after the first treatment dose and during and after CRS. Patients receiving concomitant CYP substrates where minimal concentration changes may lead to serious adverse reactions should be monitored for toxicity or CYP substrate concentrations. The dose of the concomitant CYP substrate drug should be adjusted as needed.
Labeling	Overall, the proposed labeling recommendations are acceptable upon the Applicant's agreement to the FDA revisions to the label.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:

Teclistamab exhibited approximately dose-proportional PK following IV administration across a dose range of 0.0192 to 0.72 mg/kg and SC administration across a dose range of 0.08 to 3 mg/kg. Mean half-life following the first IV treatment dose was 3.8±1.7 days (n=66, individual values range up to 8.8 days). Following the treatment dose of teclistamab SC RP2D, individual T_{max} occurred 2 to 7 days after SC injection, and C_{trough} was maintained above the maximum EC_{90} value identified in the ex vivo cytotoxicity study, which was set as a target threshold for sustained clinical activity. PK steady state was reached in Cycle 3 following teclistamab SC weekly dosing. Mean accumulation ratio at steady state was 2.71- and 3.05-fold for C_{max} and AUC_{tau}, respectively. Based on available AUC_{tau} values at steady state from IV and SC weekly dosing data, mean

bioavailability following teclistamab SC weekly administration for the treatment dose was 69% (see also Section 6.3.1).

The observed teclistamab serum concentration-time data following IV and SC administration were adequately described by a 2-compartment model with first-order absorption and parallel time-independent and time-dependent (decrease over time) elimination pathways. The final PPK model included effects of body weight on time-independent clearance (CL_1), volume of distribution of the central compartment (V_1), and volume of distribution of the peripheral compartment (V_2), the effect of ISS on CL_1, and the effect of type of myeloma (IgG versus non-IgG) on CL_1 and clearance associated with time-dependent clearance (CL_2; see also Section 6.3.1).

E-R analyses indicated a trend toward increased ORR (assessed by investigator based on IMWG 2011 criteria) with increased teclistamab exposure in a wide range of SC doses (0.08 to 3 mg/kg weekly), approaching plateau at the RP2D of 1.5 mg/kg. Responders and non-responders (assessed by IRC based on IMWG 2016 criteria), who received teclistamab at RP2D in Phase 1 and in Cohort A of Phase 2, had comparable and overlapping exposure range. No apparent positive E-R trend was observed in the incidence of Grade ≥3 TEAEs of anemia, neutropenia, lymphopenia, thrombocytopenia, and infections across the predicted exposure quartiles in subjects who received teclistamab SC (see also Section 6.3.1).

The Applicant's Position:

The clinical pharmacology findings in this application, including PPK and E-R analyses, are consistent with the observed clinical benefit of the recommended dose of teclistamab (1.5 mg/kg administered weekly [SC], with the first treatment dose preceded by step-up doses of 0.06 and 0.3 mg/kg), with clinically manageable side effects. Overall, the clinical pharmacology findings support the above proposed registrational dose of teclistamab in adults with relapsed or refractory multiple myeloma.

The FDA's Assessment:

The FDA agrees with the Applicant's summary of pharmacology and clinical pharmacokinetics with the following exceptions or clarifications:

- Teclistamab PK parameters after IV administration are not reported in labeling given that only the SC route of administration is recommended.
- At the recommended SC dosage regimen, the median (range) T_{max} of teclistamab after the first treatment dose was 139 (19 to 168) hours.
- Based on the PPK model for teclistamab, approximately 100% steady state exposure is achieved after the 24th treatment dose at the recommended SC dosage regimen. Ninety percent of steady state exposure is achieved after 12 weekly treatment doses. Therefore, FDA revised all reported PK parameters (including accumulation ratios and bioavailability) based on the 13th treatment dose (see **Section 6.3.1 – General Pharmacology and Pharmacokinetic Characteristics**).
- The E-R analysis for ORR (assessed by investigator based on IMWG 2011 criteria) included 72 patients treated with various SC dosage regimens during the Phase 1 portion of MajesTEC-1.
- The E-R analyses for safety included 199 patients treated with various SC dosage regimens in the Phase 1 portion of MajesTEC-1 or Phase 2 Cohort A of MajesTEC-1.

- No clear E-R safety associations were identified for select TEAEs including Grade ≥3 cytopenias, TEAEs leading to dose modifications, or neurologic toxicity.
- FDA conducted exploratory E-R safety analyses for CRS following step-up dose 1 and step-up dose 2 in order to assess whether the proposed step-up dosing regimen resulted in any exposure peaks associated with unacceptably high CRS incidence. The exploratory E-R analysis did not identify any safety concerns regarding CRS for the proposed 0.06/0.3/1.5 mg/kg SC step-up dosing regimen. Additionally, this multivariate analysis suggested that tocilizumab administration to treat CRS with step-up dose 1 may impact the rate of CRS with step-up dose 2. Refer to **Section 19.4.3.5** for additional details.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:

The registrational treatment dose of teclistamab (1.5 mg/kg SC administered weekly, with the first treatment dose preceded by step-up doses of 0.06 and 0.3 mg/kg) was selected based on the following results from Phase 1 dose escalation: 1) PK data indicating the selected dose achieved desired target exposure above the maximum EC90, 2) pharmacodynamic data demonstrating T cell activation; and 3) favorable early clinical safety and efficacy profiles of the selected dose which were evaluated and confirmed by the Part 2 expansion at RP2D. SC was chosen as the route of administration for ease and convenience for patients and healthcare providers compared with IV administration.

Moreover, E-R trend was observed for ORR assessed by investigator based on IMWG 2011 criteria in Phase 1 (Phase 1 ORR) where ORR increased with teclistamab exposure across SC doses ranging from 0.08 to 3 mg/kg weekly, approaching plateau at the RP2D. Phase 2 further established 1.5 mg/kg SC weekly as a safe and effective dose for the treatment of relapsed or refractory multiple myeloma.

Clinical efficacy and safety data for subjects treated at pivotal RP2D are summarized in Section 8.

The Applicant's Position:

RP2D achieved exposure consistently above the maximum EC_{90}, optimal activation of T cells and induction of cytokines, a favorable safety profile, and compelling efficacy results. The clinical PK, pharmacodynamics, safety, and efficacy findings support the proposed teclistamab 1.5 mg/kg SC weekly regimen in adults with relapsed or refractory multiple myeloma.

The FDA's Assessment:

The FDA agrees that the recommended SC dosage regimen of teclistamab is acceptable for the general population of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody. Data supporting the recommended SC dosage regimen are described in detail below.

6.2.2.2. Therapeutic Individualization

Data:

The individual patient characteristics (covariates) of interest assessed in the PPK analysis based on all subjects in MajesTEC-1 (including Phase 1, pivotal RP2D, and Cohort C) include the following: demographic characteristics (body weight, age, sex, race, region, ethnicity [Hispanic versus non-Hispanic; Asian versus non-Asian]), disease characteristics and biomarkers (baseline total T cells, baseline sBCMA and sBCMA over time, baseline bone marrow percent plasma cells, baseline plasmacytoma, baseline type of myeloma, baseline lesion number, baseline lytic lesion, baseline ECOG status, baseline ISS, baseline revised ISS staging, cytogenetic risk), clinical laboratory characteristics (baseline creatinine clearance, baseline albumin, baseline alanine aminotransferase, baseline alkaline phosphatase, renal function, hepatic function), prior treatment and refractory status (prior use of anti-CD38 antibodies, prior use of anti-PD1/anti-programmed cell death-ligand 1, prior use of anti-BCMA treatment, triple refractory status, penta-refractory status, number of prior lines of therapies [≤3 versus >3]) and drug products.

The model-predicted individual PK exposure metrics, predicted average concentration of the first treatment dose ($C_{ave,1stdose}$) and predicted steady-state trough concentration ($C_{trough,ss}$) at the RP2D, were compared across different strata for covariates of interest. No clinically meaningful differences (ie, <20%-30%) in the exposure to teclistamab were observed in subjects with different body weight when teclistamab was administered on the weight proportional dosing regimen. Exposure of teclistamab largely overlapped across body weight subgroups. The disease status variables including multiple myeloma type (IgG vs non-IgG) and ISS staging (II vs I and III vs I) affected teclistamab exposure. The simulated $C_{ave,1stdose}$ and $C_{trough,ss}$ were approximately 33% and 47% lower in subjects with IgG type of multiple myeloma, respectively, compared with those with non-IgG type of multiple myeloma. The simulated $C_{ave,1stdose}$ and $C_{trough,ss}$ were approximately 15% and 31% lower in subjects with ISS stage II, respectively, compared with those with ISS stage I. The simulated $C_{ave,1stdose}$ and $C_{trough,ss}$ were approximately 28% and 43% lower in subjects with ISS stage III, respectively, compared with those with ISS stage I. However, further clinical efficacy subgroup analyses and E-R analyses demonstrated that these covariates had no clinically relevant effect on efficacy at the recommended dose regimen. Additionally, results of PPK analysis indicated that mild or moderate renal impairment and mild hepatic impairment did not influence teclistamab PK. Limited data were available from patients with severe renal impairment, and no data were available from patients with moderate or severe hepatic impairment. Furthermore, E-R analyses, which are detailed in the PPK report, indicated a near flat E-R trend for ORR assessed by IRC based on IMWG 2016 criteria in subjects who received teclistamab at RP2D, and responders and non-responders had comparable and overlapping exposure range.

The Applicant's Position:

The PPK and E-R analyses supported the selected teclistamab RP2D of 1.5 mg/kg SC administered

weekly, with the first treatment dose preceded by step-up doses of 0.06 and 0.3 mg/kg for the treatment of relapsed or refractory multiple myeloma. No dose adjustment is recommended based on the investigated factors.

The FDA's Assessment:
The FDA agrees that therapeutic individualization of teclistamab is not required based on intrinsic patient factors including age, sex, race, ethnicity, renal impairment, and hepatic impairment. With the recommended SC dosage regimen, no exposure differences with clinically relevant impacts are expected according to body weight, myeloma type (IgG versus non-IgG), ISS stage, or race (White compared to Black or African American), or any other patient characteristic. Refer to **Section 19.4.2.2** for additional details.

6.2.2.3. Outstanding Issues

Data and Applicant's Position:
Not applicable.

The FDA's Assessment:
The FDA agrees that there are no outstanding clinical pharmacology issues.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:
The clinical pharmacology of teclistamab has been studied in subjects with relapsed or refractory multiple myeloma who received teclistamab by IV infusion or SC injection. Levels of serum teclistamab, biomarkers and anti-teclistamab antibodies were measured to evaluate PK, pharmacodynamics, and immunogenicity.

Pharmacokinetics

- Following treatment with teclistamab at RP2D of 1.5 mg/kg administered SC weekly, teclistamab mean C_{trough} was maintained above the maximum EC_{90} identified in an ex vivo cytotoxicity assay. Following multiple 1.5 mg/kg SC weekly doses, the mean accumulation ratio (Cycle 3:Cycle 1) was 2.71- and 3.05-fold for C_{max} and AUC_{tau}, respectively.
- In Phase 1, following the first treatment dose of teclistamab SC in Cycle 1 and Cycle 3, PK exposure (C_{max} and AUC) increased in an approximately dose-proportional manner across the dose range of 0.08 to 3 mg/kg weekly. PK steady state was attained in Cycle 3 following teclistamab weekly SC dosing. Based on available AUC_{tau} values at steady state from all IV and SC weekly dosing cohorts, mean bioavailability following SC weekly administration for the treatment dose was 69%.
- After the first treatment dose of teclistamab IV in Cycle 1 and Cycle 3, PK exposure (C_{max} and AUC) increased in an approximately dose proportional manner across the dose range of 0.0192 to 0.72 mg/kg. The estimated mean±SD half-life ($t_{1/2}$) based on the pooled data from

IV cohorts was 91.5±41.1 hours (n=66, individual $t_{1/2}$ ranging from 20.4 to 210.2 hours) following the first treatment dose in Cycle 1.

Population Pharmacokinetic and Exposure-response Analysis

Population Pharmacokinetics

- The observed teclistamab serum concentration-time data were adequately described by a 2-compartment model with first-order absorption and parallel time-independent and time-dependent (decrease over time) elimination pathways.
- The typical population values of time-independent clearance (CL_1), clearance associated with time-dependent clearance (CL_2), inter-compartmental clearance (Q), volume of distribution of the central compartment (V_1), and volume of distribution of the peripheral compartment (V_2) in subjects with a median weight of 74 kg (based on the patient population in MajesTEC-1) were 0.545 L/day, 0.327 L/day, 0.0473 L/day, 4.09 L, and 1.29 L, respectively. The rate constant for CL_2 decrease over time (K_{DES}) was 0.0328 day^{-1}. The median of time- dependent clearance (CL_t), of teclistamab is approximately 31% of the total clearance (CL_1+CL_t) at initial treatment and decreased rapidly thereafter, <5% after Week 8. The typical values of first-order absorption rate constant K_a and SC bioavailability were 0.140 day^{-1} and 67.2%, respectively. This estimate is similar to the one calculated by the non-compartmental analysis (69%).
- The final population PK model included effects of body weight on CL_1, V_1, and V_2, the effects of ISS on CL_1, and the effect of type of myeloma (IgG versus non-IgG) on CL_1 and CL_2.
- Although body weight, type of myeloma, and ISS staging were statistically significant covariates on the PK of teclistamab, further clinical efficacy subgroup analyses and E-R analyses demonstrated that these covariates had no clinically relevant effect on the efficacy at the recommended dose regimen.
- None of the investigated factors (ie, age, sex, body weight, race, region, ethnicity, creatinine clearance, albumin concentration, renal and hepatic function, baseline sBCMA, bone marrow percent plasma cells, plasmacytoma, ECOG status, ISS/revised ISS stage, type of myeloma [IgG versus non-IgG], number of prior lines of therapy, prior use of daratumumab, prior use of anti-PD1/anti-programmed cell death-ligand 1, prior use of anti-BCMA treatment, refractory status, immune response status, and drug product) had meaningful effect on teclistamab PK. No dose adjustment is recommended based on these investigated factors.

Exposure-response

- E-R analyses indicated a near flat E-R trend for ORR assessed by IRC based on IMWG 2016 criteria in subjects who received RP2D dose regimen (RP2D ORR). Responders and non-responders had comparable and overlapping exposure range. The prognostic factors that were significantly associated with the overall (or best) response in the multivariate analysis based on current analysis dataset were baseline sBCMA and PD1 expression. In addition, duration of response, progression-free survival, and overall survival were not significantly

correlated with teclistamab exposures at the RP2D dose.

- An E-R trend was observed for ORR assessed by investigator based on IMWG 2011 criteria in SC subjects in Phase 1 (Phase 1 ORR) where ORR increased with teclistamab exposure across SC doses ranging from 0.08 to 3 mg/kg weekly, approaching plateau at the RP2D of 1.5 mg/kg.
- No apparent positive E-R trend was observed in the incidence of Grade ≥3 TEAEs of anemia, neutropenia, lymphopenia, thrombocytopenia, and infections across the predicted exposure quartiles in subjects who received teclistamab SC.

Pharmacodynamics

- A rapid decrease in total sBCMA was observed in a majority of responders within the first month of treatment, and a greater reduction in sBCMA tended to occur in subjects with deeper responses to teclistamab at pivotal RP2D and in Phase 1. Responders to teclistamab also showed a trend of sBCMA reduction over time.
- Cytokine induction was observed in subjects treated at the pivotal RP2D and in Phase 1, as demonstrated by increases in IL-6, IL-10, IL-2Rα, interferon-gamma (Phase 2 only), and tumor necrosis factor-alpha (Phase 2 only).
- T-cell activation was induced following initial doses of teclistamab for subjects treated at RP2D in both Phase 1 and Phase 2, as evidenced by upregulation of CD25, CD38, PD1, human leukocyte antigen-DR isotype, lymphocyte activation gene-3, or T-cell immunoglobulin and mucin domain-containing protein 3 on CD8 and CD4 T cells.
- T-cell redistribution was observed in subjects treated at RP2D in both Phase 1 and Phase 2, as demonstrated by reduction in peripheral CD4+ and CD8+ T cells after the initial doses of teclistamab.
- Reduction of CD19+ B cells was observed in subjects treated at pivotal RP2D within the first cycle. Persistently decreased levels were noted at Cycle 3.

Immunogenicity

- One of 82 subjects (1.2%) receiving teclistamab IV and 1 of 219 subjects (0.5%) receiving teclistamab SC developed ADAs. These ADAs were neutralizing antibodies to teclistamab. These ADAs had a low titer of 20 and seemed to have no impact on safety in these 2 subjects. Based on available PK data from the subject with IV administration, these ADAs did not seem to affect teclistamab PK.
- None (0%) of the 173 subjects who were ADA evaluable for RP2D were identified as positive for antibodies to teclistamab. Overall, the incidence of antibodies to teclistamab was low in subjects treated with either teclistamab IV or SC.

The Applicant's Position:

Clinical pharmacology findings support the registrational treatment dose of teclistamab:
1.5 mg/kg SC administered weekly, with the first treatment dose preceded by step-up doses of 0.06 and 0.3 mg/kg.

The FDA's Assessment:

General pharmacology and PK characteristics of teclistamab based on FDA review are summarized in **FDA Table 3**. PK characteristics are reported based on the teclistamab population PK model and the recommended SC dosing regimen unless otherwise noted. Teclistamab PK parameters after IV administration are not reported given that only the SC route of administration is recommended.

FDA Table 3: Teclistamab General Pharmacology and Pharmacokinetic Characteristics

General Information	
Bioanalysis	The concentration of teclistamab in serum samples from patients in MajesTEC-1 was quantified using validated analytical methods. Refer to **Section 19.4.1**.
Dose Proportionality	The C_{max} and AUC_{tau} of teclistamab after the first subcutaneous treatment dose increase proportionally over a dosage range of 0.08 mg/kg to 3 mg/kg.
Accumulation	Ninety percent of steady-state exposure was achieved after 12 weekly treatment doses of teclistamab. The mean accumulation ratio between the first and 13th weekly treatment dose of teclistamab 1.5 mg/kg SC was 4.2-fold for C_{max}, 4.1-fold for C_{trough}, and 5.3-fold for AUC_{tau}.
Drug Exposure	The geometric mean (CV%) PK parameters for teclistamab after the 13th treatment dose of 1.5 mg/kg SC were 23.8 mcg/mL (55%) for C_{max}, 21.1 mcg/mL (63%) for C_{trough}, and 3,838 mcg*h/mL (57%) for AUC_{tau}.
Population PK Model	Teclistamab PK was described by a 2-compartment model with first-order absorption (SC route) and both time-dependent and time-independent clearance. Refer to **Section 19.4.2** for details.
Absorption	
Bioavailability	The mean bioavailability of teclistamab was 72% when administered SC.
T_{max}	The median (range) T_{max} of teclistamab after the first and 13th treatment doses were 139 (19 to 168) hours and 72 (24 to 168) hours, respectively.
Distribution	
Volume of Distribution	The mean (CV%) volume of distribution of teclistamab was 5.63 L (29%). The volume of distribution of teclistamab increases with increasing body weight (41 to 139 kg).
Elimination	
Half-Life and Clearance	Teclistamab clearance decreases over time, with a mean (CV%) maximal reduction from baseline to the 13th treatment dose of 40.8% (56%). The geometric mean (CV%) clearance is 0.472 L/day (64%) at the 13th treatment dose. The clearance of teclistamab increases with increasing body weight (41 to 139 kg). At the 13th treatment dose, the mean (SD) alpha half-life was 5.7 (2.4) days and the mean (SD) terminal elimination (i.e., beta) half-life was 27.7 (8.2) days. Patients who discontinue teclistamab-cqyv after the 13th treatment dose are expected to have a 50% reduction from C_{max} in teclistamab-cqyv concentration at a median (5th to 95th percentile) time of 15 (7 to 33) days after T_{max} and a 97% reduction from C_{max} in teclistamab-cqyv concentration at a median time of 69 (32 to 163) days after T_{max}.

Specific Populations	
Intrinsic Factors	There were no clinically significant differences in the PK of teclistamab based on age (24 to 84 years), sex, race (White, Black or African American), ethnicity (Hispanic/Latino, not Hispanic/Latino), mild or moderate renal impairment (individualized estimated glomerular filtration rate [eGFR] by Modification of Diet in Renal Disease [MDRD] method: 30 to 89 mL/min), or mild hepatic impairment (total bilirubin less than or equal to upper limit of normal [ULN] with AST greater than ULN or total bilirubin greater than 1 to 1.5 times ULN with any AST). The effects of severe renal impairment (individualized eGFR less than 30 mL/min) or moderate to severe hepatic impairment (total bilirubin greater than 1.5 times ULN with any AST) on the pharmacokinetics of teclistamab are unknown.
Other	
Immunogenicity	During treatment in MajesTEC-1 (up to 27 months), 1/186 (0.5%) of patients treated with SC teclistamab developed anti-teclistamab antibodies. No patients treated with the recommended SC dosage regimen developed anti-teclistamab antibodies. Because of the low occurrence of anti-drug antibodies, the effect of these antibodies on the PK, PD, safety, and effectiveness of teclistamab is unknown.
Drug Interactions	No clinical drug interaction studies were conducted with teclistamab. Teclistamab causes release of cytokines (including IL-6 and IL-10) that may suppress activity of cytochrome P450 (CYP) enzymes, resulting in increased exposure of CYP substrates. The highest risk of drug-drug interaction is expected to occur from initiation of the step-up dosing schedule up to 7 days after the first treatment dose and during and after CRS.
Pharmacodynamics	Serum concentrations of cytokines (IL-6, IL-10, TNF-α, and IFN-γ) and IL-2R were measured before and after administration of step-up dose 1, step-up dose 2, and the first three treatment doses of teclistamab. Increased concentrations of IL-6, IL-10, and IL-2R were observed during this period.
Formulation Effect	In MajesTEC-1, PK data was collected following administration of the drug product used in Phase 1 and the pivotal drug product. In the PPK model, the drug product formulation was evaluated as a time-varying covariate and was not associated with any clear differences in teclistamab PK parameters or teclistamab exposure.

6.3.2. Clinical Pharmacology Questions

6.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:

Teclistamab treatment doses ranging from 0.08 to 6 mg/kg SC were evaluated in MajesTEC1, and the registrational treatment dose of 1.5 mg/kg SC weekly was selected based on the PK, pharmacodynamic, safety, and efficacy data in MajesTEC1. Following teclistamab treatment dose of 1.5 mg/kg SC weekly, mean trough concentrations of teclistamab were maintained above the maximum EC_{90} value identified in the ex vivo cytotoxicity assay and set as a target exposure for sustained clinical activity. A positive E-R relationship was observed for ORR assessed by investigator based on IMWG 2011 criteria in Phase 1 across the teclistamab exposure range associated with SC doses from 0.08 to 3 mg/kg weekly, and the response at the concentration range of RP2D is approaching the ORR plateau (ie, maximum response). Additionally, no apparent positive E-R trend was observed in the incidence of Grade ≥3 TEAEs of anemia, neutropenia, lymphopenia, thrombocytopenia, and infections across the predicted exposure quartiles in subjects who received teclistamab SC. None of the subjects who received teclistamab at RP2D developed antidrug antibodies against teclistamab.

The Applicant's Position:

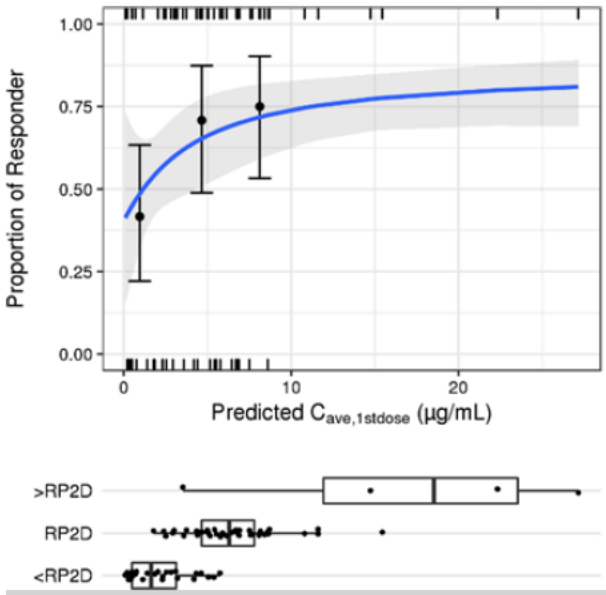
The clinical pharmacology findings, including PPK and E-R analyses, provide the scientific and quantitative justification for the selected dose of teclistamab SC in treatment of relapsed or refractory multiple myeloma.

The FDA's Assessment:

The FDA agrees that the clinical pharmacology program provides supportive evidence of effectiveness. The primary evidence of effectiveness is the ORR of 61.8% in the primary efficacy analysis set (refer to **Section 8.1.2 – Study Results**). Supportive evidence of effectiveness from the clinical pharmacology program is summarized below.

E-R for Efficacy: Among 72 patients treated with SC dosage regimens (treatment dose range 0.08 to 3 mg/kg QW) during Phase 1 of MajesTEC-1, there was a positive relationship between the teclistamab average concentration after the first treatment dose ($C_{ave,1stdose}$) and ORR (assessed by investigator based on IMWG 2011 criteria; **FDA Figure 2**).

FDA Figure 2: Exposure-Response Relationship of the Overall Response in the Phase 1 SC Subjects Versus the Predicted Cave,1stdose (Investigator Assessment, 2011 IMWG)



Notes: Error bars are the 95% CI of ORR in the respective exposure tertile groups. Shaded areas of the logistic regression plots represent the 95% CI of the predicted ORR. Short vertical lines at the lower and upper part of the plotting area represents the exposure metrics in non-responders and responders, respectively.
$C_{ave,1stdose}$=average concentration during the first treatment dose; CI=confidence interval; IMWG=International Myeloma Working Group; ORR=overall response rate; RP2D=recommended Phase 2 dose, which is the SC teclistamab recommended dosage regimen (0.06 mg/kg SC, followed 2 to 4 days later by 0.3 mg/kg SC, followed 2 to 4 days later by 1.5 mg/kg SC and then 1.5 mg/kg SC once weekly thereafter); SC=subcutaneous.
Source: Figure 10 in **Section 19.4.3.2**

Additional E-R analyses conducted with data from 150 patients treated with the recommended SC dosage regimen during either Phase 1 or Phase 2 of MajesTEC-1 did not identify relationships between teclistamab exposure ($C_{ave,1stdose}$ and $C_{trough,4doses}$) and efficacy outcomes including ORR (assessed by IRC based on IMWG 2016 criteria), progression-free survival (PFS), duration of response (DOR), or overall survival (OS). This finding is not unexpected given that only one dosage regimen was included in the analyses. Patient covariates including baseline sBCMA and PD-1 expression had statistically significant associations with ORR. The interpretability of this finding is confounded by correlations between multiple covariates including teclistamab exposure, body weight, myeloma type, ISS, baseline sBCMA, and baseline PD-1 expression. Refer to **Section 19.4.3.2** for details.

Pharmacodynamics: Additional supportive data came from assessment of changes in sBCMA over time. **FDA Table 4** summarizes median percent change from baseline sBCMA in the 40 patients treated with the recommended SC dosage regimen during Phase 1 of MajesTEC-1. After three treatment doses (Cycle 2 Day 1), the median change from baseline in sBCMA was -18.6% in patients who had a response and 151.2% in patients who did not have a response. Reduction from baseline in soluble BCMA was observed in 64% of patients who had a response and not observed in patients who did not have a response. A similar pattern was observed for patients treated with the recommended SC dosage regimen during Phase 2 of MajesTEC-1 but collection

of sBCMA samples was conducted in only a subset of Phase 2 patients (52/110 patients with available sBCMA sample at Cycle 2 Day 1). Overall, these results support the pharmacologic activity of the recommended SC dosage regimen.

FDA Table 4: Change from Baseline in sBCMA for Patients Treated with the Recommended SC Dosage Regimen in Phase 1 of MajesTEC-1

Visit	Responder by IRC	N (of 40)	Percent Change from Baseline in sBCMA		
			Median	Min	Max
C1D1	Yes	25	-5.7%	-61.8%	+58.3%
	No	13	-1.4%	-18.9%	+61.3%
C1D8	Yes	25	+34.9%	-71.9%	+238.5%
	No	12	+40.4%	-14.0%	+1,077.1%
C2D1	Yes	25	-18.6%	-84.0%	+204.9%
	No	11	+151.2%	+62.6%	+1,699.4%
C3D1	Yes	26	-60.2%	-91.2%	+190.6%
	No	6	+194.5%	+88.5%	+2,619.6%
C4D1	Yes	22	-76.2%	-95.3%	+49.9%
	No	2	-	+453.7%	+2,590.4%

Source: Reviewer's analysis

6.3.2.2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data:

The registrational treatment dose of teclistamab (1.5 mg/kg SC administered weekly, with the first treatment dose preceded by step-up doses of 0.06 and 0.3 mg/kg) was selected based on the PK, pharmacodynamic, safety, and efficacy data available following Phase 1 dose escalation in MajesTEC1: 1) ease and convenience of SC administration compared with IV administration; 2) PK data indicating the selected dose achieving desired target exposure and pharmacodynamic data demonstrating T cell activation; and 3) favorable early clinical safety and efficacy profiles of the selected dose which were evaluated and confirmed by the Part 2 expansion at RP2D. Moreover, a trend in E-R was observed for ORR assessed by investigator based on IMWG 2011 criteria in Phase 1 where ORR increased with teclistamab exposure across SC doses ranging from 0.08 to 3 mg/kg weekly, approaching a plateau at the RP2D. Phase 2 further established

1.5 mg/kg SC weekly as a safe and effective dose for the treatment of relapsed or refractory multiple myeloma.

Pharmacokinetics: Following the treatment dose of teclistamab at 1.5 mg/kg SC weekly, mean trough concentration was maintained above the maximum EC_{90} value identified in the ex vivo cytotoxicity assay. This assay assessed the ability of teclistamab to induce killing using mononuclear cells from bone marrow samples from patients with multiple myeloma in coculture with T cells from healthy donors. At lower dose levels, the exposure dropped below the maximum EC_{90}. In addition, SC dosing had a more favorable PK profile, with a low peak-to-trough ratio compared to IV infusion.

Pharmacodynamics: Subjects who received teclistamab SC starting at the 0.24 mg/kg weekly dose level demonstrated consistent pharmacodynamic changes indicative of the proposed mechanism of action, including T cell activation, induction of cytokines, and T cell redistribution. Optimal pharmacodynamic changes were observed in subjects who received 1.5 mg/kg SC. Greater induction of T cell activation markers such as PD-1, CD38, LAG-3, TIM-3, and HLA-DR was seen for subjects treated at the 1.5 mg/kg SC weekly dose level compared with the increases observed for subjects treated at the 0.72 mg/kg SC weekly dose level. Markers for T cell activation did not increase consistently with further increases in dose. Consistent increases in cytokines such as IL-10, IL-2Rα, and IL-6 were observed for subjects treated at the 1.5 mg/kg SC weekly dose level. Optimal activation of cytokines was observed at 1.5 mg/kg SC weekly as evidenced by consistently high median values for maximum fold change of cytokines when compared to other dose levels evaluated.

Safety: The safety profile observed at the 1.5 mg/kg SC weekly dose level was consistent with that observed at lower dose levels. Two step-up doses were used to mitigate the risk of high-grade CRS.

As of 07 September 2021, 165 subjects were evaluated for safety at 1.5 mg/kg SC weekly in Phase 1 or Phase 2 Cohort A (pivotal RP2D). No DLTs were observed at this dose level among subjects evaluated by the SET for this purpose. The most frequently reported (≥20%) TEAEs were CRS (71.5%), neutropenia (65.5%), anemia (49.7%), thrombocytopenia (38.2%), lymphopenia (33.9%), injection site erythema (25.5%), fatigue (24.8%), nausea (24.2%), headache (21.8%), and diarrhea (20.6%). Overall, a low rate of treatment discontinuation due to TEAE was observed, with only 1 subject (<1%) discontinuing treatment due to TEAE, and no subject reducing the dose of teclistamab. No subject died due to a TEAE judged by the investigator as related to teclistamab.

Among subjects in the pivotal RP2D population, CRS was manageable and reversible. Eighty-two subjects (49.7%) experienced maximum Grade 1 CRS and 35 (21.2%) experienced maximum Grade 2 CRS. One subject experienced Grade 3 CRS in the context of concurrent

pneumonia. Sixty subjects (36.4%) were treated with tocilizumab, 13 (7.9%) received steroids, and 21 (12.7%) received low-flow oxygen to treat CRS. The subject who experienced Grade 3 CRS required a single vasopressor. No subject required treatment discontinuation for CRS; all events resolved.

Neurotoxicity was observed infrequently (21 subjects [12.7%]) and was low grade at 1.5 mg/kg SC weekly. The most frequently reported neurotoxicity event was headache. Five subjects (3.0%) had ICANS, all Grade 1 or Grade 2. Nearly all neurotoxicity (33/36 events) resolved, with events of Grade 2 hypoesthesia, Grade 2 dysgeusia, and Grade 1 headache ongoing as of the clinical cutoff.

None of the subjects who received RP2D developed antidrug antibodies against teclistamab.

At 3 mg/kg SC weekly (n=5), the CRS and neurotoxicity profile appeared consistent with those for 1.5 mg/kg SC weekly; however, 1 subject had a dose reduction to 1.5 mg/kg SC weekly for TEAEs of vomiting, nausea, and diarrhea. The safety profile at 6 mg/kg SC weekly appeared consistent with that for lower dose levels, but analysis for this dose level was limited by short duration of follow-up.

Efficacy: As of the clinical cutoff of 07 September 2021 that was used for this analysis, 150 subjects were evaluated for safety at 1.5 mg/kg SC weekly in Phase 1 or Phase 2 Cohort A (pivotal RP2D Efficacy Analysis Set). This dose of teclistamab led to a compelling efficacy profile for heavily pretreated subjects with myeloma, with an ORR of 62.0% (95% CI: 53.7% to 69.8%) and rapid median onset of response of approximately 1 month. Responses to teclistamab deepened over time, where 58.0% of subjects achieved VGPR or better and 28.7% achieved CR or better. Among subjects who achieved CR or better, the MRD-negativity rate at 10^{-5} was 41.9%. The response was also durable, with a median DOR based on progressive disease or death due to PD that was not reached. The probabilities of responders remaining in response at 6 and 9 months were 92.5% (95% CI: 80.6% to 97.2%) and 85.9% (95% CI: 70.0% to 93.7%), respectively.

At SC dose levels below 0.72 mg/kg SC weekly, the ORR was lower (n=13, ORR was 46.2%). Subjects assigned to the 0.72 mg/kg SC weekly dosing cohort had an ORR of 60% (9 of 15 subjects); however, 1 of 9 responders had their first response observed after increasing the teclistamab dose to 1.5 mg/kg. Importantly, the 6-month event-free rate for DOR at the 0.72 mg/kg SC weekly dose level was only 77.8%, compared with 92.1% for responders treated at 1.5 mg/kg SC weekly in Phase 1 (n=26). Efficacy analysis for subjects treated at 3 mg/kg SC weekly is limited by small numbers or short duration of follow-up, but it appears consistent with the 1.5 mg/kg SC weekly dose level.

**In conclusion, the registrational treatment dose of teclistamab at 1.5 mg/kg SC weekly achieved exposure consistently above the max EC_{90}, optimal activation of T cells and induction of cytokines, a favorable safety profile, and compelling efficacy results.

The Applicant's Position:
The recommended teclistamab SC dose is considered effective and appropriate in patients with relapsed or refractory multiple myeloma, with no need for dose adjustments based on efficacy, safety, and clinical pharmacology findings (see Section 8.1.2 and Section 8.2).

The FDA's Assessment:
The FDA agrees that the proposed SC dosage regimen of teclistamab is appropriate for the general population of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

The FDA assessment of the proposed SC dosage regimen evaluated the step-up dosing schedule and the continued treatment dosing separately.

Step-Up Dosing Schedule: At the initiation of treatment with teclistamab, the primary concern is safety, including minimizing the incidence and severity of CRS. In 165 patients treated with the recommended SC dosage regimen in MajesTEC-1, 72% of patients had CRS at any time and 87% of CRS events occurred following either step-up dose 1 (0.06 mg/kg SC), step-up dose 2 (0.3 mg/kg SC), or the first treatment dose (1.5 mg/kg SC) (Refer to **Section 8.2.5.1 – Cytokine Release Syndrome**). CRS occurred at all studied SC teclistamab dosage regimens (first step-up dose range 0.02 to 0.06 mg/kg; treatment dose range 0.08 to 6 mg/kg).

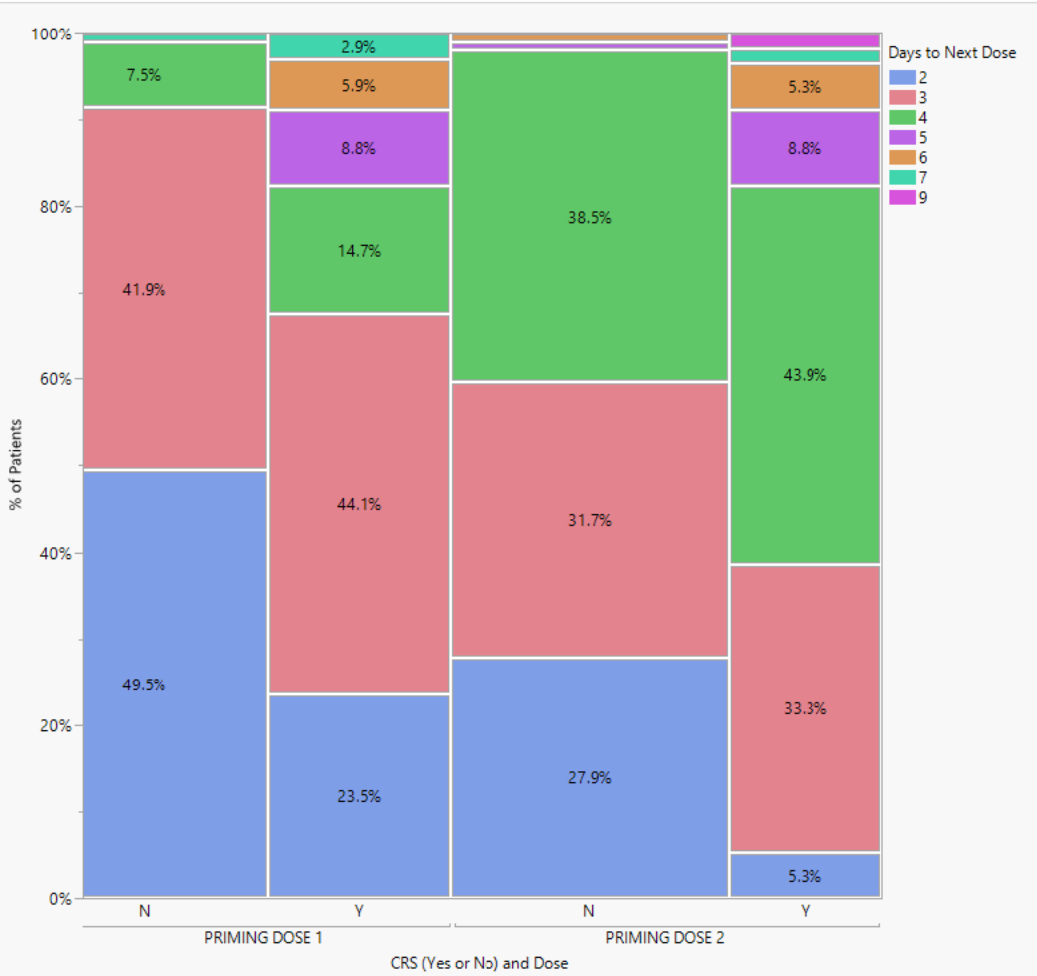
The FDA conducted exploratory multivariate E-R analyses for CRS using data from 199 patients treated with SC teclistamab in Phase 1 of MajesTEC-1 or Phase 2 Cohort A of MajesTEC-1. The exploratory analysis supports the conclusion that the proposed step-up dosing regimen has an acceptable safety profile for CRS. Additionally, the analyses suggest that tocilizumab use in patients with CRS after step-up dose 1 may impact the CRS rate with step-up dose 2.

The protocol for MajesTEC-1 allowed Investigator discretion in the choice of treatment(s) for CRS, including the use of tocilizumab, an anti-IL-6 antibody approved for the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening CRS. Among the 165 patients treated with the recommended SC dosage regimen, 22 patients had Grade 2 CRS and 49 patients had Grade 1 CRS after administration of step-up dose 1 and prior to step-up dose 2. Tocilizumab was used to treat 19/22 (86%) patients with Grade 2 CRS and 10/49 (20%) patients with Grade 1 CRS. In the E-R analyses for CRS, patients who received tocilizumab to treat CRS after step-up dose 1 had lower incidence of CRS after step-up dose 2, regardless of the teclistamab C_{max} with step-up dose 2. Given the inconsistent use of tocilizumab, the interpretability of this finding on the overall CRS rate is unclear.

The protocol for MajesTEC-1 allowed flexibility in the timing of the step-up dosing schedule (i.e.,

2-4 days between each dose with longer duration allowed if needed for resolution of toxicities). FDA evaluated observed dosing intervals and time to onset of CRS for patients treated with the recommended SC step-up dosing schedule to support labeling of the recommended schedule of administration. Four patients scheduled to receive the recommended SC step-up dosing regimen had repeat step-up doses before the first treatment dose and were excluded from this analysis. Among the 161 patients treated with the recommended SC step-up dosing regimen as planned, the median time between step-up dose 1 and step-up dose 2 was 2.9 days and the median time between step-up dose 2 and the first treatment dose was 3.1 days. **FDA Figure 3** shows the distribution of dosing intervals (days to next dose) after step-up dose 1 and step-up dose 2 split by whether the patient had CRS after the given dose. In general, patients who had CRS after a dose tended to have a longer duration to the next dose compared with patients who did not have CRS. Among patients with CRS after step-up dose 1, 82% received step-up dose 2 within 4 days and 100% received step-up dose 2 within 7 days. Among patients with CRS after step-up dose 2, 82% received the first treatment dose within 4 days and 98% received the first treatment dose within 7 days.

FDA Figure 3: Distribution of Step-Up Dosing Schedule Dosing Intervals by Occurrence of CRS and Step-Up Dose



Notes: Priming Dose 1 = Step-Up Dose 1 (0.06 mg/kg); Priming Dose 2 = Step-Up Dose 2 (0.3 mg/kg)
Source: Reviewer's analysis

A total of 71 patients had CRS after step-up dose 1 and 57 patients had CRS after step-up dose 2. Among these patients, the median (min, max) days to onset of CRS was 1 (0, 3) day for step-up dose 1 and 1 (1, 3) day for step-up dose 2. One patient had onset of CRS at least 3 days after teclistamab administration for both step-up dose 1 and step-up dose 2. A subset of patients had more precise date and time data for both teclistamab administration and onset of CRS (59 patients after step-up dose 1 and 46 patients after step-up dose 2). Among these patients, the median (min, max) time to onset of CRS was 29 (4, 72) hrs after step-up dose 1 and 31 (9, 77) hrs after step-up dose 2. One patient had onset of CRS at least 72 hours after teclistamab administration for both step-up dose 1 and step-up dose 2. Based on this assessment, an interval of 3 days between each of the doses in the step-up dosing schedule is reasonable. Given the variability in step-up dosing schedule allowed and observed in MajesTEC-1, the labeling will include a footnote describing the acceptable 2-4 day window for each dose in the step-up dosing schedule (with up to 7 days allowed for resolution of toxicities). The labeling

will also include recommendations for restarting therapy if dose delays of 8 days or longer occur.

Overall, the proposed SC step-up dosing schedule with adequate CRS prevention and monitoring strategies (see **Section 8.1.2 – Study Results**) results in an acceptable safety profile with regards to CRS incidence and severity.

Continued Treatment Dose: After completion of the step-up dosing schedule, treatment with teclistamab continues indefinitely based on patient response. During this continued treatment period, concerns include attainment and maintenance of response and chronic safety and tolerability.

As described above, a positive relationship between teclistamab exposure and ORR was observed in patients treated with various SC dosage regimens in Phase 1 of MajesTEC-1. This E-R analysis supported selection of 1.5 mg/kg QW as the recommended SC treatment dosage for further evaluation in Phase 2.

Small numbers of patients (5 to 12 per cohort) were treated at weekly SC treatment dose levels other than the recommended SC treatment dose (1.5 mg/kg). During Phase 1, weekly SC treatment dose levels ranged from 0.08 mg/kg to 6 mg/kg. The ORR and time to first response are summarized in **FDA Table 5** (per Investigator assessment). Responses were observed at all weekly SC treatment dose levels and the median time to first response was similar regardless of weekly SC treatment dose level.

FDA Table 5: Summary of ORR and Time to First Response by SC Treatment Dose Level

Weekly SC Treatment Dose	ORR; % (n/N)	Time to First Response, months; median (min, max)
0.08 mg/kg	50% (3/6)	1.6 (1.0, 1.7)
0.24 mg/kg	43% (3/7)	1.9 (1.2, 5.1)
0.72 mg/kg	60% (9/15)	1.5 (0.9, 6.0)
1.5 mg/kg	62% (102/165)	1.2 (0.1, 5.4)
3 mg/kg	100% (5/5)	1.1 (1.0, 1.6)
6 mg/kg	67% (8/12)	1.1 (0.3, 1.6)

Source: Reviewer's analysis

Due to the dose escalation design of MajesTEC-1, patients treated at lower dose levels had longer potential duration of follow-up. In addition, intra-patient dose modifications, including increasing the weekly SC treatment dose and reducing the frequency of treatment dose administration (i.e., to every other week [Q2W] or every 4 weeks [Q4W]) was allowed. Both issues confound assessment of DOR by weekly SC treatment dose level. However, multiple patients treated with SC treatment dosages substantially below the recommended SC treatment dosage (1.5 mg/kg QW) maintained responses for long durations. For example, 3 patients treated initially in the two lowest treatment dose cohorts (0.08 mg/kg and 0.24 mg/kg) each remained in CR for more than a year while receiving teclistamab 0.24 mg/kg SC Q2W (8% of the

recommended SC treatment dosage).

From a safety perspective, E-R analyses for selected safety events were conducted based on data from 199 patients treated with various SC dosage regimens during either the Phase 1 or Phase 2 portion of MajesTEC-1. No E-R relationships were identified for teclistamab dose modification due to treatment-emergent adverse events (TEAEs), Grade ≥3 cytopenias (anemia, lymphopenia, leukopenia, thrombocytopenia, and neutropenia), Grade ≥3 infection, Grade ≥3 TEAEs, or neurologic toxicity TEAEs. Refer to **Section 19.4.3.4** for additional details regarding E-R safety analysis.

Overall, the available data, including a positive E-R relationship for ORR and lack of E-R relationships for key safety events, support the Applicant's proposed SC treatment dosage of 1.5 mg/kg QW as the recommended dosage after completion of the step-up dosing schedule. Limited data are available for SC treatment dose levels or dosing frequencies other than the recommended SC treatment dosage (1.5 mg/kg QW). The Applicant is evaluating alternative teclistamab regimens in ongoing studies of teclistamab as a single agent or in combination with other treatments.

6.3.2.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Data:

In population pharmacokinetic analyses, potential covariates influencing the teclistamab pharmacokinetics have been evaluated (Section 6.2.2.2). Although body weight, type of myeloma, and ISS staging were statistically significant covariates on the PK of teclistamab, further clinical efficacy subgroup analyses and E-R analyses demonstrated that these covariates had no clinically relevant effect on the efficacy at the recommended dose regimen. Results of PPK analysis indicated that mild or moderate renal impairment and mild hepatic impairment did not influence teclistamab PK. Limited data were available from subjects with severe renal impairment, and no data were available from subjects with moderate or severe hepatic impairment. Furthermore, E-R analyses, which are detailed in the PPK report, indicated a near flat E-R trend for ORR assessed by IRC based on IMWG 2016 criteria in subjects who received teclistamab at RP2D, and responders and non-responders had comparable and overlapping exposure range.

The Applicant's Position:

No alternative dosing regimen is proposed for teclistamab SC based on intrinsic or extrinsic factors. Results of PPK analysis indicated that mild or moderate renal impairment and mild hepatic impairment did not influence the PK of teclistamab. Limited data were available from subjects with severe renal impairment, and no data were available from subjects with moderate or severe hepatic impairment. The effects of the investigated intrinsic factors on teclistamab exposure had no clinically meaningful impact and there is no need for dose adjustment based on intrinsic (mild or moderate renal impairment and mild hepatic impairment) or extrinsic factors.

The FDA's Assessment:

The FDA agrees that no alternative dosing regimen of teclistamab is required based on intrinsic patient factors including age (24 to 84 years), sex, race (White, Black or African American), ethnicity (Hispanic/Latino, not Hispanic/Latino), mild or moderate renal impairment (eGFR by MDRD method: 30 to 89 mL/min), or mild hepatic impairment (total bilirubin less than or equal to ULN with AST greater than ULN or total bilirubin greater than 1 to 1.5 times ULN with any AST). Refer to **Section 19.4.2.2** for details regarding covariate evaluation on PK parameters and exposure. Dedicated studies in patients with severe renal impairment or moderate or severe hepatic impairment are not required given that teclistamab is a large biologic and PK is not expected to be significantly altered by renal or hepatic impairment.

6.3.2.4. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data:

Teclistamab is administered via SC injection and its absorption is not expected to be impacted by food. Teclistamab is not metabolized via CYP enzymes and is not expected to directly affect the CYP enzymes. Therefore, no nonclinical or clinical drug-drug interaction studies were performed.

The Applicant's Position:

The initial release of cytokines associated with the start of teclistamab treatment could suppress CYP enzymes. CYP substrates with a narrow therapeutic index should be used with caution in patients receiving teclistamab. These patients should be monitored for toxicity (eg, warfarin) or drug concentrations (eg, cyclosporine) for 48 hours after administration of all doses within teclistamab step-up dosing schedule and for patients who develop CRS. The dose of the concomitant drug should be adjusted as needed.

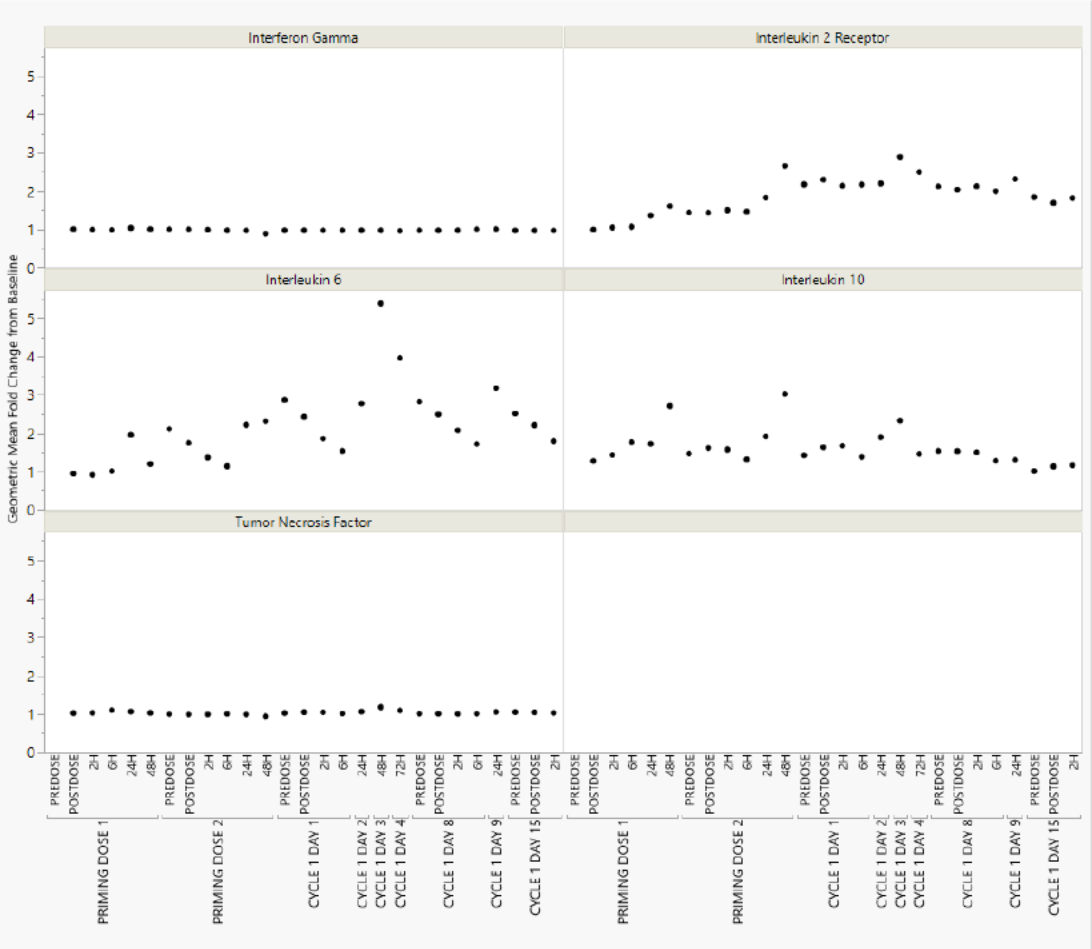
The FDA's Assessment:

The FDA agrees that teclistamab is not expected to have relevant food-drug interactions or drug-drug interactions as a victim.

Teclistamab may act as a perpetrator of drug-drug interactions. Increased concentrations of cytokines may reduce expression and activity of cytochrome P450 (CYP) enzymes (Lee 2010). Teclistamab causes release of cytokines due to its mechanism of action. Serum concentrations of IL-6, IL-10, TNF-α, IFN-γ, and IL-2R were measured before and after administration of step-up dose 1, step-up dose 2, and the first 3 treatment doses in patients treated with the recommended SC dosage regimen during Phase 1 of MajesTEC-1 (n=40). IL-6, IL-10, and IL-2R were elevated after administration of teclistamab, with the largest geometric mean fold change from baseline observed 48 hours after the first treatment dose for IL-6 and IL-2R or 48 hours after step-up dose 2 for IL-10 (**FDA Figure 4**). Limited sample size (n=9) was available at the 48 hr post-dose timepoint for both step-up dose 1 and step-up dose 2. Excluding these data, the largest geometric mean fold change from baseline for IL-10 was observed 48 hours after the first treatment dose, consistent with the time of peak fold change in IL-6 and IL-2R. Additional sparse cytokine data (IL-6, IL-10, TNF-α, and IFN-γ at baseline, prior to the first treatment dose, and 48 hours after the first treatment dose) were available from patients treated with the

recommended SC dosage regimen during Phase 2 of MajesTEC-1 (n=125). IL-6, IL-10, TNF-α, and IFN-γ were elevated after administration of teclistamab.

FDA Figure 4: Geometric Mean Fold Change from Baseline in Cytokines and IL-2R



Notes: Priming Dose 1 = Step-Up Dose 1 (0.06 mg/kg); Priming Dose 2 = Step-Up Dose 2 (0.3 mg/kg); Includes patients treated with the recommended SC dosage regimen during Phase 1 of MajesTEC-1
Source: Reviewer's analysis

FDA requested additional information during the review of BLA 761291 regarding the potential for teclistamab to cause drug-drug interactions with CYP substrates including a quantitative assessment of the effects of teclistamab-induced cytokine release on CYP enzyme activities. The Applicant submitted a physiologically based pharmacokinetic (PBPK) model based on a published model of blinatumomab-induced IL-6 release on CYP activity (Xu 2015). The model was used to predict exposure of substrates of CYP1A2 (caffeine), CYP2C9 (S-warfarin), CYP2C19 (omeprazole), and CYP3A4/3A5 (midazolam, cyclosporine, and simvastatin) with and without administration of teclistamab.

Based on the Applicant's PBPK model, the mean observed IL-6 profile is predicted to cause no clinically significant interaction with substrates of CYP1A2, CYP2C9, CYP2C19, CYP3A4, and CYP3A5 (i.e., <20% change in substrate AUC). In the single patient with the highest IL-6 C_{max}, CYP

activity is predicted to return to at least 80% of baseline within approximately 7 to 8 days (depending on the enzyme) of the first treatment dose. Limitations of the Applicant's PBPK model include the lack of clinical drug interaction data for model verification, the evaluation of only IL-6 effects on CYP activity, and sensitivity of the model predictions to assumed parameters (e.g., *in vitro* CYP suppression parameters from previous publications).

While uncertainties remain in the absolute magnitude of potential drug interactions after administration of teclistamab, the available cytokine data, the profile of CRS occurring primarily after the step-up doses and first treatment dose (see **Section 8.2.5.1 – Cytokine Release Syndrome**), and the predictions from the Applicant's PBPK model all suggest the highest risk of drug-drug interaction is expected to occur early during treatment with teclistamab (up to approximately one week after the first treatment dose) and during and after CRS. Patients receiving concomitant sensitive CYP substrates where small changes in concentration may lead to increased adverse events should be monitored for toxicity or concentration as appropriate. The dose of the CYP substrate should be adjusted as needed.

X X

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7. Sources of Clinical Data

7.1 Table of Clinical Studies

Data and Applicant's Position:

Data from MajesTEC-1 (Table 3) are presented in this BLA.

Table 3: Applicant - Listing of Clinical Trial Relevant to this BLA for Teclistamab

Trial Identity [NCT No.]	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/Follow-Up Cutoff date	No. of Patients Treated	Study Population	No. of Centers and Countries
Open-label Study to Support Efficacy and Safety							
Main Study: 64007957MMY1001 (MajesTEC-1) NCT03145181 (Phase 1), NCT04557098 (Phase 2)	Phase 1/2 Open-label, single-arm, multicenter study Part 1 (Dose Escalation): To identify the proposed RP2D(s). Part 2 (Dose Expansion): To characterize the safety and tolerability of teclistamab at the proposed RP2D(s). Part 3 (Phase 2): To evaluate the efficacy of teclistamab at the RP2D.	Part 1 (Dose Escalation): *Up to proposed RP2Ds:* Q2W or weekly therapy with either teclistamab IV (treatment doses of 0.0003 to 0.0192 mg/kg Q2W and 0.0192 to 0.72 mg/kg weekly) or teclistamab SC (treatment doses of 0.08 to 1.5 mg/kg weekly). *Higher than RP2D:* 3 mg/kg weekly, other dosing schedules with treatment doses of 6 mg/kg, and flat dose. Part 2 (Dose Expansion): 0.72 mg/kg teclistamab IV weekly and 1.5 mg/kg teclistamab SC weekly. Part 3 (Phase 2): 1.5 mg/kg teclistamab SC weekly.	Pivotal RP2D: Primary endpoint: ORR by IRC using IMWG 2016 Secondary endpoints: DOR, VGPR or better rate, CR or better rate, sCR rate, TTR, PFS, OS, MRD-negativity rate, ORR in subjects with high-risk cytogenetics, safety, PK, and PRO	Until confirmed progressive disease, death, intolerable toxicity, withdrawal of consent, or end of the study Follow-up until death, withdrawal of consent, loss to follow-up, or end of the study See Table 6 for detail regarding the clinical cutoff dates.	All Treated Populations: Pivotal RP2D: 165 subjects (40 of whom were treated in Phase 1 and are also included in the total for that phase) Phase 1 (Dose Escalation/Dose Expansion): 177 subjects. Cohort C: 38 subjects.	Adult subjects ≥18 years of age with with documented diagnosis of multiple myeloma (relapsed or refractory) and who have previously received 1 to 3 prior line(s) of therapy including a PI, IMiD, and anti-CD38 monoclonal antibody	39 centers in 10 countries

Abbreviations: CR=complete response; DOR=duration of response; IMiD=immunomodulatory drug; IMWG=International Myeloma Working Group; IRC=Independent Review Committee; IV=intravenous; MRD=minimal residual disease; NCT=National Clinical Trial; OS=overall survival; PFS=progression-free survival; PI=proteasome inhibitor; PK=pharmacokinetic(s); PRO=patient-reported outcome; RP2D=recommended Phase 2 dose; SC=subcutaneous; sCR=stringent complete response; TTR=time to response; VGPR=very good partial response.

The FDA's Assessment:

FDA agrees that MajesTEC-1 trial is the single study supporting this BLA. However, FDA does not agree with the description of the study population in the Applicant's Table 3.

FDA notes that eligible patients for phase 1 were patients with MM that was relapsed or refractory to, or who were intolerant of, established therapies with known clinical benefit in RRMM, and whose prior therapy included a PI, an IMiD, and an anti-CD38 mAb.

Eligible patients for phase 2 Cohort A were patients with RRMM with at least 3 prior lines of therapy, including a PI, an IMiD, and an anti-CD38 mAb. Patients with prior BCMA-directed therapy (CAR T-cells or antibody drug conjugate) were excluded from Cohort A. Cohort C enrolled patients with RRMM with at least 3 prior lines of therapy, including a PI, an IMiD, an anti-CD38 mAb, and a BCMA-directed therapy. However, Cohort C is not relevant to this BLA because the proposed indication does not include patients with prior BCMA-directed therapy and the sample size of Cohort C is too small to draw any conclusions regarding safety and efficacy of teclistamab in patients with prior BCMA-directed therapy. FDA otherwise concurs with the information presented in the Applicant's Table 3.

8. Statistical and Clinical Evaluation

8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. 64007957MMY1001(MajesTEC-1)

Trial Design

The Applicant's Description:

Basic Study Design: MajesTEC-1 is a first-in-human, Phase 1/2, open-label, multicenter, dose escalation study to evaluate the safety, tolerability, PK, and anti-myeloma activity of teclistamab administered to adult subjects with relapsed or refractory multiple myeloma. The study was conducted in 3 parts:

- Part 1: dose escalation (either IV or SC) to identify the proposed RP2Ds
- Part 2: dose expansion at proposed RP2Ds
- Part 3: Phase 2 dose expansion in subjects with unmet need differing by prior therapy including Cohort A (subjects with at least 3 prior lines of therapy and triple-class exposed) and Cohort C (subjects with at least 3 prior lines of therapy and triple-class exposed and whose prior therapy also included an ADC or CAR-T directed against BCMA). All subjects in Phase 2 received teclistamab at the selected RP2D.

Data from a study with an single-arm, open-label design have been the basis for accelerated approval of novel therapies for advanced, refractory cancers with high unmet medical need such as relapsed and refractory multiple myeloma (see Section 2). This study design can adequately characterize anti-tumor activity demonstrated by a robust response rate and DOR. A more comprehensive characterization of efficacy, defined by time-to-event endpoints such as PFS and OS, requires subsequent randomized studies utilizing a standard-of-care control arm. Study 64007957MMY3001, a multicenter, randomized, open-label, Phase 3 study in multiple myeloma patients who have previously received 1 to 3 prior line(s) of therapy including a PI and lenalidomide, is ongoing and will compare the efficacy of teclistamab in combination with daratumumab SC (Tec-Dara) with that of an investigator's choice of DPd or DVd as assessed by PFS. While the lack of a direct comparator in MajesTEC-1 may limit the overall assessment of the benefit/risk profile for teclistamab, patients who progress after receiving IMiD, PI, and anti-CD38 monoclonal antibody therapies have limited therapeutic options. As described in this document, teclistamab offers considerable advantages over the approved options fo this population.

Trial Location: This study was conducted at 39 centers that treated at least 1 subject in Belgium (2), Canada (4), France (6), Germany (3), Italy (2), Netherlands (1), Spain (7), Sweden (3), the United Kingdom (3), and the United States (8).

Choice of Control Group: not applicable (see also Section 2.2 regarding current treatment options for the population of patients evaluated in MajesTEC-1)

Study Evaluations: After providing written consent for study participation, all subjects were screened for study eligibility within 28 days prior to the first dose of teclistamab. Study procedures were consistent during the Phase 1 and Phase 2 except as noted below and in Section 8.2.1. The timing of study procedures is provided in the relevant Time and Events Schedules presented in the protocol. Study drug was administered to subjects until disease progression, unacceptable toxicity, withdrawal of consent, death, or end of study (defined as 2 years after the last subject's first dose).

Safety was measured by AEs, laboratory test results, vital sign measurements, triplicate ECGs (Phase 1 only), physical examination findings (including neurological examination), assessment of ICE Tool scores (for Phase 2), and assessment of ECOG Performance Status grade.

Efficacy was measured based on response to treatment and duration of response. A central laboratory was used for disease evaluations (M-protein and serum free light chain measurements, and immunofixation determinations in serum and 24-hour urine). Bone marrow samples to assess for plasma cell percentage and clonality were analyzed locally; bone marrow samples to assess for MRD negativity were analyzed centrally. Response was assessed using IMWG criteria. IMWG 2011 response criteria were used for all investigator assessments in Phase 1. IMWG 2016 response criteria were used for the following:

- All investigator assessments in Phase 2
- All IRC assessments (pivotal RP2D, including subjects treated at RP2D in Phase 1, and Cohort C)
- All validated computerized algorithm assessments (pivotal RP2D and Cohort C).

Blood, serum, and bone marrow samples were collected for assessment of teclistamab PK, immunogenicity (antibodies to teclistamab), pharmacodynamic markers, and predictive biomarkers of response or resistance to teclistamab.

Key Inclusion and Exclusion Criteria: Eligible subjects were required to be at least 18 years of age, have a documented diagnosis of multiple myeloma according to IMWG diagnostic criteria, have measurable disease at screening informed by IMWG (except for in Part 1), and have an ECOG Performance Status score of 0 or 1. Subjects enrolled in Phase 1 early in study conduct were required to have multiple myeloma that was relapsed or refractory to established therapies with known clinical benefit in relapsed/refractory multiple myeloma or be intolerant of established therapies. A minimum number of prior lines of therapy was not established for Phase 1. The current protocol requires that subjects in Phase 1 had received a PI, an IMiD, and an anti-CD38 monoclonal antibody in any order during the course of treatment. Note that use of anti-CD38 monoclonal antibodies became increasingly more common throughout the duration of study conduct and prior exposure to this class of therapy was not required for subjects in Phase 1 until Amendment 10 (Table 4). All subjects enrolled in Phase 2 from Amendment 10 and later were to

have received at least 3 prior lines of therapy, including a PI, an IMiD, and an anti-CD38 monoclonal antibody. For subjects in Phase 1 and Cohort A in Phase 2, prior therapy could not include an BCMA-targeting treatment. For subjects in Cohort C, prior therapy must have included an anti-BCMA treatment (ADC or CAR-T) in addition to requirement to have received at least 3 prior lines of therapy that included a PI, IMiD, and an anti-CD38 monoclonal antibody.

For subjects in Phase 2, measurable disease was defined as either of the following: serum M-protein level at least 1.0 g/dL or urine M-protein level at least 200 mg/24 hours or serum immunoglobulin FLC at least 10 mg/dL and abnormal serum immunoglobulin kappa lambda FLC ratio (for subjects with light chain multiple myeloma without measurable disease in the serum or the urine). Subjects in Phase 2 were also required to have undergone at least 1 complete cycle of treatment for each prior line of therapy (unless progressive disease was the best response), as well as have documented disease progression during or within 12 months of the most recent anti-myeloma therapy. Subjects with documented evidence of progressive disease within the previous 6 months and who were refractory or non-responsive to their most recent line of therapy afterwards were also eligible.

Dose Selection: A wide range of dose levels of teclistamab up to RP2D were evaluated during dose escalation/dose expansion in Phase 1, including both IV dosing (0.0003 to 0.0192 mg/kg Q2W and 0.0192 to 0.72 mg/kg weekly; N=84) and SC dosing (0.08 mg/kg weekly to RP2D; N=68 for these cohorts). Escalation continued higher than RP2D to explore the therapeutic range and inform future dosing schedules.

Study Treatments: The registrational dose for teclistamab monotherapy, which was evaluated in a subset of subjects in Phase 1 and all subjects in Cohort A in Phase 2, is 1.5 mg/kg teclistamab SC administered weekly, with the first treatment dose preceded by step-up doses of 0.06 and 0.3 mg/kg

Assignment to treatment: Randomization was not applicable.

Dose modification and dose discontinuation: In Phase 1, subjects were permitted to undergo dose reduction to the next lower dose level for the applicable route of administration. In Phase 2, dose reductions by 50% teclistamab SC weekly could have been considered in exceptional circumstances and after consultation with the Applicant. Dose delay was the primary method for managing toxicities related to teclistamab. Subjects in Phase 1 were permitted to undergo intra-subject dose escalation up to RP2Ds selected for dose expansion if specified criteria were met. The treatment interval for teclistamab could be extended for a subject after meeting criteria defined in the protocol.

Concurrent medications: Throughout the study, investigators were allowed to prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed as prohibited therapies in the protocol.

Pretreatment Medications: Per protocol, all subjects were required to receive the following pretreatment medications prior to each step-up dose and the first treatment dose of teclistamab:

steroids (dexamethasone; 16 mg), antihistamines (diphenhydramine [50 mg] or equivalent), and antipyretics (acetaminophen [650 mg to 1000 mg] or equivalent). Additionally, subjects who experienced Grade ≥2 CRS or sARRs were required to receive dexamethasone prior to the next dose of teclistamab and subjects who experienced any grade CRS or sARRs were required to receive the antihistamine and antipyretic prior to at least the next dose of teclistamab.

The FDA's Assessment:
FDA agrees with the Applicant's description of the study design. Study 64007957MMY1001 (MajesTEC-1) is a phase 1/2 single-arm trial with 3 parts – Part 1: phase 1 dose escalation, Part 2: phase 1 dose expansion, and Part 3: phase 2, which included Cohort A (no prior BCMA-targeted therapy) and Cohort C (prior BCMA-targeted therapy). Parts 1 and 2 had primary objectives to identify the proposed RP2D and schedule assessed to be safe, and to characterize the safety and tolerability of teclistamab at the proposed RP2D, respectively. Part 3 was designed with the primary objective to evaluate the efficacy of teclistamab at the RP2D. Therefore, FDA considers Cohort A in phase 2 the primary population to support the efficacy of teclistamab as monotherapy in BCMA-targeted therapy naïve patients with RRMM. The disease assessments were performed by Independent Review Committee (IRC), clinical investigators and computerized algorithm. The pre-specified primary efficacy endpoint is the ORR by IRC. As noted below (Applicant's Table 4), there were 11 amendments to the MajesTEC-1 protocol, including the addition of Part 3 (phase 2) with protocol amendment 9. The full eligibility criteria are noted in **Appendix 19.5.**

Study Endpoints

The Applicant's Description:
The primary endpoint for the pivotal efficacy analysis was overall response per IRC using IMWG 2016 criteria. Key secondary efficacy endpoints to further characterize the efficacy of teclistamab included DOR, status of VGPR or better, CR or better, sCR as defined by the IMWG response criteria, MRD-negativity status, TTR, PFS, OS, and overall response in subjects with high-risk molecular features. Safety endpoints included the frequency and type of DLTs (Part 1), and the incidence and severity of TEAEs, serious TEAEs, and laboratory values (all Parts).

The FDA's Assessment:
FDA agrees with the Applicant's description of the study endpoints. The endpoints that FDA used to evaluate efficacy are ORR by IRC and DOR. All other secondary endpoints, though noted by the Applicant as key secondary endpoints, are considered exploratory. Time-to event endpoints such as TTR, PFS and OS are not interpretable in single-arm studies, because it is unclear to what extent the outcomes can be attributed to the treatment effect vs. the underlying disease.

Statistical Analysis Plan and Amendments

The Applicant's Description:
The original SAP was finalized on 18 December 2020, approximately 3 months after the first subject being treated in Phase 2 of MajesTEC-1. Amendment 1 of the SAP was submitted to FDA on 29 July 2021 and Amendment 2 was finalized prior to database lock for the primary analysis

of MajesTEC-1 (30 September 2021).

Analysis of efficacy endpoints was based on the Efficacy Analysis Set. The primary efficacy variable (ORR) was based on response assessment performed by an IRC. The primary efficacy measure (ORR) and its 2-sided 95% exact CI for each cohort were presented. Subjects with no postbaseline data were considered as non-responders. Response after the start of subsequent therapy was not considered. Sensitivity analyses of ORR was performed using disease response based on computerized algorithm and investigator assessment according to IMWG criteria. The kappa statistics and 95% CI were calculated for assessing agreement between IRC assessment and computerized algorithm assessment for response (response of PR or better versus. no response). The key secondary efficacy endpoints are noted above. DOR was calculated for each subject in the Efficacy Analysis Set who achieved a response (PR or better) based on disease progression or death due to any cause for the purposes of this Assessment Aid. The distribution of DOR was estimated using the Kaplan-Meier method. For VGPR or better rate, CR or better rate, sCR rate, and ORR in subjects with high risk, the rate and its 2-sided 95% exact CI will be presented. The MRD-negative rate and its 2-sided 95% exact CI were presented; the threshold value of 10^{-5} was used for the primary MRD-negativity analysis. TTR was analyzed for subjects who achieved a response (PR or better) and descriptive statistics are provided. The Kaplan-Meier method was used to estimate the distribution of overall PFS and OS and the medians with 95% CI were provided.

The FDA's Assessment:

The FDA does not agree with basing the primary efficacy analysis on the Efficacy Analysis Set. According to the statistical analysis plan (SAP), the Efficacy Analysis Set included all treated patients who received the first dose of study intervention on or before 18 March 2021 in phase 1 at the RP2D and in phase 2 Cohort A. However, the FDA considered the primary efficacy results for phase 1 and phase 2 separately. Phase 1 was designed as a dose finding study with the primary objective to determine the RP2D and evaluate safety and tolerability. Heterogeneity may be introduced in combining data from the two phases with different primary objectives. Therefore, FDA's primary efficacy analysis was based on the 110 patients from phase 2 Cohort A only.

According to the SAP, the primary hypothesis test was comparison of the null hypothesis (H0) of ORR ≤30% against the alternative hypothesis (H1) of ORR >30% (45% was used for the sample size calculation). To demonstrate efficacy of the product, the study planned to enroll at least 100 patients to achieve >85% power to reject H0 at a 2-sided significance level of 0.05. The FDA noticed that the justification for the historical 30% reference rate was not documented in the BLA submission. In February 2022, the Agency sent an information request to the Applicant requesting justification for the historical reference rates. The Applicant responded that the ORR threshold of 30% established for Cohort A was based on the published results at the time for approved therapies. Specifically, these included belantamab mafodotin from the DREAMM-2 trial (ORR 31%; 97.5% CI: 20.8% to 42.6%; Lonial 2020) and selinexor from the STORM trial (ORR 26%; 95% CI: 19% to 35%; Chari 2019).

An interim analysis for futility was conducted for Cohort A in phase 2 when the first 30 patients became evaluable for futility. The stopping boundary was exceeded since more than 6 responders were observed among the first 30 patients. Therefore, the trial was continued.

The planned primary analysis for this BLA was based on a clinical cut-off of September 7th, 2021. However, the efficacy results presented here are based on a clinical cut-off of November 9th, 2021, with longer follow-up. Refer to the Applicant's Table 6 for more detailed information. The FDA also assessed the efficacy results based on the planned primary data cut-off of September 7th, 2021 and considered the results as supportive analyses. The efficacy results based on the clinical cut-off of November 9th, 2021 will be used for the USPI. An additional 15 African American patients were enrolled after March 18th, 2021 in phase 2 Cohort A to ensure greater representation to better reflect the U.S. population of patients with MM. These patients were not included in the primary efficacy analysis due to the inadequate duration of follow-up as of the clinical cut-off of November 9th, 2021.

Protocol Amendments

The Applicant's Description:
There were 11 global amendments (Table 4) to the original protocol dated 10 February 2017, as well as a US-specific amendment (Table 5). The protocol amendments did not have a significant impact on trial integrity or interpretation of study results.

Table 4: Overall Reasons for MajesTEC-1 Global Protocol Amendments

Protocol Version	Overall Reason
Amendment 1 20 March 2017	• To provide additional clarity to safety measures and to revise the targeted toxicity interval from (0.2, 0.33) to (0.17, 0.28) • To add a definition of measurable disease and also note that prior lines of therapy for subjects in Part 1 and Part 2 must include a PI and an IMiD
Amendment 2 28 September 2017	• To implement additional safety measures, and to add further explanation to the risks section, to clarify that the risks with the study drug were unknown because the toxicological profiles in monkeys might not be relevant to human
Amendment 3 12 December 2017	• To specify the grade for TLS that was considered to be a DLT • To remove the recommendation for anti-IL-6 therapy for the treatment of Grade ≥2 neurotoxicity
Amendment 4 26 March 2018	• To increase the dosing frequency from Q2W to weekly in new subjects enrolled in the study to allow to sufficient teclistamab exposure over the dosing interval – For the weekly dosing schedule, the DLT period was changed to 21 days to allow for observation over 3 separate doses. If step-up dosing was initiated, then the DLT window would be 28 days to include the initial step-up dose. • Previously enrolled subjects who were originally dosed on a Q2W schedule continued on the Q2W schedule
Amendment 5 30 October 2018	• To permit modification of the dosing schedule to align with PK data (weekly versus Q2W dosing schedule), including the potential for an additional step-up dose

Amendment 6 12 March 2019	• To investigate an SC administration method of teclistamab, which would reduce study drug administration duration and was hypothesized to reduce the risk of CRS, compared with IV dosing • To clarify the SET could recommend alternative dosing schedules that gradually extended the dosing interval from weekly dosing to Q2W dosing
Amendment 7 23 May 2019	• To add Time and Events Schedules to support twice-weekly dosing, and to update rules for dose escalation in the standard titration phase based on the safety and pharmacodynamic profile

Table 4: Overall Reasons for MajesTEC-1 Global Protocol Amendments

Protocol Version	Overall Reason
Amendment 8 30 July 2019	• To add the option of a commercially available saline IV bag plus sponsor-provided Diluent Additive liquid for dilution of study drug prior to administration • To increase sample size to allow for continued enrollment in IV dose escalation • To clarify an exclusion criterion for toxicities from previous anticancer therapies • To allow for 2-hour infusion time for newly enrolled subjects • To update intra-subject dose escalation criteria and discontinuation criteria • To clarify that Grade 4 hematologic toxicity does not require discontinuation in Phase 1 unless the event also meets DLT criteria
Amendment 9 02 July 2020	• To add Part 3 (Phase 2) • To add rules to stop enrollment during Part 2 if the DLT rate reached a specified range • To include the definition of women of childbearing potential • To add ASTCT Consensus Grading System for CRS and ICANS in Part 3 • To clarify the SET could recommend alternative dosing schedules that gradually extended the dosing interval from weekly dosing to monthly dosing
Amendment 10 26 October 2020	• To provide updated data for RP2D • To add methods and parameters for a futility analysis in Part 3 (Cohort A and Cohort B) • To clarify inclusion criteria for Part 3 cohorts and the plan for enrollment of the cohorts (ie, Cohorts A and C enrolled first) • To clarify that subjects enrolled in Part 1 and Part 2 should have received or been intolerant of an anti-CD38 monoclonal antibody • To clarify that subjects enrolled in Part 3 must have received ≥3 prior lines of therapy (ie, double refractory to PI and an IMiD is not sufficient for inclusion in this this cohort)

AE=adverse event; ASTCT=American Society for Transplantation and Cellular Therapy; CRS= cytokine release syndrome; DLT=dose limiting toxicity; ICANS=Immune Effector Cell-Associated Neurotoxicity Syndrome; IL 6=interleukin 6; IV=intravenous(ly); Q2W=every 2 weeks; RP2D=recommended Phase 2 dose; SC=subcutaneous(ly); SET=Safety Evaluation Team; TLS=tumor lysis syndrome

Table 5: Overall Reasons for MajesTEC-1US-specific Protocol Amendments

Protocol Version	Overall Reason
United States Amendment 10 10 February 2021 United States Amendment 11 13 July 2021	• To allow ongoing enrollment of African American/Black subjects in Cohort A in Phase 2 to ensure representation reflecting the multiple myeloma population (and align the country-specific amendment with global Amendment 11)

The FDA's Assessment:

FDA agrees with the Applicant's summary of protocol amendments.

8.1.2. Study Results

Compliance with Good Clinical Practices

Data:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCP and applicable regulatory requirements.

The study protocol and amendments were reviewed by an Independent Ethics Committee or

APPEARS THIS WAY ON ORIGINAL

Institutional Review Board. Subjects provided their written consent to participate in the study after having been informed about the nature and purpose of the study, participation/termination conditions, and risks and benefits of treatment.

The Applicant's Position:
This study was conducted in accordance with the CFR governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligation of clinical investigators to GCP (21 CFR 312.50 to 312.70).

The FDA's Assessment:
FDA agrees with the Applicant's position. The MajesTEC-1 trial was compliant with Good Clinical Practices and no issues were identified that indicate a significant risk to the data quality.

Financial Disclosure

Data:
The 1362 principal investigators and subinvestigators participating in MajesTEC-1 were assessed for financial disclosures as defined in 21 CFR Part 54, and none had disclosable financial interests. Further details of financial disclosure are provided in Section 19.2.

The Applicant's Position:
The Applicant has adequately assessed clinical investigators for any financial interest/arrangements and no disclosable financial interests were found.

The FDA's Assessment:
FDA reviewed the submitted financial disclosure form 3454 and agrees with the Applicant's position.

Patient Disposition

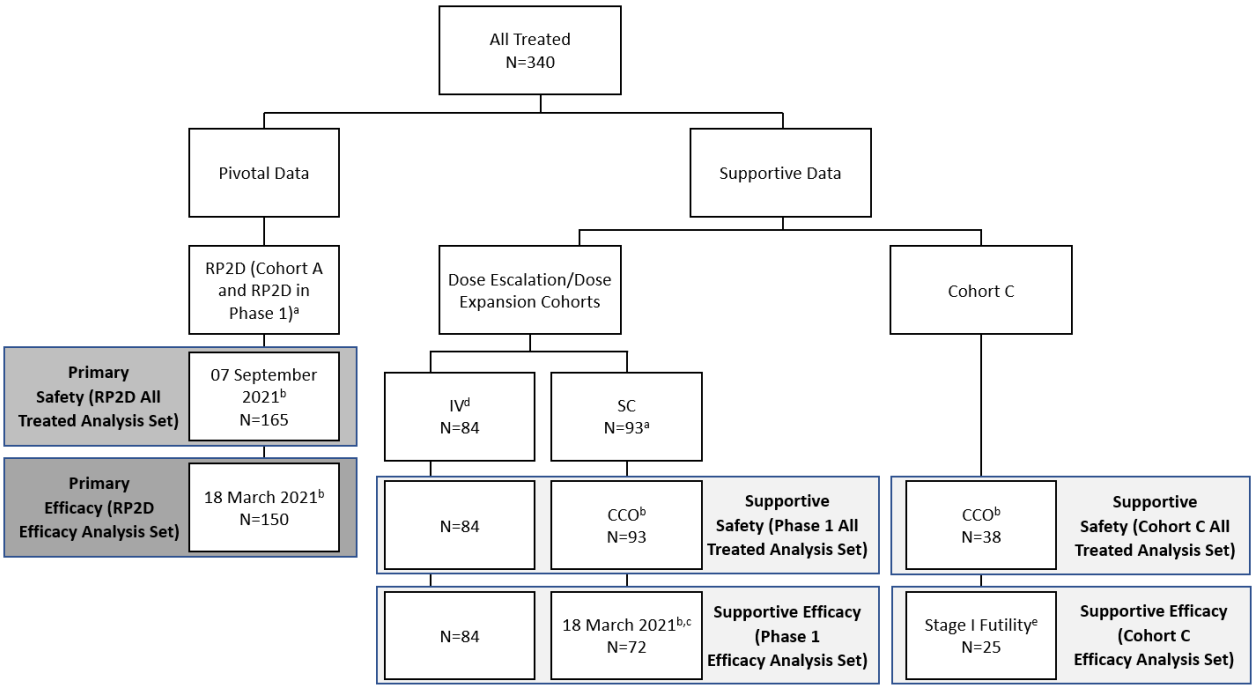
Data:
Analysis Populations

The Applicant proposes an initial BLA to be based on data in which teclistamab is administered as monotherapy in adult patients with relapsed or refractory multiple myeloma. These data are derived from the Phase 1/2 Study 64007957MMY1001 (MajesTEC-1).

The primary efficacy analyses presented in this section are based on the Efficacy Analysis Set, which is defined as all subjects who received at least 1 dose of teclistamab on or before 18 March 2021. The primary safety analyses presented in Section 8.2.1 are based on the All Treated Analysis Set, which is defined as all subjects who received at least 1 dose of teclistamab on or before 07 September 2021. Pivotal data are from subjects treated at RP2D in either Phase 1 or Cohort A in Phase 2. The same rules to determine analysis sets were applied to supportive data from subjects treated in Phase 1 (dose escalation/dose expansion) and subjects treated in Cohort C, except that the Efficacy Analysis Set for Cohort A consisted of subjects included in Stage 1 of the Simon's 2-stage analysis. Figure 1 summarizes the pivotal and supportive efficacy and safety

populations from MajesTEC-1.

Figure 1: Analysis Populations; MajesTEC-1



CCO=clinical cutoff; IV=intravenous(ly); RP2D=recommended Phase 2 dose, SC=subcutaneous(ly)

a. Subjects treated at RP2D in Phase 1 are presented in both pivotal RP2D data and Phase 1 (dose escalation/dose expansion) data.
b. A subject must have received the first dose of teclistamab on or before this date to be included in the indicated population.
c. One subject in the 6 mg/kg SC cohort who received their first step-up dose on 17 March 2021 was excluded from the efficacy analyses for Phase 1 (dose escalation/dose expansion) because the cohort was incomplete at the time of the data cutoff for inclusion in efficacy analysis and the only subject enrolled in it had not yet received a treatment dose.
d. All subjects treated with teclistamab IV received their first dose prior to 18 March 2021.
e. As described in this section, subjects evaluated in Stage 1 of the analysis for Cohort C were included in the efficacy analysis, all of whom received at least 1 dose of teclistamab on or before 23 March 2021.

Clinical Cutoff Dates

Per protocol for MajesTEC-1, the primary analysis for the BLA is based on a clinical cutoff of 07 September 2021. A subset of key efficacy data were also analyzed based on a clinical cutoff of 09 November 2021 to assess these parameters with longer follow-up. Specifically, analyses reflecting longer follow-up are provided for the pivotal RP2D primary efficacy endpoint of ORR (subjects with PR or better) by IRC assessment, as well as for selected secondary and exploratory efficacy endpoints. These data are presented in addenda to the CSR, SCE, and CO. Table 6 summarizes the clinical cutoffs for each type of data presented in this Assessment Aid, which is aligned with data reported in the proposed USPI.

Table 6: Clinical Cutoffs by Data Type

07 September 2021 Clinical Cutoff (Per Protocol Primary Analysis)	09 November 2021 Clinical Cutoff (Additional Follow-up)
Study and treatment disposition	Major protocol deviations
Demographics	Primary efficacy endpoint: ORR, including subgroups
Baseline characteristics	Key secondary and exploratory endpoints: DOR, TTR, MRD negativity, PFS, OS
Prior therapies	
Concomitant medications	
Pretreatment medication	
ORR and DOR for non-RP2D doses	
Patient-reported outcomes	
All safety analyses	

DOR=duration of response; MRD= minimal residual disease; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; TTR=time to response

Study Disposition

From the All Treated Analysis Set, 45 subjects (27.3%) treated at pivotal RP2D discontinued study participation as of the clinical cutoff. Thirty-nine subjects (23.6%) completed the study at the time of death and 6 (3.6%) withdrew consent.

Treatment Disposition

From the All Treated Analysis Set, 95 subjects (57.6%) treated at pivotal RP2D (All Treated Analysis Set) remained on treatment as of the clinical cutoff, with 45 subjects (27.3%) discontinuing treatment due to progressive disease (Table 7).

Table 7: Treatment Disposition; All Treated Analysis Set (Study 64007957MMY1001; Pivotal RP2D)(Study 64007957MMY1001; Pivotal RP2D)

	RP2D		
	Phase 1	Phase 2 Cohort A	Total
Analysis set: All Treated	40	125	165
Subjects who are still on treatment	20 (50.0%)	75 (60.0%)	95 (57.6%)
Subjects who discontinued study drug	20 (50.0%)	50 (40.0%)	70 (42.4%)
Reason for discontinuation			
Progressive disease	16 (40.0%)	29 (23.2%)	45 (27.3%)
Physician decision	3 (7.5%)	7 (5.6%)	10 (6.1%)
Death	0	9 (7.2%)	9 (5.5%)
Death - COVID-19	0	5 (4.0%)	5 (3.0%)
Subject refused further treatment[a]	1 (2.5%)	4 (3.2%)	5 (3.0%)
Adverse event	0	1 (0.8%)	1 (0.6%)
Adverse event - COVID-19	0	0	0

Key: RP2D=recommended Phase 2 dose
Note: Percentages are based on the number of all treated subjects.

[a] Subject refused further treatment includes 'Withdrawal by subject' from Phase 1 RP2D.

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The Applicant's Position:
The analysis populations for MajesTEC-1 were presented to the Agency in the context of the Type B Format and Content Meeting and the Type B Pre-BLA Meeting.

A majority of subjects in the All Treated Analysis Set remained on treatment as of the clinical cutoff and the most common reason for discontinuation (progressive disease) was consistent with the disease under study.

The FDA's Assessment:
FDA agrees with the Applicant's summary of the treatment disposition data based on the clinical cut-off of September 7th, 2021. In addition, the Applicant provided the treatment disposition summary based on the updated data with additional follow-up. As of the clinical cut-off of November 9th, 2021, among the 110 efficacy patients in Cohort A, 56 (50.9%) patients remained on treatment and 54 (49.1%) patients had discontinued study treatment, including 35 (31.8%) due to progressive disease, 7 (6.4%) due to physician decision, 10 (9.1%) due to death, and 2 (1.8%) due to refusal of further treatment.

Protocol Violations/Deviations

Data:
Major protocol deviations were reported for 15 subjects (9.1%) in the All Treated Analysis Set (Table 8). The most frequent major protocol deviation was not meeting eligibility criteria (8 subjects [4.8%]).

Data for protocol deviations related to the COVID-19 pandemic were collected for all subjects who received treatment during the study. All of these deviations were minor and most were related to either missed procedures/visits or visits and/or assessments being performed remotely. None of these minor deviations led to exclusion of data from the efficacy and safety analyses.

Table 8: Summary of Subjects With Major Protocol Deviations; All Treated Analysis Set (Study 64007957MMY1001; Pivotal RP2D)

	RP2D		
	Phase 1	Phase 2 Cohort A	Total
Analysis set: All Treated	40	125	165
Subjects with major protocol deviations	1 (2.5%)	14 (11.2%)	15 (9.1%)
Entered but did not satisfy criteria	1 (2.5%)	7 (5.6%)	8 (4.8%)
Received wrong treatment or incorrect dose	0	5 (4.0%)	5 (3.0%)
Developed withdrawal criteria but not withdrawn	0	1 (0.8%)	1 (0.6%)
Received a disallowed concomitant treatment	0	1 (0.8%)	1 (0.6%)
Other	0	0	0
Other - COVID-19	0	0	0

Key: RP2D = recommended Phase 2 dose

Note: Subjects may appear in more than one category.

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The Applicant's Position:

None of the major protocol deviations affected subject safety or data integrity.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. Among the 8 patients with major protocol deviations related to entering but not satisfying eligibility criteria, the reasons are summarized in **FDA Table 6**. FDA notes that among the 5 patients listed as having received the wrong treatment or incorrect dose, the reason in all 5 cases was failure to delay the next dose of teclistamab for adverse events that met criteria for dose delay. One patient did not discontinue study treatment after first occurrence of Grade 3 CRS lasting >48 hours. The disallowed concomitant treatment received by 1 patient was plasmapheresis on day 20 due to hyperviscosity. None of the major protocol deviations are expected to impact the overall trial results or data integrity.

FDA Table 6: Major Protocol Deviations (MajesTEC-1 Safety Population)

Patient ID (b) (6)	Cohort	Reason	Details
	Phase 1 RP2D	Exclusion criterion 7.1 met	Plasma cell count 3.8 x 10^9/L on Day -1
	Phase 2 Cohort A	Inclusion criterion 5.3 not met	Serum creatinine 1.77 mg/dL and CrCL 31 mL/min/1.73 m^2 on Day 1
	Phase 2 Cohort A	Exclusion criterion 4.1 met	Cumulative dose of corticosteroids equivalent to ≥140 mg prednisone within 14 days of first dose of study treatment
	Phase 2 Cohort A	Inclusion criterion 5.3 not met	RBC and platelet transfusions within 7 days
	Phase 2 Cohort A	Inclusion criterion 3.3 not met	Serum and urine M-protein not measurable; normal baseline serum FLC ratio although serum FLC ≥10 mg/dL
	Phase 2 Cohort A	Inclusion criterion 5.3 not met	ANC 0.8 x 10^9/L on Day 1
	Phase 2 Cohort A	Inclusion criterion 5.3 not met	ANC 0.7 x 10^9/L on Day 1

Source: FDA reviewer's analysis [MMY1001 DV and IE datasets]

Demographic Characteristics

Data:

In the Efficacy Analysis Set, median age was 64.5 years (range: 33 to 84) and 15.3% of subjects were at least 75 years of age (Table 9). Most subjects were male (58.7%) and White (89.3%), with 6 subjects (4.0%) who were Black or African American.

Table 9: Summary of Demographics, Baseline Characteristics, and Prior Therapies; Efficacy Analysis Set (Study 64007957MMY1001; Pivotal RP2D)

Analysis set: Efficacy	150
Age, years	
Median (Range)	64.5 (33; 84)
≥75 years	23 (15.3%)
Sex	
Female	62 (41.3%)
Male	88 (58.7%)
Race	
Asian	3 (2.0%)
Black or African American	6 (4.0%)
White	134 (89.3%)
Multiple	1 (0.7%)
Other	2 (1.3%)
Not reported	4 (2.7%)
Time from multiple myeloma diagnosis to first dose (years)	6.11 (0.8; 22.7)
Number of extramedullary plasmacytomas	
0	123 (82.0%)
≥1	27 (18.0%)
Bone marrow plasma cells ≥60%[a] (**n=145**)	14 (9.7%)
Baseline ECOG score	
0	53 (35.3%)
1	97 (64.7%)
ISS staging[b] (**n=148**)	
I	79 (53.4%)
II	52 (35.1%)
III	17 (11.5%)
High risk cytogenetic profile (**n=133**)	36 (27.1%)
del(17p)	22 (16.5%)
t(4;14)	15 (11.3%)
t(14;16)	3 (2.3%)
Median (Range) number of prior lines of therapy[c]	5.0 (2; 14)
Triple-class exposed (PI, IMiD, anti-CD38)	150 (100.0%)
Penta-drug exposed (2 PI, 2 IMiD, anti-CD38 antibody)	103 (68.7%)
Triple-class refractory	116 (77.3%)
Penta-drug refractory	44 (29.3%)
Refractory to last line of prior therapy	134 (89.3%)

Key: ECOG=eastern cooperative oncology group; IMiD=Immunomodulatory agent; ISS=international staging system; PI=proteasome inhibitor; RP2D=recommended Phase 2 dose;
Note: N's for each parameter reflect non-missing values.
[a] Maximum value from bone marrow biopsy or bone marrow aspirate is selected if both the results are available.
[b] ISS staging is derived based on serum β2-microglobulin and albumin.
[c] Based on data recorded on prior systemic therapy eCRF page.
Adapted from: TSIDEM01ARP2D.RTF] [JNJ-64007957\MMY1001_P3\DBR_CSR\RE_ CSR\PROD\ TSIDEM01ARP2D.SAS] 15OCT2021, 05:19; [TSIDEM04ARP2D.RTF] [JNJ-64007957\MMY1001 P3\DBR CSR\RE CSR\PROD\TSIDEM04ARP2D.SAS] 16OCT2021, 18:14; [TSICM02ARP2D.RTF] [JNJ-64007957\MMY1001 P3\DBR_CSR\RE_CSR\PROD\TSICM02ARP2D.SAS] 16OCT2021, 15:14; [TSICM03ARP2D.RTF] [JNJ-64007957\MMY1001_P3\DBR_CSR\RE_CSR\PROD\TSICM03ARP2D.SAS] 22OCT2021, 16:54

The Applicant's Position:

The demographic characteristics of subjects in the Efficacy Analysis Set were generally representative of the relapsed and refractory multiple myeloma population and the proposed indication.

The FDA's Assessment:
FDA does not agree with the Applicant's definition of the Efficacy Analysis Set in the summary of baseline demographic characteristics. The Efficacy Analysis Set based on the Agency's definition consists of the 110 patients from phase 2 Cohort A.

Among the 110 efficacy patients in Cohort A, the median age was 66 years (range: 33 to 82 years). There were 52 patients (47.3%) <65 years of age, 40 (36.4%) ≥65 to <75 years of age, and 18 (16.4%) ≥75 years of age. There were 62 male patients (56.4%) and most patients were White (90.9%). Only 5% of patients were Black or African American. The ECOG score was 0 in 36 patients (32.7%) and 1 in 74 (67.3%).

An additional 15 African American patients were enrolled after March 18th, 2021 in phase 2 Cohort A to ensure greater representation to better reflect the U.S. population of patients with MM.

Considering the low percentages of patients who were Black or African American and patients who were ≥75 years of age, the PMR issued to verify the clinical benefit of teclistamab in a randomized trial in patients with RRMM will state that the trial should enroll sufficient numbers of racial and ethnic minority patients and older patients (ages 65-74 and 75 and above) to enable an evaluation of teclistamab in a study population that better reflects the U.S. population of patients with MM.

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

Data:
In the Efficacy Analysis Set , median time from initial diagnosis was 6.11 years (Table 9). IgG was the most common immunoglobulin isotype (54.0%) and 18.0% of subjects had 1 or more extramedullary plasmacytomas at baseline. Of the 133 subjects with baseline cytogenetic data reported, 27.1% had at least 1 high-risk abnormality, most frequently del(17p). Seventeen subjects (11.5%) were ISS Stage III at baseline.

The Applicant's Position:
The baseline characteristics of subjects in the Efficacy Analysis Set were generally representative of the relapsed and refractory multiple myeloma population and the proposed indication.

The FDA's Assessment:
FDA does not agree with the Applicant's definition of the Efficacy Analysis Set in the summary of baseline disease characteristics. FDA's primary efficacy analysis only includes the 110 patients from phase 2 Cohort A.

Among the 110 efficacy patients in Cohort A, the median time from MM diagnosis to first dose was 6.4 years (range: 1.1 to 22.7 years). There were 19 patients (17.3%) who had at least one extramedullary plasmacytoma and 11 out of 107 (10.3%) with bone marrow plasma cells ≥60%. Thirteen out of 109 (11.9%) had advanced (ISS Stage III) disease at baseline. Among the 96

patients with assessment of high-risk cytogenetic profile, del(17p) was noted in 13 (13.5%), t(4;14) in 11 (11.5%) and t(14;16) in 2 (2.1%).

Prior Therapies

Data:
In the Efficacy Analysis Set, median number of lines of prior therapy was 5 (range: 2 to 14; Table 9). Five subjects (3.3%) received 2 prior lines of therapy, 31 subjects (20.7%) received exactly 3 prior lines of therapy, and 114 subjects (76.0%) received more than 3 prior lines of multiple myeloma therapy. All 150 subjects (100.0%) were triple-class exposed (PI, IMiD, and anti-CD38 monoclonal antibody) and 103 (68.7%) were penta-exposed (at least 2 PIs, at least 2 IMiDs, and at least 1 anti-CD38 monoclonal antibody). In total, 134 subjects (89.3%) treated at pivotal RP2D were refractory to their last line of therapy. Notably, 116 subjects (77.3%) were triple-class refractory and 44 (29.3%) were penta-refractory.

The Applicant's Position:
The pivotal population from MajesTEC-1 was heavily pretreated for multiple myeloma. The prior therapies received by subjects in the Efficacy Analysis Set were generally representative of the population with relapsed or refractory multiple myeloma who have received at least 3 prior therapies which included a PI, an IMiD, and an anti-CD38 monoclonal antibody.

The FDA's Assessment:
FDA does not agree with the Applicant's definition of the Efficacy Analysis Set in the summary of prior therapies. FDA's primary efficacy analysis only includes the 110 patients from phase 2 Cohort A.

The median number of prior lines of therapy in phase 2 Cohort A was 5 (range 2 to 14). All patients (100%) were triple-class exposed and 77 patients (70%) were penta-drug exposed. There were 84 patients (76%) who were triple-class refractory and 28 patients (26%) who were "penta-refractory." One hundred and one patients (92%) were refractory to their last line of prior therapy.

Within the primary efficacy analysis set of 110 patients, 86 (78%) had 4 or more prior lines of therapy; only 22 (20%) had 3 prior lines of therapy. Twelve out of the 22 were triple-class refractory (55%).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:
Teclistamab was administered per protocol by qualified healthcare professionals. See Section 8.2.2 for a discussion of exposure in the All Treated Analysis Set.

All 165 subjects in the All Treated Analysis Set treated at pivotal RP2D received at least 1 concomitant medication. The most frequently used (≥50% subjects) concomitant medications by ATC class were:

- Nucleosides and nucleotides excluding reverse transcriptase inhibitors: 155 subjects (93.9%)
- Anilides: 134 subjects (81.2%)
- Proton pumps inhibitors: 99 subjects (60.0%)
- Natural opium alkaloids: 94 subjects (57.0%)
- Combinations of sulfonamides and trimethoprim, including derivatives: 87 subjects (52.7%).

The Applicant's Position:
All concomitant medications administered were representative of commonly prescribed treatments in patients with relapsed or refractory multiple myeloma.

The FDA's Assessment:
FDA agrees with the Applicant's position. For clarity, the reviewer notes the most common nucleosides and nucleotides were valacyclovir and acyclovir. The most common anilide was paracetamol. The most common sulfonamide and trimethoprim combination was sulfamethoxazole trimethoprim. FDA notes that patients with MM undergoing treatment commonly receive antimicrobial prophylaxis based on consensus and/or institutional guidelines. The USPI will state that prophylactic antimicrobials should be administered according to guidelines.

Pretreatment Medications

Data:
All subjects (100.0%) in the All Treated Analysis Set for pivotal RP2D received pretreatment medication with steroids, antipyretics (anilides), and antihistamines (H_1 receptor antagonists).

The Applicant's Position:
All subjects received pretreatment medications through step-up dosing and the first treatment dose per protocol. The proposed USPI for teclistamab provides specific guidance in the Dosage and Administration section for the recommended use of pretreatment medications.

The FDA's Assessment:
FDA generally agrees with the Applicant's position. FDA notes that the MajesTEC-1 protocol specified that all patients should receive dexamethasone 16 mg, diphenhydramine 50 mg or equivalent, and acetaminophen 650 to 1000 mg or equivalent as pretreatment medications prior to each of the step-up doses and the first full treatment dose on Cycle 1 Day 1 (C1D1). The protocol also required pretreatment with corticosteroids prior to the next dose in any patients who experienced Grade ≥2 CRS or infusion-related reactions (IRRs) and pretreatment with antihistamines and antipyretics prior to the next dose in patients with any grade CRS or IRR. While all patients (100%) received premedication with corticosteroids, antipyretics, and antihistamines during step-up dosing and through the first full treatment dose (C1D1), FDA notes that the incidence of CRS was high (72%), despite consistent premedication use, though most events were Grade 1 or 2 in severity (refer to **Section 8.2.5.1** for details). In addition, a portion of patients received pre-medications beyond C1D1, with use decreasing over time. For example, on C5D1, 10% of patients received pre-medication with steroids, 40% of patients received pre-

medication with anilides, and 32% of patients received pre-medication with an H1 receptor antagonist. To reduce the risk of CRS, the USPI will include recommendations to administer pretreatment medications before all doses in the step-up dosing schedule, including in patients who repeat doses within the step-up dosing schedule after dose delays meeting certain criteria, and in patients who experienced CRS with the previous dose.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

In the Efficacy Analysis Set, ORR (PR or better), as assessed by the IRC based on IMWG 2016 criteria was 62.7% (95% CI: 54.4% to 70.4%; Table 10). Many responses deepened over time (Figure 2; see also additional detail in the discussion of time to response as a secondary endpoint). Median duration of follow-up for responders was 9.9 months (see also additional detail in the discussion of DOR as a secondary endpoint). Of the 94 responders, note:

- 75 responders (79.8%) maintained their responses: 73 subjects were still receiving teclistamab, 1 subject discontinued study treatment due to physician decision, and 1 subject discontinued study treatment due to other reason (subject refused further study treatment)
- 14 responders (14.9%) had disease progression after initial response, including 2 subjects who died after disease progression
- 5 responders (5.3%) died without documented disease progression by IRC: 4 subjects were receiving study treatment at the time of death (2 due to COVID-19) and 1 discontinued study treatment (physician decision) prior to death.

ORR based on assessment by computerized algorithm and based on assessment by investigator are in line with ORR assessed by the IRC. ORR in the Response Evaluable Analysis Set for pivotal RP2D and in the Efficacy Analysis Set for pivotal RP2D excluding 3 subjects who died due to COVID-19 and were not evaluable were also consistent with the primary analysis.

Subgroup analyses of ORR at pivotal RP2D, based on IRC assessment, including evaluation by baseline data for age, sex, race, renal function, ECOG performance score, number of lines of prior therapy, refractory status, type of myeloma, cytogenetic risk, baseline tumor BCMA expression, bone marrow plasma cells, ISS, revised ISS, and extramedullary plasmacytomas, as well as prior autologous stem cell transplant and prior allogeneic stem cell transplant are presented in Figure 3. ORR interpretation in some subgroups was limited by small sample sizes.

Table 10: Summary of Overall Best Confirmed Response based on IRC Assessment; Efficacy Analysis Set (Study 64007957MMY1001; Pivotal RP2D)

	RP2D					
	Phase 1		Phase 2 Cohort A		Total	
	n (%)	95% CI for %	n (%)	95% CI for %	n (%)	95% CI for %
Analysis set: Efficacy	40		110		150	
Response category						
Stringent complete response (sCR)	13 (32.5%)	(18.6%, 49.1%)	25 (22.7%)	(15.3%, 31.7%)	38 (25.3%)	(18.6%, 33.1%)
Complete response (CR)	4 (10.0%)	(2.8%, 23.7%)	6 (5.5%)	(2.0%, 11.5%)	10 (6.7%)	(3.2%, 11.9%)
Very good partial response (VGPR)	8 (20.0%)	(9.1%, 35.6%)	32 (29.1%)	(20.8%, 38.5%)	40 (26.7%)	(19.8%, 34.5%)
Partial response (PR)	1 (2.5%)	(0.1%, 13.2%)	5 (4.5%)	(1.5%, 10.3%)	6 (4.0%)	(1.5%, 8.5%)
Minimal response (MR)	0	(NE, NE)	1 (0.9%)	(0.0%, 5.0%)	1 (0.7%)	(0.0%, 3.7%)
Stable disease (SD)	7 (17.5%)	(7.3%, 32.8%)	19 (17.3%)	(10.7%, 25.7%)	26 (17.3%)	(11.6%, 24.4%)
Progressive disease (PD)	7 (17.5%)	(7.3%, 32.8%)	17 (15.5%)	(9.3%, 23.6%)	24 (16.0%)	(10.5%, 22.9%)
Not evaluable	0	(NE, NE)	5 (4.5%)	(1.5%, 10.3%)	5 (3.3%)	(1.1%, 7.6%)
Overall response (sCR + CR + VGPR + PR)	26 (65.0%)	(48.3%, 79.4%)	68 (61.8%)	(52.1%, 70.9%)	94 (62.7%)	(54.4%, 70.4%)
VGPR or better (sCR + CR + VGPR)	25 (62.5%)	(45.8%, 77.3%)	63 (57.3%)	(47.5%, 66.7%)	88 (58.7%)	(50.3%, 66.6%)
CR or better (sCR + CR)	17 (42.5%)	(27.0%, 59.1%)	31 (28.2%)	(20.0%, 37.6%)	48 (32.0%)	(24.6%, 40.1%)

Key: CI = confidence interval; NE = not estimable; RP2D = recommended Phase 2 dose; IRC = independent review committee; IMWG = international myeloma working group
Note: Response was assessed by IRC, based on IMWG consensus criteria (2016).
Note: Percentages calculated with the number of subjects in the efficacy analysis set as denominator.
Note: Exact 95% confidence intervals are provided.

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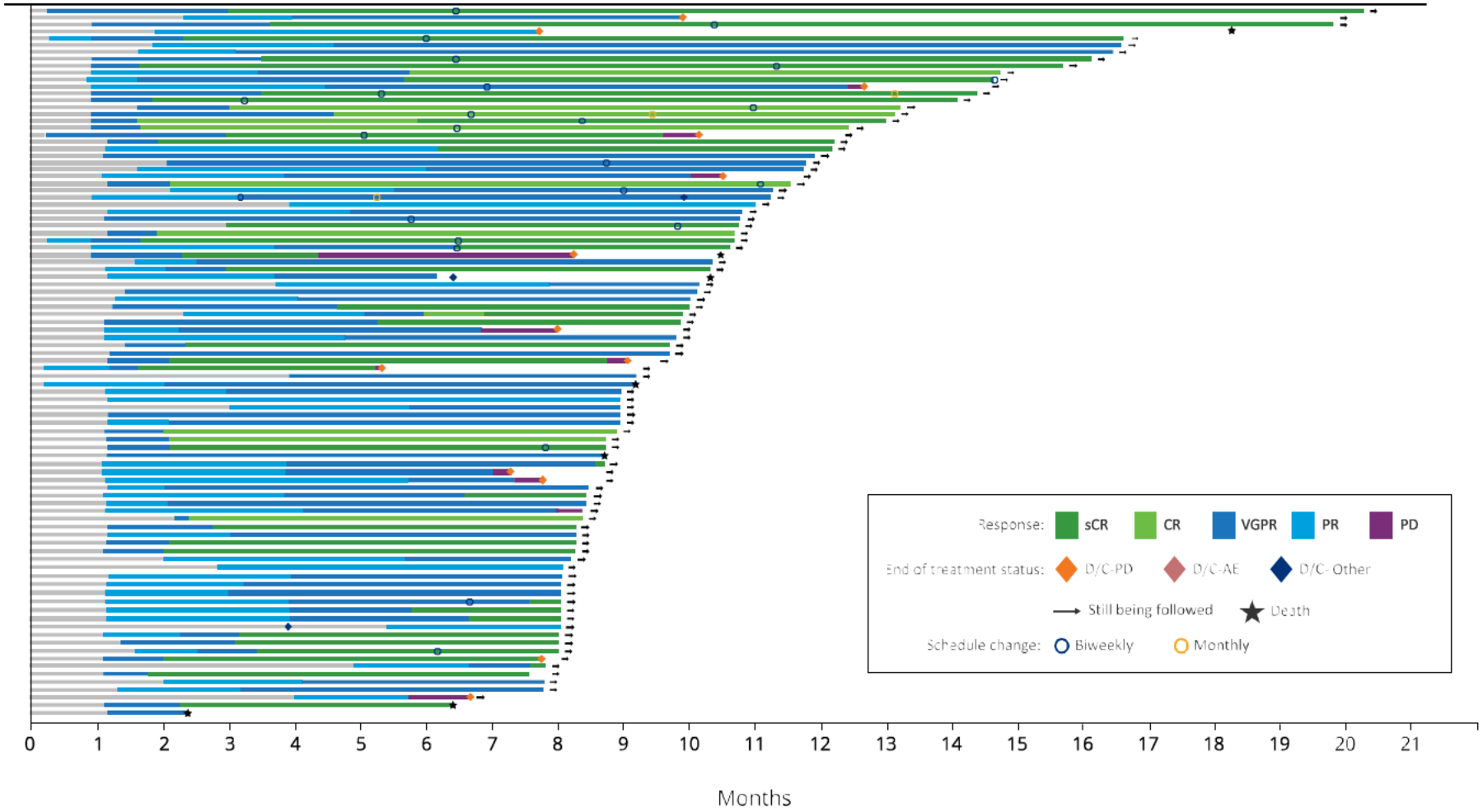
Figure 2: Response and Follow-up Based on IRC Assessment; Responders in the Efficacy Analysis Set (Study 64007957MMY1001; Pivotal RP2D)



Key: AE=adverse event; CR=complete response; D/C=discontinued; IRC=independent review committee; PD=progressive disease; PR=partial response; RP2D=recommended Phase 2 dose; sCR=stringent response; VGPR=very good partial response.
Note: Response was assessed by IRC, based on IMWG consensus criteria (2016).

Adapted from [GEFRESP05RP2D.RTF] [JNJ-64007957\MMY1001_P3\DBR_EFFICACY_ADDENDUM\RE_EFFICACY_ADDENDUM\PROD\GEFRESP05RP2D.SAS] 13DEC2021, 23:07

Figure 3: Forest Plot of Subgroup Analyses on Overall Response Rate Based on Independent Review Committee (IRC) Assessment; Efficacy Analysis Set (Study 64007957MMY1001; Pivotal RP2D)

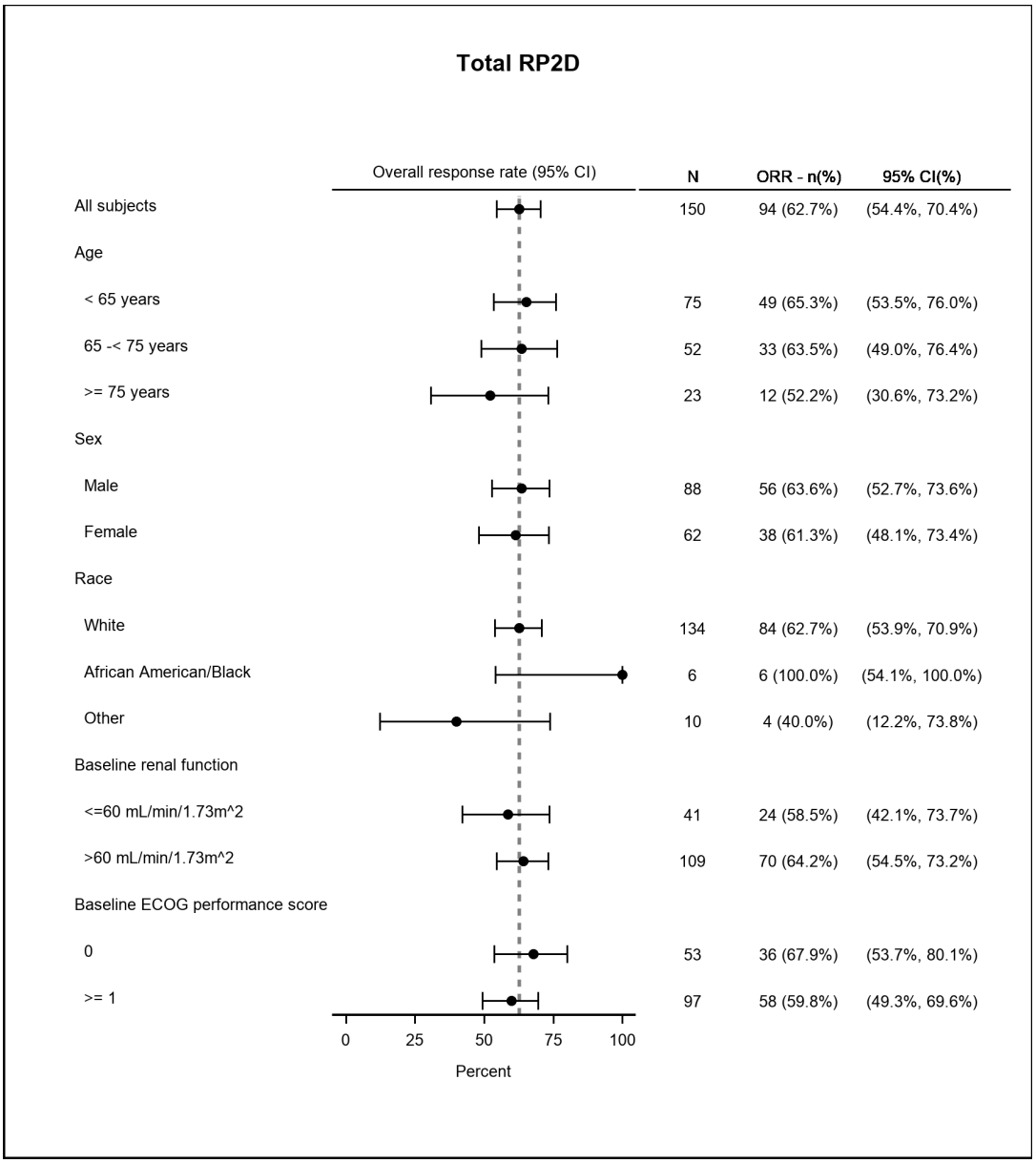


Figure 3: Forest Plot of Subgroup Analyses on Overall Response Rate Based on Independent Review Committee (IRC) Assessment; Efficacy Analysis Set (Study 64007957MMY1001; Pivotal RP2D)

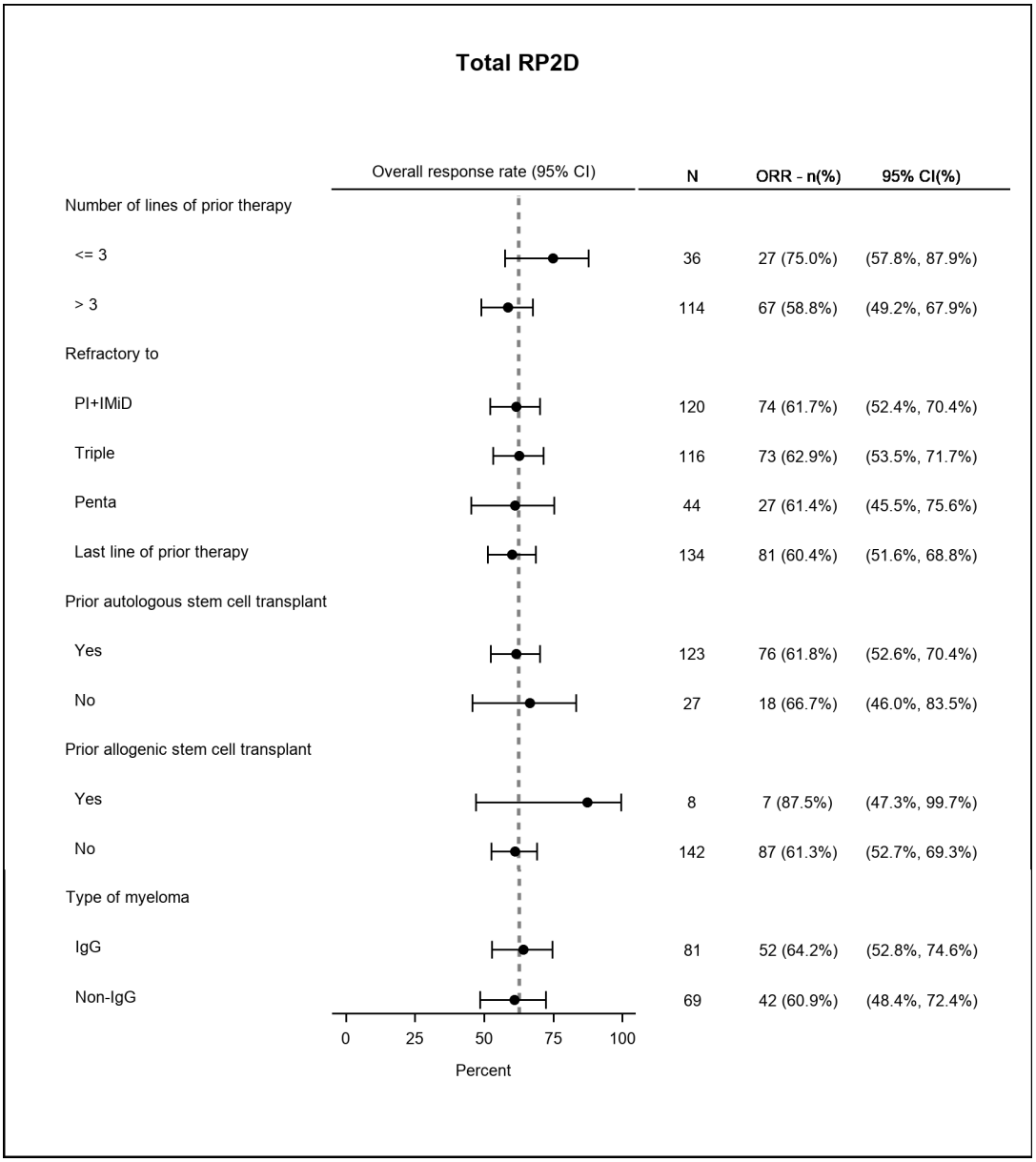


Figure 3: Forest Plot of Subgroup Analyses on Overall Response Rate Based on Independent Review Committee (IRC) Assessment; Efficacy Analysis Set (Study 64007957MMY1001; Pivotal RP2D)

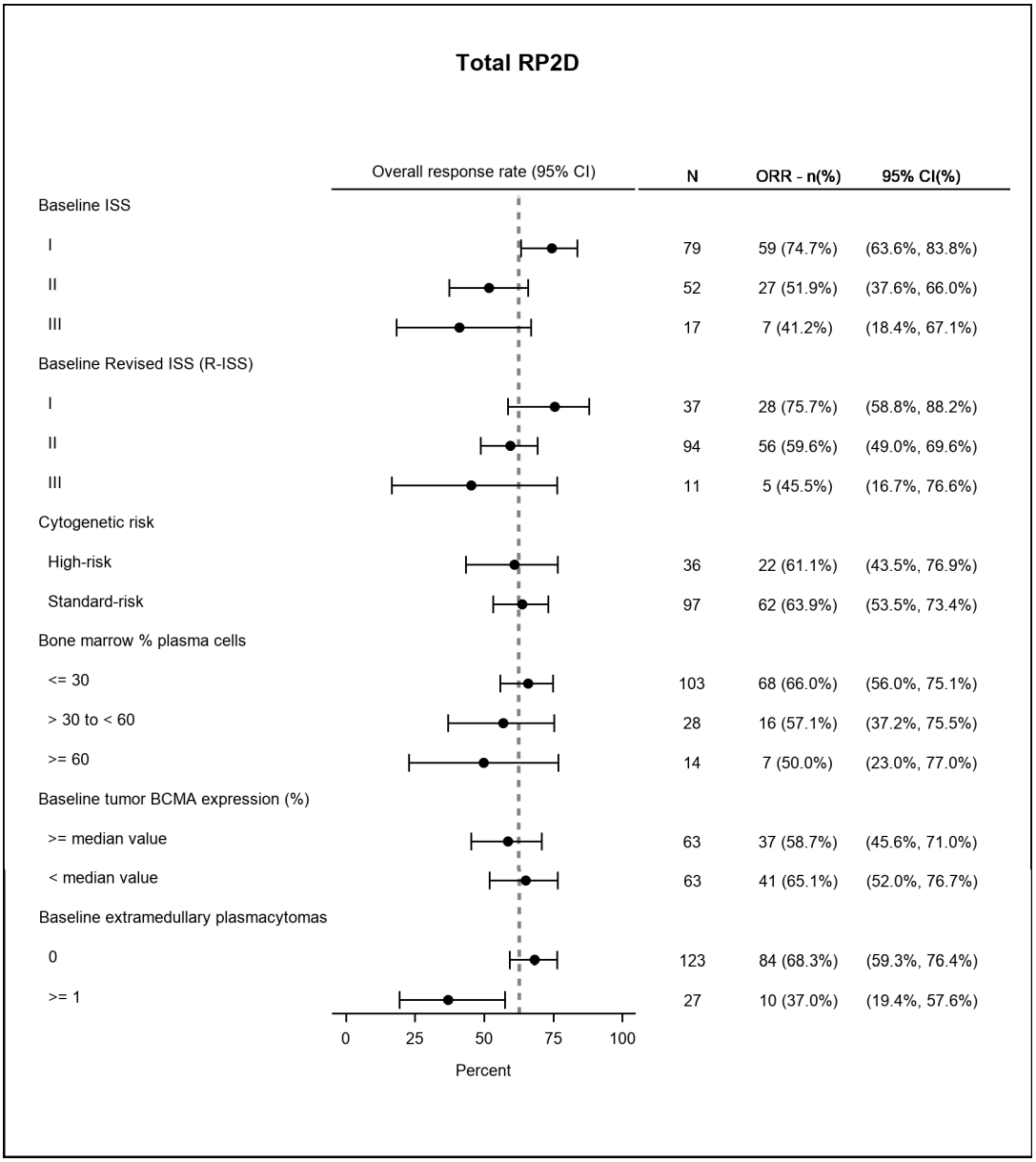


Figure 3: Forest Plot of Subgroup Analyses on Overall Response Rate Based on Independent Review Committee (IRC) Assessment; Efficacy Analysis Set (Study 64007957MMY1001; Pivotal RP2D)

Key: ECOG = Eastern Cooperative Oncology Group; CI = confidence interval; RP2D = recommended Phase 2 dose; BCMA = B-cell maturation antigen; IRC = independent review committee; IMWG = international myeloma working group; ISS = international staging system; R-ISS = revised international staging system; ORR = Overall Response Rate
Note: Refractory includes last line of prior therapy, PI+IMiD, Triple (PI+IMiD+anti-CD38 antibody), Penta (at least 2 PIs + at least 2 IMiDs + 1 anti-CD38 antibody).
Note: Baseline ISS is derived based on the combination of serum β2-microglobulin and albumin.
Note: Baseline R-ISS is derived based on the combination of serum β2-microglobulin and albumin, genetic risk, and level of lactate dehydrogenase level (LDH).
Note: High risk is defined by participants having t (4; 14); t (14; 16) and/or 17p deletion.
Note: Response was assessed by IRC, based on IMWG consensus criteria (2016).
Note: Race Other includes Asian (3 subjects), Multiple (1 subjects), Other (2 subjects) and Not Reported (4 subjects).
Note: Percentages are calculated with the number of subjects in each subgroup as denominator.
Note: Exact 95% confidence intervals are provided.
Note: The median for baseline tumor BCMA expression is 67.2% (range: 23.2%, 99.7%) in the efficacy analysis set.

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The Applicant's Position:

Teclistamab administered at RP2D led to a compelling efficacy profile for subjects who had received at least 3 prior therapies, including a PI, an IMiD, and an anti-CD38 monoclonal antibody, with ORR of 62.7% (95% CI: 54.4% to 70.4%) that was robust across multiple pre-specified sensitivity analyses and consistent across subgroups. With a substantial follow-up in responders (median: 9.9 months), a majority of responders (75 of 94) maintained response and many subjects deepened response over time, suggesting a robust and durable effect. Compelling efficacy, as measured by ORR, was observed in subjects regardless of the number of prior lines of therapy, refractoriness to the prior therapy, and the presence of standard-risk or high-risk cytogenetics at baseline.

The FDA's Assessment:

The FDA does not agree with the Applicant's use of the Efficacy Analysis Set to evaluate the primary efficacy endpoint. Refer to FDA's Assessment of the **Statistical Analysis Plan and Amendments**.

The primary efficacy result based on the patients from phase 2 Cohort A presented in Table 10 above can be reproduced by the statistical reviewer. As of the clinical cut-off of November 9th, 2021, the ORR by IRC estimate was 61.8% with the lower bound of its 95% CI of 52.1% which could exclude the pre-specified null hypothesis rate of 30%. Therefore, the study met its pre-specified primary objective.

Sensitivity analyses for the primary endpoint were based on investigator assessment and computerized algorithm. Based on the Applicant's results, the ORR by investigator assessment was 60.9% (95% CI: 51.1%, 70.1%), which was the same as the ORR by computerized algorithm. Therefore, the sensitivity analysis results indicated that the results were consistent with those based on IRC assessment.

In addition, the ORR by IRC based on the planned primary clinical cut-off of September 7th, 2021 was 60.9% (95% CI: 51.1%, 70.1%), which also demonstrated the consistency of the study results. FDA does not agree with the Applicant's statement regarding the duration of follow-up in responders. In general, a minimum of 9-12 months follow-up from the onset of first response (PR or better) is recommended to allow for an adequate assessment of durability of response. However, at the time of the data cut-off of November 9, 2021, the median duration of follow-up for the 68 responders in phase 2 Cohort A was 7.4 months (95% CI: 6.7, 7.6) and for all 94 responders, including patients in phase 1, was 7.8 months (95% CI: 7.4 to 8.5) using reverse KM method. Therefore, the duration of follow-up was inadequate to provide a robust assessment of the durability of response. A post-marketing commitment (PMC) will be issued to obtain additional data from the MajesTEC-1 trial with longer follow-up to further assess durability of response.

Among the 110 patients from phase 2 Cohort A, there were 86 patients (78%) who received 4 or more prior lines of therapy and were exposed to a PI, an IMiD and an anti-CD38 mAb. As of the clinical cut-off of November 9th, 2021, the ORR by IRC estimate for these patients was 59.3% (95% CI: 48.2%, 70.0%). The median duration of response was 9.1 months (95% CI: 9.0, NE) and the median duration of follow-up for the 51 responders was 7.4 months (95% CI: 6.7 to 7.6) using the reverse KM method.

FDA does not agree with the Applicant's promotional statement that (b) (4) . FDA notes that changes in response category over time are depicted in the Applicant's Figure 2, and categories for best overall response are shown in the Applicant's Table 10.

FDA does not agree with the Applicant's promotional statement about the subgroup analyses on ORR. Since the number of patients in subgroups are relatively small, all subgroup analysis results of ORR are considered exploratory.

FDA notes that the primary analysis set included all patients who received their first dose prior to March 18, 2021; 15 additional African American patients were enrolled after March 18th, 2021, in phase 2 Cohort A for a total of 21 African American patients treated at the RP2D. As of the data cut-off date of November 9, 2021, 10 out of 15 (67%) African American patients had a response of PR or better, including 1 sCR, 1 CR, 5 VGPR, and 3 PR. Among the 10 responders, one patient died and 9 were censored at the data cut-off; the median DOR was not reached, and the median duration of follow-up was 3.7 months (95% CI: 0, 5.8) using reverse KM method. The duration of follow up for the 20 patients in phase 2 Cohort A (5 + 15) was 4.9 months (95% CI: 1, 6).These patients are not included in the Efficacy Analysis Set or FDA's primary efficacy analysis due to short duration of follow-up.

The FDA reviewer notes that 46 out of 150 patients had a disagreement among 3 IRC reviewers in final response assessment. Therefore, FDA requested that the Applicant provide additional

data to further clarify how the final response was determined and the reasons for the discrepant response assessments. The Applicant confirmed that the final IRC response was based on the assessment agreed upon by at least 2 of the 3 IRC members and no other factors were used to select the final IRC response. However, the reasons for discrepancy were not collected. FDA review of the response assessments did not find any major disagreements that would affect the ORR results.

Data Quality and Integrity

Data:
Not applicable.

The Applicant's Position:
No data integrity concerns were reported following completion of study center/site monitoring and/or audits.

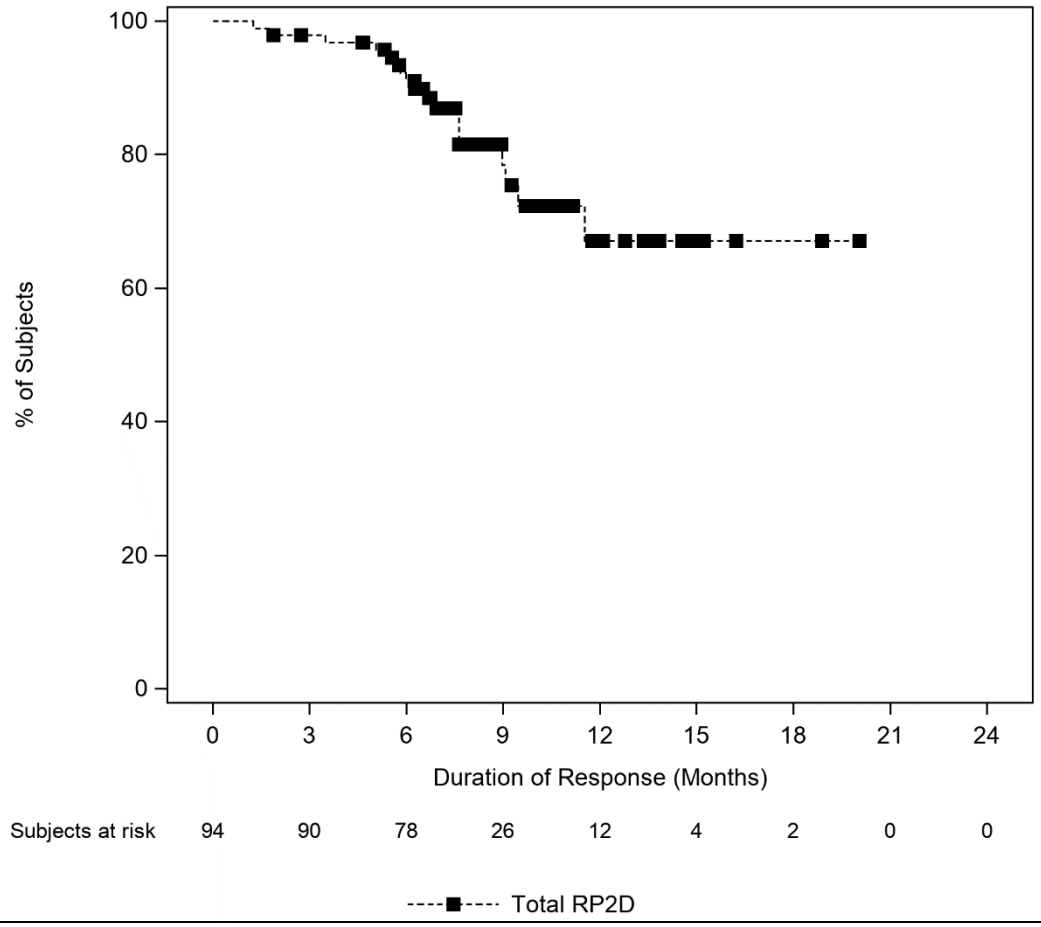
The FDA's Assessment:
No issues were identified with the data quality or integrity from the study which could affect the efficacy results. The submitted datasets are generally consistent, and variables are clearly labeled and/or explained.

Efficacy Results – Secondary and Other Relevant Endpoints

Data:

DOR at pivotal RP2D: Median duration of follow-up for responders was 9.9 months. All 94 responders by IRC assessment had at least 6 months of follow-up from initial treatment and all but 5 responders (95% of the responders) had at least 6 months of follow-up from initial response or had progressed or died. Median DOR (time from initial response to disease progression or death due to any cause) was not reached (Figure 4). The probability of responders remaining in response at 6 and 9 months was 91.0% (95% CI: 82.9% to 95.4%) and 78.5% (95% CI: 65.7% to 87.0%), respectively. At 12 months, 67.2% (95% CI: 49.4% to 79.9%) of responders were still in response.

Figure 4: Kaplan-Meier Plot for Duration of Response Based on IRC Assessment (Events Defined as Disease Progression or Death due to Any Cause); Responders in the Efficacy Analysis Set (Study 64007957MMY1001; Pivotal RP2D)



Key: RP2D = recommended Phase 2 dose; IRC = independent review committee; IMWG = international myeloma working group
Note: Response and progression were assessed by IRC, based on IMWG consensus criteria (2016).

[GEFDOR01CRP2D.RTF] [JNJ-64007957\MMY1001_P3\DBR_EFFICACY_ADDENDUM\RE_EFFICACY_ADDENDUM\PROD\GEFDOR01CRP2D.SAS] 13DEC2021

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Subjects with CR or better had more durable responses than subjects with VGPR. Of the 48 subjects who achieved CR or better, it was estimated that 83.2% (95% CI: 64.9% to 92.5%) were still in response at 12 months and median was not reached. Among 40 subjects with VGPR, median DOR was 11.5 months (95% CI: 9.0 to not estimable). Subgroup analysis of DOR among 6 subjects with PR was limited by the small sample size.

DOR for non-RP2D doses: Informative data are also available from subjects treated in Phase 1. Among responders enrolled in non-RP2D cohorts (n=50), including IV and SC, with a median duration of follow-up of 21.0 months, 31 subjects (62.0%) had a DOR of ≥12 months, and median DOR was not reached.

Depth of response: The VGPR or better rate, CR or better rate, and sCR rate in subjects treated at pivotal RP2D (Efficacy Analysis Set) are shown in Table 10.

Time to Response: Median times to first response (PR or better), best response, VGPR or better, and CR or better were 1.2, 3.1, 2.1, and 3.0 months, respectively, in subjects treated at pivotal RP2D (Efficacy Analysis Set). Most subjects demonstrated their first response by the start of Cycle 2.

MRD negativity: MRD negativity (at 10^{-5}) in bone marrow was achieved for 39 subjects treated at pivotal RP2D (Efficacy Analysis Set; 26.0%; 95% CI: 19.2% to 33.8%). In subjects with CR or better by IRC, the MRD-negativity (at 10^{-5}) was 41.7% (95% CI: 27.6% to 56.8%).

PFS: With a median follow-up of 9.8 months for all subjects treated at pivotal RP2D (Efficacy Analysis Set), median PFS was 10.1 months (95% CI; 8.0, NE); however, the PFS data were not mature with 56.0% subjects censored. The 6-month PFS rate was 64.6% (95% CI: 56.2% to 71.8%) and the 9-month PFS rate was 56.1% (95% CI: 47.2% to 64.0%).

OS: With a median follow-up of 9.8 months for all subjects treated at pivotal RP2D (Efficacy Analysis Set), median OS was 18.3 months (95% CI: 18.3, NE); however, the data were not mature with 72.0% of subjects censored. The estimated OS rate was 80.3% (95% CI: 72.9% to 85.9%) at 6 months and 76.5% (95% CI: 68.7% to 82.7%) at 9 months.

The Applicant's Position:

Key secondary endpoints support the robust response observed for the primary endpoint. Responses were achieved rapidly (generally within the first month) and deepened over time (see Figure 2), with almost all observed responses for pivotal RP2D being VGPR or better (ie, 58.7% of responses in the in the Efficacy Analysis Set being VGPR or better and 32.0% of responses in this population being CR or better). Subjects who achieved CR or better had an MRD-negativity rate (10^{-5}) of 41.7%. Responses were durable, with a median DOR that was not reached and probabilities of responders remaining in response at 6, 9, and 12 months of 91.0%, 78.5%, and 67.2%, respectively. Deeper responses appeared to be more durable. DOR data from non-RP2D dose levels evaluated in Phase 1 that have longer follow-up also support longevity of response. Median PFS (10.1 months, with 56.0% of subjects censored) and median OS (18.3 months, with

72.0% of subjects censored) were immature, but supported durability of response to teclistamab with favorable long-term outcomes.

The FDA's Assessment:
FDA does not agree with the Applicant's promotional statement about the secondary and other endpoints. In a single-arm trial, both the magnitude of the treatment effect and duration of response are critical components to establish efficacy. FDA notes that although the response rate at 6 months and 9 months appears high numerically, given the limited duration of follow-up and high proportion of censoring, the durability of responses should be interpreted with caution. Refer to FDA's Assessment under **Efficacy Results – Primary Endpoint**. In addition, the time-to-event endpoints, such as time to response, PFS, and OS are not interpretable in a single-arm study and therefore considered exploratory.

FDA does not agree with the Applicant's proposal to include the MRD data in the USPI. FDA notes that MRD-negativity rate was a key secondary endpoint for Part 3 (phase 2) of the MajesTEC-1 trial and was assessed using the NGS-based Adaptive ClonoSEQ assay (v2.0) with a threshold of 10^{-5}. However, FDA notes that there was a high rate of calibration failure (i.e., inability to detect a baseline diagnostic clone) of 29.3% in all responders and 31.6% in patients achieving CR or sCR, among patients who had a baseline sample available for testing. A list of all patients treated at the RP2D in phase 1 and in phase 2 Cohort A who had calibration failure was provided in the Applicant's response to the FDA 22 March 2022 Clinical Information Request. The Applicant also provided details regarding the baseline bone marrow plasma cell (BMPC) % and amount of DNA input used. FDA notes that the recommended genomic DNA input for the ClonoSEQ assay is 500 ng – 20 µg. Of the 23 samples with failed calibration, 12 samples had DNA input below 500 ng, though only 1 sample had a DNA input (136 ng) that was well below the threshold (the remainder of samples below the threshold had DNA input ranging from 467 to 494 ng). Regarding low baseline BMPC % as a possible reason for calibration failure, FDA notes that 18/23 patients with failed calibration had BMPC % <10%; however, calibration also failed in patients with higher BMPC %, including in patients with 94% and 95% BMPC (one of the two also had DNA input below the recommended threshold for the assay). Because of the high rates of calibration failure resulting in missing MRD status for those patients, the MRD data was not considered sufficiently robust to support inclusion in the USPI.

Dose/Dose Response

Data:
RP2D for teclistamab was established based on the totality of PK, pharmacodynamic, safety, and efficacy data obtained in the dose escalation (Part 1) and dose expansion (Part 2) phases of MajesTEC-1 and further evaluated in Phase 2. Data from Phase 2 supported selection of this dose for weekly, weight-based dosing in the patient population.

The Applicant's Position:
The totality of the efficacy data from subjects treated at pivotal RP2D in MajesTEC-1 demonstrates that teclistamab delivers robust evidence of clinical activity and a compelling treatment effect for patients with heavily pretreated, relapsed/refractory multiple myeloma who

had received at least 3 prior lines of therapy including a PI, an IMiD and an anti-CD38 monoclonal antibody. The magnitude of anti-myeloma clinical activity is further supported by deep and durable responses (including those for the dose level immediately prior to RP2D, which had similar ORR and subjects from which remain in response with longer follow-up); these data are likely to predict clinical benefit. Regarding safety, as discussed in Section 8.2, teclistamab at pivotal RP2D has a generally well tolerated and favorable safety profile with predictable and clinically manageable risks when used as monotherapy for the treatment of subjects with heavily pretreated relapsed or refractory multiple myeloma. The safety profile is consistent with the mechanism of action with respect to T cell activation and targeting of B cells.

Congruent with data from MajesTEC-1, the recommended dose for teclistamab SC is presented as follows in the proposed USPI:

- Step-up Dose 1: 0.06 mg/kg on Day 1, then
- Step-up Dose 2: 0.3 mg/kg, 2 to 4 days after Step-up dose 1, then
- Treatment Dose: 1.5 mg/kg (weekly), starting 2 to 4 days after Step-up dose 2.

The FDA's Assessment:
FDA does not agree with the Applicant's promotional statements that "(b) (4) " FDA notes that the observed ORR is clinically relevant, representing a treatment benefit in the indicated population. Due to the limited duration of follow-up the durability of response should be interpreted with caution and a PMC will be issued to obtain additional data from the MajesTEC-1 trial with longer follow-up to further assess durability of response. In addition, while ORR has been used as an intermediate endpoint to support accelerated approval in MM, a PMR will be issued to conduct a randomized trial in patients with RRMM to verify the clinical benefit of teclistamab. Regarding the Applicant's statement that (b) (4) ," FDA notes that due to the risks of CRS and neurologic toxicity, including ICANS, a REMS with ETASU will be needed to ensure that the benefits of teclistamab outweigh the risks in the post-market setting. Refer to **Section 8.2.5** and **Section 12** for further details regarding the risks of CRS and neurologic toxicity, including ICANS, and the REMS with ETASU, respectively. Refer to **Section 6.3.2.2** of the FDA Clinical Pharmacology review for further details regarding the proposed registrational dose of teclistamab.

Durability of Response

Data:
Median DOR based on disease progression or death due to any cause was not reached. See above for a detailed discussion of duration of response, which was a key secondary efficacy endpoint

for pivotal RP2D.

The Applicant's Position:
See above discussion of duration of response, which was a key secondary efficacy endpoint for the pivotal RP2D population.

The FDA's Assessment:
Refer to FDA's Assessment of **Efficacy Results – Secondary and Other Relevant Endpoints**.

Persistence of Effect

Data and Applicant's Position:
See the above discussion of DOR, which was a key secondary efficacy endpoint for pivotal RP2D. Subjects in MajesTEC-1 received study drug until disease progression, unacceptable toxicity, withdrawal of consent, death, or end of study (defined as 2 years after the last subject's first dose).

The FDA's Assessment:
Refer to FDA's Assessment of **Efficacy Results – Secondary and Other Relevant Endpoints**.

Efficacy Results – Secondary or Exploratory COA (PRO) Endpoints

Data:
EORTC QLQ-C30: Achievement of a meaningful (10-point) improvement from baseline through Cycle 6 using the literature based MCT (Cocks 2008) was reported by up to 35.8% of subjects for global health status, up to 23.9% of subjects for physical functioning, up to 68.7% of subjects for fatigue, and up to 78.8% of subjects for pain score.

EQ 5D-5L: The LS mean from baseline to Cycle 6 in the mixed model for repeated measures was 8.9 (95% CI: 4.6 to 13.2). A meaningful (7-point) improvement from baseline in VAS scores at Cycles 2, 4, and 6 was reported by 23.8%, 28.6%, and 30.2% of subjects, respectively.

PGIS: At baseline, 13.7% of subjects reported disease severity was none or mild; at Cycles 2, 4, and 6, 25.9%, 47.7%, and 55.3% of subjects, respectively, reported severity of none or mild.

The Applicant's Position:
HRQoL evaluations conducted in Phase 2 showed meaningful reductions in pain and improvements in health status through Cycle 6.

The FDA's Assessment:
FDA does not agree with Applicant's promotional statement about PRO assessments. There was no pre-specified formal hypothesis in the analysis plan. Additionally, the HRQoL PRO data has limited interpretability in the open label and single-arm trial setting. The treatment effect may be subject to systematic overestimation due to patients' knowledge of treatment assignment. Therefore, these PRO assessments are only considered exploratory and should be interpreted with caution.

Additional Analyses Conducted on the Individual Trial

Data and Applicant's Position:
Not applicable.

The FDA's Assessment:
Not applicable.

8.1.3. Integrated Review of Effectiveness

Data and Applicant's Position:
Not applicable.

The FDA's Assessment:
Not applicable.

8.1.4. Assessment of Efficacy Across Trials

Primary Endpoints

Data and Applicant's Position:
Not applicable.

The FDA's Assessment:
Not applicable.

Secondary and Other Endpoints

Data and Applicant's Position:
Not applicable.

The FDA's Assessment:
Not applicable.

Subpopulations

Data and Applicant's Position:
Not applicable.

The FDA's Assessment:
Not applicable.

Additional Efficacy Considerations

Data and Applicant's Position:
Not applicable.

The FDA's Assessment:
Not applicable.

8.1.5. Integrated Assessment of Effectiveness

Data and Applicant's Position:
Efficacy data presented in this BLA are derived from a single ongoing study of teclistamab (MajesTEC-1) and thus there was no integration with other Applicant-conducted clinical trial data. As discussed in Section 8.1.2, teclistamab administered at RP2D led to a compelling efficacy profile for subjects who had received at least (b) (4) prior therapies, including a PI, an IMiD, and an anti-CD38 monoclonal antibody.

The FDA's Assessment:
FDA does not agree with the Applicant's position. The approved indication under this application is for patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody. The observed ORR, supported by DOR, represents a clinically relevant treatment effect in this population. For more detailed information to support this indication, refer to FDA's Assessment of **Efficacy Results – Primary Endpoint**.

8.2 Review of Safety

8.2.1. Safety Review Approach

The Applicant's Position:
The pivotal population for safety (All Treated Analysis Set) includes subjects treated at 1.5 mg/kg SC weekly (RP2D) in Phase 1 (n=40) and subjects treated in Cohort A in Phase 2 (n=125, for a total of 165). Figure 1 summarizes this population (termed pivotal RP2D) and the supportive populations for safety from MajesTEC-1.

The safety of teclistamab was assessed based on the incidence and severity of AEs, laboratory test results, vital sign measurements, triplicate ECGs (Phase 1 only), physical examination findings (including neurological examination), assessment of ICE Tool scores (Phase 2 only), and assessment of ECOG Performance Status score. TEAEs were reported from signing of the ICF until 100 days after the last dose of teclistamab (Phase 1) and up to 30 days after last dose of teclistamab (Phase 2) or until the start of subsequent systemic anticancer treatment, if earlier.

TEAE severity was graded per NCI-CTCAE Version 4.03 except for events of CRS and ICANS, which were graded per ASTCT for subjects treated in Phase 2 (Table 11). CRS was graded per Lee 2014 criteria for subjects treated in Phase 1. For the purposes of this study, neurologic AEs were defined as TEAEs reported in either the Nervous System Disorder or Psychiatric Disorders SOCs, regardless of investigator assessment of relatedness to teclistamab. Neurologic AEs judged by the investigator to be related to teclistamab were termed neurotoxicity. The presentation of neurologic AEs and neurotoxicity events includes grouped terms for aphasia, delirium, encephalopathy, and tremor as follows:

- Aphasia: aphasia and dysphasia
- Delirium: agitation, delirium, delusion, disorientation, hallucination, and restlessness
- Encephalopathy: cognitive disorder, confusional state, depressed level of consciousness, disturbances in attention, encephalopathy, hypersomnia, leukoencephalopathy, memory impairment, mental status changes, paranoia, somnolence, and stupor
- Tremor: head titubation and tremor.

ICANS was assessed as a distinct subset of neurotoxicity.

Table 11: Summary of Adverse Event Grading Criteria

Phase	CRS	Neurologic AEs and Neurotoxicity, Including ICANS	All Other AE
1 (Part 1 and Part 2)	Lee 2014 criteria[a]	NCI-CTCAE Version 4.03[c]	NCI-CTCAE Version 4.03
2 (Part 3)	ASTCT Consensus Grading System[b]	Neurologic AEs, neurotoxicity, and symptoms of ICANS: NCI-CTCAE Version 4.03 ICANS: ASTCT Consensus Grading System	NCI-CTCAE Version 4.03

AE=adverse event; ASTCT=American society for Transplantation and Cellular Therapy; CRS=cytokine release syndrome; CSR=Clinical Study Report; ICANS=Immune effector cell-associated neurotoxicity syndrome; NCI-CTAE=National Cancer; RP2D=recommended Phase 2 dose

a. CRS events were graded per Lee 2014 criteria by the investigator in Phase 1, but were re-evaluated per ASTCT during analysis for subjects treated at RP2D in Phase 1 to allow comparability across both Phase 1 and Phase 2 of the study for the dose most relevant to the initial marketing application.

b. During data analysis, all events of CRS reported for subjects treated Phase 2 were re-evaluated per Lee 2014 criteria.

c. ICANS could not be formally identified or excluded for subjects in Phase 1. The Applicant retrospectively evaluated the following in subjects treated at RP2D in Phase 1 to make a clinical determination of whether these were consistent with ICANS: neurotoxicity events reported at any time and all neurologic AEs that occurred within the 28 days after the first dose of teclistamab (ie, time period when CRS and ICANS are most likely to occur).

The Applicant's Position:

Methodology to collect safety data were robust and relevant to the study population and disease under study.

The FDA's Assessment:

Safety analyses were conducted on the complete datasets provided by the Applicant for the MajesTEC-1 trial based on a 07 September 2021 data cut-off. FDA notes that the primary safety population based on the Applicant's All-Treated Analysis Set (N=165) included 40 patients from phase 1 (N=12 from Part 1 phase 1 dose escalation and N=28 from Part 2 phase 1 dose expansion) and 125 patients from phase 2 (Part 3 phase 2 Cohort A) who received the RP2D of teclistamab 1.5 mg/kg SC weekly, preceded by step-up doses of 0.06 mg/kg and 0.3 mg/kg SC. This includes an additional 15 patients (all African American) from phase 2 Cohort A who received their first dose of teclistamab after 18 March 2021 and were not included in the primary Efficacy Analysis Set.

Because of the differences between the phase 1 and phase 2 populations and differences in the protocol for phase 1 and phase 2 (a detailed list of differences was provided in the Applicant's response to the FDA 15 April 2022 Clinical Information Request), including the treatment emergent AE (TEAE) window (until 100 days after the last dose for phase 1 and up to 30 days after the last dose for phase 2, or until start of subsequent therapy, if earlier), grading of CRS (Lee 2014 criteria in phase 1 and ASTCT (Lee 2019) criteria in phase 2), and evaluation of ICANS (formally assessed in phase 2 and retrospectively assessed in phase 1), the FDA safety analyses considered the phase 1 and phase 2 populations both separately and pooled.

FDA analysis of TEAEs included FDA grouping of related preferred terms, some of which differed from the grouped terms used in the Applicant's analysis (see **Appendix 19.6** for the full listing of FDA grouped terms).

In a single arm trial, FDA considers all TEAEs. Therefore, FDA does not agree with the Applicant's distinction between neurologic TEAEs and "neurotoxicity" based on Investigator attribution of relatedness to teclistamab. FDA's analysis of neurologic toxicity included all neurologic TEAEs, including certain relevant preferred terms that were outside of the nervous system and psychiatric disorders system organ classes (SOCs) (**Appendix 19.6**).

8.2.2. Review of the Safety Database

Overall Exposure

Data:
Median duration of treatment for subjects in the All Treated Analysis Set treated at pivotal RP2D (n=165) was 5.9 months (range: 0.2 to 18.0) and the median number of treatment cycles was 7 (range: 1 to 22). Among subjects treated at pivotal RP2D, 77 (46.7%) received teclistamab for at least 6 months, 27 (16.4%) received therapy for at least 9 months, and 11 (6.7%) received therapy for at least 12 months. One subject received therapy for at least 18 months. The median relative dose intensity for subjects treated at pivotal RP2D was 94.5%. The median duration of follow-up was 7.2 months (range 0.3 [subject died] to 18.0).

Overall, 46 subjects in MajesTEC-1 received at least 12 months of therapy. Eighteen subjects (all but 1 of whom were treated with dose levels below RP2D) received at least 18 months of therapy as of the clinical cutoff.

Follow up remains ongoing for these subjects and an additional 4 months of safety data will be provided in the 120-day safety update report in April 2022 (clinical cut off of 04 January 2022).

The Applicant's Position:
The Applicant considers that sufficient data to assess the safety profile of teclistamab are available for the pivotal analysis set (ie, duration of treatment and follow-up) and anticipates the safety profile to be further supported by data to be analyzed from the clinical cutoff for the safety update.

Exposure data also demonstrate that sufficient safety data from subjects with longer duration of treatment and follow-up were available from Phase 1. As discussed in **adequacy of the safety database**, data from dose escalation/dose expansion cohorts in Phase 1 are also relevant because the safety profile of teclistamab observed in efficacious non-RP2D cohorts was similar to that for pivotal RP2D. Data from these Phase 1 subjects with long treatment and follow-up durations also suggest that the safety profile of teclistamab is stable over time.

The FDA's Assessment:
FDA notes that the median duration of follow-up of 7.2 months reported by the Applicant was based on analysis using the reverse Kaplan-Meier method (as confirmed by the Applicant in their

response to the FDA 07 July 2022 Clinical Information Request). FDA notes that because median duration of follow-up for all treated subjects is not a time-to-event analysis, calculation of the simple median is considered the appropriate approach. Based on FDA analysis using this approach, the median duration of follow-up was 6.4 months for the 165 patients in the primary safety population based on the 07 September 2021 data cut-off.

FDA otherwise concurs with the exposure data presented by the Applicant. FDA's review was focused on the 165 patients treated at the RP2D in the MajesTEC-1 trial (referred to as the 'primary safety population'). Regarding the Applicant's statement that "the safety profile of teclistamab observed in efficacious non-RP2D cohorts was similar to that for pivotal RP2D," FDA reviewed, but did not independently confirm the exposure or safety results for patients in the non-RP2D cohorts.

Relevant Characteristics of the Safety Population

Data:
Subject demographics, baseline characteristics, and prior therapies for the All Treated Analysis Set for subjects treated at pivotal RP2D were consistent with those for the Efficacy Analysis Set for pivotal RP2D presented in Section 8.1.2 and adequately represent the proposed indication for teclistamab.

The Applicant's Position:
See position for the Efficacy Analysis Set in Section 8.1.2.

The FDA's Assessment:
FDA notes that the primary safety population (N=165) includes an additional 15 patients (all African American) from phase 2 who received their first dose of teclistamab after 18 March 2021 who were not included in the primary Efficacy Analysis Set. The trial enrolled a younger population of patients (median age of 65) compared to the U.S. population of patients with MM (median age at diagnosis of 69). Otherwise, the baseline demographics and disease characteristics were representative of the general population of patients with RRMM in the U.S. FDA notes that 74% of patients treated at the pivotal RP2D had received 4 or more prior lines of therapy, while only 23% of patients received 3 prior lines. While the efficacy was similar in patients who had received only 3 prior lines of therapy, given the safety concerns regarding risk of CRS and neurologic toxicity, including ICANS, as discussed in **Sections 8.2.5.1** and **8.2.5.2** below, and the availability of approved therapies for patients with RRMM who have received 3 prior lines of therapy, the benefit-risk assessment did not support inclusion of this population as part of the indicated population for teclistamab.

Adequacy of the Safety Database

Data and Applicant's Position:
The safety population for pivotal RP2D includes 165 subjects (Figure 1). An additional 137 subjects (the vast majority of whom had also received at least 3 prior lines of therapy and were triple-class exposed) received teclistamab at a wide range of doses during dose escalation/dose expansion. Thirty-eight subjects who had received prior anti-BCMA therapy were

treated at RP2D in Cohort C in Phase 2. Safety data are available from a total of 340 subjects.

The overall safety profile of teclistamab in the dose escalation/dose expansion cohorts was similar among all biologically active dose levels (ie, cohorts with ORR exceeding 50%) and similar to that of the pivotal RP2D population. No safety parameter showed a clear dose-dependent relationship. Dose levels 4-fold higher than RP2D were evaluated and no MTD was identified. One subject who received teclistamab IV developed a Grade 4 neurotoxicity (delirium) that appeared to be consistent with ICANS and resolved but resulted in treatment discontinuation. Importantly, the overall incidence of TEAEs, TEAEs by severity grade, serious TEAEs, and deaths

due to TEAEs reported at least 12 months or more after the start of treatment (for subjects on treatment longer than 12 months) tended to be lower compared with reporting rates over the full treatment period. This suggests that the safety profile of teclistamab was consitent across the treatment course, with no additional safety issues being observed following long-term treatment.

The safety profile for subjects treated at RP2D in Cohort C in Phase 2 was also similar to pivotal RP2D, with the notable addition of 1 subject who experienced Grade 3 ICANS. This event occurred concurrently with CRS, was treated with tocilizumab and anakinra, and resolved in 2 days.

In summary, data from both pivotal RP2D and the total study safety population are considered to be adequate to assess the safety of teclistamab monotherapy in the treatment of subjects with relapsed or refractory multiple myeloma who have received at least 3 prior therapies, including a PI, an IMiD, and an anti-CD38 monoclonal antibody.

The FDA's Assessment:
The size of the safety database of 165 patients who received the RP2D of teclistamab and the extended safety database, which included a total of 340 patients who received teclistamab monotherapy, is considered adequate based on teclistamab being a product that is intended to treat a life-threatening disease in a circumstance where there is no alternative satisfactory treatment. However, the assessment of safety is limited by the MajesTEC-1 single arm trial design, and there is currently no randomized data available comparing teclistamab to either placebo or standard of care therapy. FDA's analysis did not include the 38 patients from phase 2 Cohort C due to the limited number of patients and limited duration of follow up in this cohort precluding an adequate assessment of safety in patients with prior BCMA-directed therapy. FDA does not agree with the Applicant's statement that no additional safety issues were observed following long-term treatment. The 120-day safety update included two additional serious neurological TEAEs (Grade 4 seizure and Grade 5 (fatal) Guillain-Barré syndrome) that occurred with longer follow-up. Therefore, the current safety database may represent an underestimate of cumulative neurological toxicity. A PMR will be issued to further characterize neurologic toxicity with longer follow-up and in a randomized setting.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:
Sites in MajesTEC-1 were monitored following study-specific monitoring plans for consistency. Data were reviewed by Data Management personnel in accordance with the prespecified Data Management Plan. The Applicant's medical team conducted ongoing clinical review. All available data as of the clinical cutoff date were included in the safety assessment presented in the BLA. See Section 8.1.2 for information related to data quality/integrity related to COVID-19 pandemic.

The Applicant's Position:
No issues were identified regarding the integrity and quality of the safety data included in this

BLA.

The FDA's Assessment:
The quality of the safety data submitted was adequate for substantive primary review. The Applicant provided full datasets for patients enrolled in MajesTEC-1.

Categorization of Adverse Events

Data and Applicant's Position:
Summaries of reported AEs are based on TEAEs, defined as those with an onset after start of the first study drug through 100 (Phase 1) or 30 (Phase 2) days after the last dose of study drug (or the day prior to start of subsequent therapy, whichever was earlier). Events that worsened after the first dose of study drug or were judged to be related to study drug were also considered treatment-emergent. For all reported AEs, the investigator provided his/her opinion regarding the relationship of the event to teclistamab according to the definitions provided in the protocol.

AEs of clinical interest were selected based on the expected safety profile of teclistamab, accounting for mechanism of action, the disease state, and the safety profile of other compounds with a similar or related mechanism of action (ie, T cell activation and targeting of B cells).

Information on all deaths occurring at any time during the study, including the Treatment and Follow-up periods, was collected and analyzed. Sponsor guidance regarding reporting of Grade 5 TEAEs differed between Phase 1 and Phase 2 with respect to fatal events in the context of progressive disease. In Phase 1, Grade 5 events could be entered per investigator discretion for subjects who were reported with cause of death as progressive disease during the treatment-emergent window. In Phase 2, Grade 5 events (eg, signs and symptoms of clinical sequelae resulting from disease progression) were requested to be entered if the death occurred within the treatment-emergent window.

Narratives were written based on criteria agreed with FDA via the written feedback received 21 May 2021 for the Type B Format and Content Meeting.

The Applicant's Position:
The recording, coding, and categorization of AEs are reasonable, appropriate, and consistent with typical clinical development practices for oncology agents.

The FDA's Assessment:
As discussed in the FDA assessment in Section 8.2.1, because of the differences between the phase 1 and phase 2 populations and differences in adverse event collection and grading, the FDA's safety review considered the phase 1 and phase 2 populations both separately and pooled. FDA's review of safety is also focused on TEAEs that occurred within 30 days of the last dose of study treatment. Although the Applicant states that for all reported AEs, the investigator opinion regarding the relationship to teclistamab was provided, for a single arm trial, FDA considers all TEAEs regardless of investigator attribution. FDA notes that given the difference between phase 1 and phase 2 in Sponsor guidance regarding reporting of Grade 5 TEAEs in the setting of death

due to progressive disease, it is possible that some Grade 5 TEAEs that occurred in the setting of progressive disease were not captured for the phase 1 cohort.

Routine Clinical Tests

Data:
See information in Section 8.2.1 regarding safety parameters for which data were collected and analyzed.

The Applicant's Position:
The assessment methods and time points for collection and analysis of safety measures other than AEs were appropriate for the disease and indication investigated in MajesTEC-1.

The FDA's Assessment:
The frequency of safety monitoring was considered adequate in the context of the study.

8.2.4. Safety Results

Deaths

Data:
Forty subjects (24.2%) treated at pivotal RP2D had died as of the clinical cutoff (Table 12). According to investigator assessment of primary cause of death, 30 subjects (18.2%) died due to disease progression, 9 (5.5%) died due to AE, and 1 (0.6%) died due to other causes.

Twenty subjects (12.1%) died from any cause within 30 days of the last dose of study treatment (Table 12). The most frequently reported primary cause of death within this period was progressive disease (13 subjects [7.9%]). Six subjects (3.6%) had AEs identified as the primary cause of death, all of which were considered by the investigator to be unrelated to teclistamab. One subject's death due to respiratory failure was categorized as "other," as it occurred after the start of subsequent therapy and was therefore not considered treatment-emergent.

Grade 5 TEAEs were reported for 18 subjects (10.9%) treated at pivotal RP2D, none of which were judged by the investigator to be related to teclistamab. Of the 18 subjects for whom a Grade 5 TEAE was reported, 9 had progressive disease reported as cause of death and the following 9 occurred in subjects for whom AE was reported as the cause of death: COVID-19 (7 subjects, including 3 subjects for whom the Grade 5 event occurred more than 30 days after the last dose of study drug but was considered treatment-emergent because a lower grade event was reported earlier), pneumonia (1 subject), and hemoperitoneum (1 subject; Table 13). Of these 9 subjects, 3 had progressive disease prior to death (events of pneumonia [1 subject] or COVID-19 [2 subjects]) and 4 had no postbaseline disease evaluation performed (events of hemoperitoneum [1 subject] and COVID-19 [3 subjects]). The remaining 2 subjects also died of COVID-19, with last responses per IRC prior to death of sCR and VGPR.

Table 12: Summary of Deaths and Cause of Death; All Treated Analysis Set (Study 64007957MMY1001; Pivotal RP2D)

	RP2D		
	Phase 1	Phase 2 Cohort A	Total
Analysis set: All Treated	40	125	165
Total number of subjects who died during study	10 (25.0%)	30 (24.0%)	40 (24.2%)
Primary cause of death			
Adverse event	0	9 (7.2%)	9 (5.5%)
Study drug related[a]	0	0	0
AE(s) unrelated	0	9 (7.2%)	9 (5.5%)
Adverse event - COVID-19	0	7 (5.6%)	7 (4.2%)
Disease progression	9 (22.5%)	21 (16.8%)	30 (18.2%)
Other	1 (2.5%)	0	1 (0.6%)
Other - COVID-19 related	0	0	0
Total number of subjects who died within 30 days of last study treatment dose	2 (5.0%)	18 (14.4%)	20 (12.1%)
Primary cause of death			
Adverse event	0	6 (4.8%)	6 (3.6%)
Study drug related[a]	0	0	0
AE(s) unrelated	0	6 (4.8%)	6 (3.6%)
Adverse event - COVID-19	0	4 (3.2%)	4 (2.4%)
Disease progression	1 (2.5%)	12 (9.6%)	13 (7.9%)
Other	1 (2.5%)	0	1 (0.6%)
Other - COVID-19 related	0	0	0
Total number of subjects who died within 60 days of first study treatment dose	2 (5.0%)	16 (12.8%)	18 (10.9%)
Primary cause of death			
Adverse event	0	6 (4.8%)	6 (3.6%)
Study drug related[a]	0	0	0
AE(s) unrelated	0	6 (4.8%)	6 (3.6%)
Adverse event - COVID-19	0	4 (3.2%)	4 (2.4%)
Disease progression	1 (2.5%)	10 (8.0%)	11 (6.7%)
Other	1 (2.5%)	0	1 (0.6%)
Other - COVID-19 related	0	0	0

Key: AE=adverse event; RP2D=recommended Phase 2 dose

[a] Related if assessed by the investigator as possibly, probably, or very likely related to study agent.

Note: Percentages calculated with the number of subjects in the all treated analysis set as denominator.

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Table 13:Number of Subjects with Grade 5 TEAEs With Cause of Death Due to AE, System Organ Class and Preferred Term; All Treated Analysis Set (Study 64007957MMY1001; Pivotal RP2D)

	RP2D (N=165)
	Death due to TEAE
Subjects with 1 or more grade 5 TEAEs	9 (5%)
MedDRA system organ class/preferred term	
Infections and infestations	8 (4.8%)
COVID-19	7 (4.2%)
Pneumonia	1 (0.6%)
Gastrointestinal disorders	1 (0.6%)
Haemoperitoneum	1 (0.6%)

Key: TEAE = treatment-emergent adverse event; RP2D=recommended Phase 2 dose.
Note: RP2D includes Phase 1 RP2D treatment group and Phase 2 Cohort A.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 24.0.
Note: Adverse events are reported until 100 days (Phase 1) or 30 days (Phase 2) after the last dose of teclistamab or until the start of subsequent anticancer therapy, if earlier.

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The Applicant's Position:

The most common cause of death was progressive disease (30 subjects), which is expected for the disease population under study. Nine subjects died of AE, none of which were judged by the investigator as related to teclistamab. Of these 9 subjects, 7 died of COVID-19, consistent with the fact that the pivotal study was conducted at the height of the COVID-19 pandemic in this highly vulnerable patient population with multiple myeloma (Krejci 2021). With the increased availability of vaccines and the broader use of anti-SARS-COV-2 antibody treatments at the time of exposure, the risk of severe COVID-19-related infections and deaths may be mitigated for this patient population in the future. One subject, who had with high disease burden and baseline thrombocytopenia, died of hemoperitoneum. One subject died of pneumonia. Note that 7 subjects who died due to Grade 5 TEAE had progressive disease or were non-responders at the time of death.

The FDA's Assessment:

FDA concurs that as of the 07 Sept 2021 data cut-off, a total of 40 deaths occurred within the primary safety population, including 20 deaths within 30 days of the last dose of teclistamab. However, FDA does not agree with the cause of death presented by the Applicant for all cases. FDA adjudication of deaths within 30 days identified 3 additional deaths due to TEAEs, for a total of 11 deaths (7%) due to progressive disease and 9 deaths (5%) due to adverse events (**FDA Table 7**). Specifically, FDA does not agree with the categorization of the death in patient # (b) (6) as "other" because all deaths due to TEAEs that occur within 30 days of the last dose of study treatment should be considered regardless of start of subsequent therapy since it is not possible to distinguish between the contribution of the study treatment and subsequent therapy. The deaths due to progressive disease in patients # (b) (6) and # (b) (6) were adjudicated as death due to acute renal failure and septic shock, respectively, based on review of the patient narratives.

While FDA concurs with the overall incidence of Grade 5 TEAEs in 18 patients (11%) as presented

by the Applicant (not limited to events associated with deaths within 30 days), FDA review of the Grade 5 TEAEs reported as due to COVID-19 resulted in reclassification of 2 of the 7 fatal COVID-19 events as fatal pneumonia based on the reported verbatim terms. Fatal adverse reactions reported in the USPI (based on events that occurred within 30 days of last dose of teclistamab) will include COVID-19 (1.8%), pneumonia (1.8%), septic shock (0.6%), acute renal failure (0.6%), and hemoperitoneum (0.6%).

FDA does not agree with the Applicant's statement above that "With the increased availability of vaccines and the broader use of anti-SARS-COV-2 antibody treatments at the time of exposure, the risk of severe COVID-19-related infections and deaths may be mitigated for this patient population in the future." This statement implies that the deaths were solely due to COVID-19 and that vaccination may prevent this in the future. However, FDA notes that teclistamab may increase the risk of infections, including COVID-19. In the absence of a control arm, the impact of teclistamab on deaths due to COVID-19 cannot be ruled out. Therefore, at this time, there is insufficient information to inform the impact of teclistamab on the risk of COVID-19 infection and response to vaccination.

In addition, FDA does not agree with the Applicant's statements throughout this section regarding investigator determination of "relatedness" of fatal TEAEs to teclistamab. In a single arm trial, FDA considers all TEAEs because it is not possible to clearly distinguish between AEs related to the underlying disease versus AEs that are due to the toxicity of study treatment.

FDA Table 7: FDA Adjudication of Deaths within 30 Days (MajesTEC-1 Safety Population)

Patient ID	Reported Cause of Death	Cause of Death Agreement (FDA)	Adjudicated Cause of Death (FDA)
(b) (6)	PROGRESSIVE DISEASE	Y	PROGRESSIVE DISEASE
	OTHER	N	ADVERSE EVENT (Pneumonia)
	ADVERSE EVENT	Y	ADVERSE EVENT (Pneumonia)
	ADVERSE EVENT	Y	ADVERSE EVENT (COVID-19)
	ADVERSE EVENT	Y	ADVERSE EVENT (COVID-19)
	PROGRESSIVE DISEASE	N	ADVERSE EVENT (Acute renal failure)
	ADVERSE EVENT	Y	ADVERSE EVENT (COVID-19)
	PROGRESSIVE DISEASE	Y	PROGRESSIVE DISEASE
	PROGRESSIVE DISEASE	Y	PROGRESSIVE DISEASE
	PROGRESSIVE DISEASE	Y	PROGRESSIVE DISEASE
	ADVERSE EVENT	Y	ADVERSE EVENT (COVID-19)
	PROGRESSIVE DISEASE	N	ADVERSE EVENT (Septic shock)
	PROGRESSIVE DISEASE	Y	PROGRESSIVE DISEASE
	PROGRESSIVE DISEASE	Y	PROGRESSIVE DISEASE
	PROGRESSIVE DISEASE	Y	PROGRESSIVE DISEASE
	PROGRESSIVE DISEASE	Y	PROGRESSIVE DISEASE
	PROGRESSIVE DISEASE	Y	PROGRESSIVE DISEASE
	PROGRESSIVE DISEASE	Y	PROGRESSIVE DISEASE

(b) (6)	PROGRESSIVE DISEASE	Y	PROGRESSIVE DISEASE
	ADVERSE EVENT	Y	ADVERSE EVENT (Hemoperitoneum)

Source: FDA reviewer's analysis [MMY1001 ADAE and ADSL datasets and MMY1001 patient narratives]

Serious Adverse Events

Data:

At least 1 serious TEAE was reported for 88 subjects (53.3%) treated at pivotal RP2D, most frequently in the Infections and Infestations SOC (49 subjects [29.7%]). The most frequently reported serious TEAE preferred terms (≥5%) were CRS (13 subjects [7.9%]), COVID-19 (12 subjects [7.3%]), pneumonia (11 subjects [6.7%]), and general physical health deterioration (9 subjects [5.5%]).

Table 14:Most Frequently Reported (≥2% of Total) Serious TEAEs by System Organ Class and Preferred Term; All Treated Analysis Set (Study 64007957MMY1001; Pivotal RP2D)

	RP2D		
	Phase 1	Phase 2 Cohort A	Total
Analysis set: All Treated	40	125	165
Subjects with 1 or more serious TEAEs	19 (47.5%)	69 (55.2%)	88 (53.3%)
MedDRA system organ class / preferred term			
Infections and infestations	12 (30.0%)	37 (29.6%)	49 (29.7%)
COVID-19	3 (7.5%)	9 (7.2%)	12 (7.3%)
Pneumonia	4 (10.0%)	7 (5.6%)	11 (6.7%)
Pneumocystis jirovecii pneumonia	1 (2.5%)	3 (2.4%)	4 (2.4%)
General disorders and administration site conditions	3 (7.5%)	14 (11.2%)	17 (10.3%)
General physical health deterioration	2 (5.0%)	7 (5.6%)	9 (5.5%)
Pyrexia	1 (2.5%)	4 (3.2%)	5 (3.0%)
Immune system disorders	2 (5.0%)	11 (8.8%)	13 (7.9%)
Cytokine release syndrome	2 (5.0%)	11 (8.8%)	13 (7.9%)
Renal and urinary disorders	1 (2.5%)	8 (6.4%)	9 (5.5%)
Acute kidney injury	1 (2.5%)	7 (5.6%)	8 (4.8%)

Key: TEAE=treatment-emergent adverse event; RP2D=recommended Phase 2 dose; CRS=cytokine release syndrome;
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 24.0.
Note: The output includes the diagnosis of CRS; the symptoms of CRS are excluded.
Note: Adverse events are reported until 100 days (Phase 1) or 30 days (Phase 2) after the last dose of teclistamab or until the start of subsequent anticancer therapy, if earlier.
Note: Percentages calculated with the number of subjects in the all treated analysis set as denominator.

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The Applicant's Position:

The most frequently reported serious TEAEs in MajesTEC-1 were consistent with the disease under study and the mechanism of action of teclistamab with T cell activation and B cell reduction. As appropriate, the proposed USPI for teclistamab provides specific guidance in the Dosage and Administration and Warnings and Precautions sections to manage these events.

The FDA's Assessment:

FDA analysis showed that serious TEAEs occurred in 54% of patients, with the minor difference from the Applicant's analysis due to the FDA analysis including events flagged as symptoms of CRS.

Serious TEAEs that occurred in >2% of patients will be included in the USPI. Based on FDA analysis using grouped terms and including events flagged as symptoms of CRS, these include pneumonia (15%), CRS (8%), sepsis (6%), general physical health deterioration (6%), COVID-19 (6%), acute kidney injury (4.8%), pyrexia (4.8%), musculoskeletal pain (2.4%), and encephalopathy (2.4%).

Dropouts and/or Discontinuations Due to Adverse Effects

Data and Applicant's Position:
The incidence of TEAEs leading to treatment discontinuation among subjects treated at pivotal RP2D was low (1 subject [0.6%], preferred term of Grade 3 pneumonia adenoviral that was judged by the investigator as very likely related to teclistamab).

The FDA's Assessment:
FDA analysis of TEAEs leading to treatment discontinuation based on the AEACN variable within the ADAE dataset (based on data from the AE eCRF rather than the end-of-treatment eCRF) showed permanent discontinuation due to a TEAE in 1.2% of patients, due to pneumonia (adenoviral and pneumocystis jirovecii pneumonia in the same patient) and hypercalcemia. The event of hypercalcemia was included because it was not clearly attributable to disease progression in the setting of a single arm trial. FDA agrees with the assessment that the incidence of TEAEs leading to discontinuation was low among patients treated at the RP2D.

Dose Interruption/Reduction Due to Adverse Effects

Data:
No dose reductions occurred for subjects treated at pivotal RP2D.

Cycle delays were reported for 72 subjects (43.6%) treated at pivotal RP2D, most of which were due to AEs (64 subjects [38.8%]).

TEAEs leading to dose interruption (dose delay or dose skip) were reported in 96 subjects (58.2%) and occurred most frequently in the SOCs of Infections and Infestations (49 subjects [29.7%]) and Blood and Lymphatic System Disorders (39 subjects [23.6%]), with neutropenia and CRS being the most frequently reported preferred terms.

The Applicant's Position:
No dose reductions occurred in subjects treated at pivotal RP2D in MajesTEC-1, suggesting that management of AEs per protocol and institutional guidelines was sufficient for teclistamab administered at RP2D. Notably, median relative dose intensity was robust (94.5% for all subjects treated at pivotal RP2D [see Section 8.2.2]) despite dose interruptions. Additionally, the frequency of dose interruptions is consistent with the logistics of a weekly dosing schedule (ie, per protocol, a treatment dose of teclistamab that did not occur within 3 days, the dose was considered skipped)

The FDA's Assessment:

FDA concurs with the incidence of cycle delays, including cycle delays due to AEs, and median dose intensity. FDA notes that while dose reductions were permitted for phase 1 (Parts 1 and 2), the MajesTEC-1 protocol stated that dose delays are the primary method for managing AEs in phase 3 (Part 3) and dose reductions by 50% could only be considered in exceptional circumstances after consultation with the Sponsor.

FDA analysis of TEAEs leading to dose interruption differed from the Applicant's in that the FDA analysis utilized the AEACN variable in the ADAE dataset (based on data from the AE eCRF), which showed a 73% incidence of dose interruptions. Dose interruptions due to TEAEs that occurred in >5% of patients will be included in the USPI and include neutropenia (28%), pneumonia (18%), pyrexia (15%), cytokine release syndrome (13%), upper respiratory tract infection (13%) and COVID-19 (5%).

Significant Adverse Events

Data:

At least 1 Grade 3 or 4 TEAE was reported for 152 subjects (92.1%) treated at pivotal RP2D. Grade 3 or 4 TEAEs occurred most frequently in the Blood and Lymphatic System Disorders (137 subjects [83.0%]) and Infection and Infestations (58 subjects [35.2%]) SOCs, with the following preferred terms reported in ≥10% of subjects; neutropenia (57.0%), anemia (34.5%), lymphopenia (32.1%), and thrombocytopenia (21.2%).

Table 15: Most Frequently Reported (≥5% of Total) Grade 3 or 4 TEAEs by System Organ Class and Preferred Term; All Treated Analysis Set (Study 64007957MMY1001; Pivotal RP2D)

	RP2D		
	Phase 1	Phase 2 Cohort A	Total
Analysis set: All Treated	40	125	165
Subjects with 1 or more grade 3 or 4 TEAEs	36 (90.0%)	116 (92.8%)	152 (92.1%)
MedDRA system organ class / preferred term			
Blood and lymphatic system disorders	33 (82.5%)	104 (83.2%)	137 (83.0%)
Neutropenia	24 (60.0%)	70 (56.0%)	94 (57.0%)
Anaemia	13 (32.5%)	44 (35.2%)	57 (34.5%)

Table 15: Most Frequently Reported (≥5% of Total) Grade 3 or 4 TEAEs by System Organ Class and Preferred Term; All Treated Analysis Set (Study 64007957MMY1001; Pivotal RP2D)

	RP2D		
	Phase 1	Phase 2 Cohort A	Total
Lymphopenia	5 (12.5%)	48 (38.4%)	53 (32.1%)
Thrombocytopenia	7 (17.5%)	28 (22.4%)	35 (21.2%)
Leukopenia	7 (17.5%)	5 (4.0%)	12 (7.3%)
Infections and infestations	12 (30.0%)	46 (36.8%)	58 (35.2%)
Pneumonia	5 (12.5%)	10 (8.0%)	15 (9.1%)
COVID-19	3 (7.5%)	8 (6.4%)	11 (6.7%)
Metabolism and nutrition disorders	8 (20.0%)	31 (24.8%)	39 (23.6%)
Hypophosphataemia	3 (7.5%)	6 (4.8%)	9 (5.5%)

Key: TEAE=treatment-emergent adverse event; RP2D=recommended Phase 2 dose
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 24.0
Note: Percentages calculated with the number of subjects in the all treated analysis set as denominator.

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The Applicant's Position:

While 92.1% of subjects treated at pivotal RP2D experienced at least 1 Grade 3 or 4 TEAE, none underwent dose reduction and the incidence of TEAEs leading to treatment discontinuation was low (<1%). As appropriate, the proposed USPI for teclistamab provides specific guidance in the Dosage and Administration and Warnings and Precautions sections to characterize and manage these events.

The FDA's Assessment:

FDA notes differences in the incidences of Grade 3-4 pneumonia (17%) and COVID-19 (5%) based on FDA analysis using grouped terms. FDA otherwise concurs with the data presented by the Applicant, including the incidences of cytopenias based on AE reporting; however, the USPI will include incidences of laboratory abnormalities based on the laboratory dataset as AE reporting may underestimate the incidence of laboratory abnormalities. FDA notes that dose delays were the primary method for management of AEs.

Treatment-emergent Adverse Events and Adverse Reactions

Data:

For subjects treated at pivotal RP2D, the most frequently reported TEAEs by preferred term (≥20% subjects) included CRS (118 subjects [71.5%]), neutropenia (108 subjects [65.5%]), anemia (82 subjects [49.7%]), thrombocytopenia (63 subjects [38.2%]), lymphopenia (56 subjects [33.9%]), injection site erythema (42 subjects [25.5%]), fatigue (41 subjects [24.8%]), nausea (40 subjects [24.2%]), headache (36 subjects [21.8%]), and diarrhea (34 subjects [20.6%]).

Safety data were reviewed by the Applicant's medical experts using the definition of ADRs from the ICH E6 guideline. The assessment was based on all TEAEs and laboratory abnormalities reported in the 165 subjects in the All Treated Analysis Set for pivotal RP2D and conducted in a stepwise manner:

- Preferred terms representing the same clinical entity or closely related events were grouped to thoroughly evaluate the true incidence rate of these medical concepts. For psychiatric and

nervous system disorders, grouping was performed for delirium (agitation, delirium, and hallucination) and encephalopathy (confusional state, depressed level of consciousness, somnolence, lethargy, and memory impairment) based on TEAEs from the study dataset. Additional grouped terms proposed by the Applicant were added per clinical judgment.

- Inclusion as an ADR those AEs with an incidence rate of ≥10% (commonly reported) and meeting at least 1 specified criterion for ADR classification (ie, evidence of dose response, medical importance, biologic plausibility, class effect, and typical safety concerns such as organ toxicity).

- Inclusion as an ADR those AEs with an incidence rate <10% meeting at least 1 specified criterion for ADR classification (reported as serious in ≥2% of subjects, clinically relevant and medically important, or biologic plausibility).

- Laboratory abnormalities worsening from the baseline in ≥20% of subjects following treatment with teclistamab.

ADRs reported in ≥10% of subjects are listed by SOC and preferred term or grouped term in Table 16. The most frequent non-laboratory adverse reactions of any grade (≥20%) were hypogammaglobulinemia, CRS, musculoskeletal pain, injection-site reaction, fatigue, upper respiratory tract infection, nausea, pneumonia, headache, and diarrhea. Laboratory abnormalities meeting criteria for inclusion as common ADRs are identified separately based on clinical laboratory ADR criteria and are listed in Table 17.

Clinically relevant adverse reactions reported in <10% of subjects are listed in Table 18.

Serious adverse reactions were reported in 53% of subjects who received teclistamab. Serious adverse reactions reported in >2% of subjects included pneumonia, cytokine release syndrome, sepsis, acute kidney injury, musculoskeletal pain, pyrexia and encephalopathy. Fatal adverse reactions occurred in 5% of subjects receiving teclistamab, which included COVID-19 (7 subjects [4.2%]), pneumonia (1 subject [0.6%]), and hemoperitoneum (1 subject [0.6%]).

Dose interruptions (dose delays and dose skips) of teclistamab due to adverse reactions occurred in 58.2% of subjects. The most frequent adverse reactions (≥5%) leading to dose interruptions were neutropenia, cytokine release syndrome, and pneumonia. There were no dose reductions of teclistamab due to adverse reactions.

Permanent discontinuation of teclistamab due to an adverse reaction (adenoviral pneumonia) occurred in 1 subject.

Table 16: Adverse Reactions (≥10%) in Subjects with Multiple Myeloma Treated with Teclistamab in MajesTEC-1

		RP2D (N=165) Incidence (%)	
System Organ Class	Adverse Reaction	Any Grade	Grade 3 or 4
Gastrointestinal disorders	Nausea	40 (24%)	1 (0.6%)
	Diarrhoea	34 (21%)	4 (2.4%)
	Constipation	29 (18%)	0
	Vomiting	18 (11%)	1 (0.6%)
General disorders and administration site conditions	Injection site reaction[1]	60 (36%)	1 (0.6%)
	Fatigue[2]	58 (35%)	4 (2.4%)
	Pain[3]	30 (18%)	3 (1.8%)
	Pyrexia	29 (18%)	1 (0.6%)
	Edema[4]	20 (12%)	0
Immune system disorders	Hypogammaglobulinaemia[5]	119 (72%)	2 (1.2%)
	Cytokine release syndrome	118 (72%)	1 (0.6%)
Infections and infestations	Upper respiratory tract infection[6]	42 (26%)	4 (2.4%)
	Pneumonia[7]	37 (22%)	25 (15%)
Metabolism and nutrition disorders	Decreased appetite	18 (11%)	1 (0.6%)
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[8]	77 (47%)	12 (7%)
Nervous system disorders	Headache	36 (22%)	1 (0.6%)
	Neuropathy peripheral[9]	23 (14%)	1 (0.6%)
Respiratory, thoracic and mediastinal disorders	Cough[10]	25 (15%)	0
Vascular disorders	Hemorrhage[11]	20 (12%)	4 (2.4%)
	Hypertension[12]	19 (12%)	8 (4.8%)

Key: RP2D = recommended phase 2 dose, CRS = cytokine release syndrome.
Note: RP2D includes Phase 1 RP2D treatment group and Phase 2 Cohort A.
Note: CRS was originally graded by Lee criteria (Lee 2014) in Phase 1 and by ASTCT consensus grading system (Lee 2019) in Phase 2, with conversion of grade in Phase 1 to ASTCT based on data in eCRF. Toxicity grade by ASTCT is presented in this table, for both Phase 1 and Phase 2.
Note: Adverse events are reported until 100 days (Phase 1) or 30 days (Phase 2) after the last dose of teclistamab or until the start of subsequent anticancer therapy, if earlier.
Note: The output includes the diagnosis of CRS; the symptoms of CRS are excluded.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 24.0.
[1]Injection site reaction includes Injection site bruising, Injection site cellulitis, Injection site discomfort, Injection site erythema, Injection site haematoma, Injection site induration, Injection site inflammation, Injection site oedema, Injection site pruritus, Injection site rash, Injection site reaction and Injection site swelling.
[2]Fatigue includes Asthenia, Fatigue and Malaise.
[3]Pain includes Ear pain, Flank pain, Groin pain, Non-cardiac chest pain, Oropharyngeal pain, Pain, Pain in jaw, Toothache and Tumour pain.
[4]Edema includes Face oedema, Fluid overload, Oedema peripheral and Peripheral swelling.
[5]Hypogammaglobulinaemia includes patients with adverse events of hypogammaglobulinaemia, hypoglobulinaemia; and/or patients with laboratory IgG levels below 500 mg/dL following treatment with Teclistamab.
[6]Upper respiratory tract infection includes Bronchitis, Nasopharyngitis, Pharyngitis, Respiratory tract infection, Respiratory tract infection bacterial, Rhinitis, Rhinovirus infection, Sinusitis, Tracheitis, Upper respiratory tract infection and Viral upper respiratory tract infection.
[7]Pneumonia includes Enterobacter pneumonia, Lower respiratory tract infection, Metapneumovirus pneumonia, Pneumocystis jirovecii pneumonia, Pneumonia, Pneumonia adenoviral, Pneumonia klebsiella, Pneumonia moraxella, Pneumonia pneumococcal, Pneumonia pseudomonal, Pneumonia respiratory syncytial viral, Pneumonia staphylococcal and Pneumonia viral.
[8]Musculoskeletal pain includes Arthralgia, Back pain, Bone pain, Musculoskeletal chest pain, Musculoskeletal pain, Myalgia, Neck pain and Pain in extremity.

Table 16: Adverse Reactions (≥10%) in Subjects with Multiple Myeloma Treated with Teclistamab in MajesTEC-1

		RP2D (N=165)	
		Incidence (%)	
System Organ Class	Adverse Reaction	Any Grade	Grade 3 or 4

[9]Neuropathy peripheral includes Dysaesthesia, Hypoaesthesia, Hypoaesthesia oral, Neuralgia, Paraesthesia, Paraesthesia oral, Peripheral sensory neuropathy and Sciatica.
[10]Cough includes Allergic cough, Cough, Productive cough and Upper-airway cough syndrome.
[11]Hemorrhage includes Conjunctival haemorrhage, Epistaxis, Haematoma, Haematuria, Haemoperitoneum, Haemorrhoidal haemorrhage, Lower gastrointestinal haemorrhage, Melaena, Mouth haemorrhage and Subdural haematoma.
[12]Hypertension includes Essential hypertension and Hypertension.

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Table 17: Laboratory Abnormalities Worsening from Baseline in at least 20% of Subjects with Multiple Myeloma Treated with Teclistamab in MajesTEC-1

	RP2D (N=165)	
	Incidence (%)	
Laboratory Abnormality	Any Grade	Grade 3 or 4
Lymphocyte Count Decreased	151 (92%)	137 (83%)
White Blood Cell Decreased	142 (86%)	67 (41%)
Neutrophil Count Decreased	138 (84%)	93 (56%)
Platelet Count Decreased	117 (71%)	37 (22%)
Hypoalbuminemia	113 (69%)	10 (6%)
Anemia	111 (67%)	55 (33%)
Alkaline Phosphatase Increased	69 (42%)	4 (2.4%)
Hypophosphatemia	63 (38%)	21 (13%)
GGT Increased	60 (36%)	13 (8%)
Hyponatremia	57 (35%)	16 (10%)
Aspartate Aminotransferase Increased	56 (34%)	2 (1.2%)
Hypocalcemia (Corrected)	51 (31%)	2 (1.2%)
Creatinine Increased	49 (30%)	5 (3.0%)
Alanine Aminotransferase Increased	46 (28%)	3 (1.8%)
Hypomagnesemia	44 (27%)	0
Hypokalemia	43 (26%)	5 (3.0%)
Hypercalcemia (Corrected)	42 (26%)	7 (4.2%)
Lipase Increased	34 (21%)	7 (4.2%)

Key: RP2D = recommended Phase 2 dose.
Note: RP2D includes Phase 1 RP2D treatment group and Phase 2 Cohort A.
Note: The laboratory toxicity grades are derived based on the NCI-CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) Version 4.03.
Note: For each parameter, the percentage of subjects represents those subjects for whom the toxicity grade worsened during treatment compared to baseline. For each subject and each parameter, the worst toxicity grade is selected.

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Table 18: Adverse Reactions (<10%) in Subjects with Multiple Myeloma Treated with Teclistamab in MajesTEC-1

		RP2D (N=165) Incidence (%)	
System Organ Class	Adverse Reaction	Any Grade	Grade 3 or 4
Infections and infestations	Sepsis[1]	10 (6%)	9 (6%)
Nervous system disorders	Encephalopathy[2]	15 (9%)	0
	Immune effector cell-associated neurotoxicity syndrome	5 (3.0%)	0

Key: RP2D = recommended phase 2 dose, ICANS = immune effector cell-associated neurotoxicity.
Note: RP2D includes Phase 1 RP2D treatment group and Phase 2 Cohort A.
Note: Adverse events are graded according to the NCI-CTCAE Version 4.03, with the exception of ICANS, which was graded according to the ASTCT consensus grading system.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 24.0.
Note: Adverse events are reported until 100 days (Phase 1) or 30 days (Phase 2) after the last dose of teclistamab or until the start of subsequent anticancer therapy, if earlier.
Note: The output includes the diagnosis of ICANS; the symptoms of ICANS are excluded.
[1]Sepsis includes Bacteraemia, Meningococcal sepsis, Pseudomonal bacteraemia, Pseudomonal sepsis, Sepsis and Staphylococcal bacteraemia.
[2]Encephalopathy includes Confusional state, Depressed level of consciousness, Lethargy, Memory impairment and Somnolence.

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The Applicant's Position:

Overall, the ADRs were manageable and consistent with the mechanism of action of teclistamab with respect to T cell activation and targeting of B cells and multiple myeloma.

The FDA's Assessment:

Refer to the FDA assessments in the relevant sections above for discussion of fatal TEAEs, serious TEAEs, TEAEs leading to dose interruptions, and TEAEs leading to permanent discontinuation. The incidences of many of the adverse reactions based on FDA analysis differ from those presented by the Applicant based on differences in grouping of related preferred terms. Section 6 of the USPI will include updated percentages of any grade and grade 3 or 4 adverse reactions based on the FDA recommended grouped terms (**Appendix 19.6**), and the most common adverse reactions (excluding laboratory abnormalities) and most common laboratory abnormalities (based on worsening from baseline using the laboratory dataset) will be presented separately.

While FDA agrees that overall, the adverse reactions were consistent with the mechanism of action of teclistamab and manageable in the clinical trial setting, FDA has determined that a REMS with ETASU will be required to ensure the risks of CRS and neurological toxicity, including ICANS, can be adequately managed in the post-marketing setting (see the FDA Assessments under **Sections 8.2.5.1**, **8.2.5.2**, and **12** for further discussion).

Laboratory Findings

Data:

Among subjects treated at pivotal RP2D, the most frequently reported Grade 3 or 4 abnormal hematology values (≥30%) were lymphopenia (145 subjects [87.9%]), neutropenia (94 subjects [57.0%]), leukopenia (69 subjects [41.8%]), and anemia (55 subjects [33.3%]). By laboratory

assessment, neutrophil levels did not show a distinctive trend over time; 43.6% of subjects treated at pivotal RP2D received myeloid growth factors during treatment. Levels of platelets, hemoglobin, lymphocytes, and white blood cells declined during step-up dosing and gradually recovered thereafter.

Among subjects treated at pivotal RP2D, Grade 3 and Grade 4 chemistry laboratory abnormalities during treatment, including those related to liver function tests such as ALT, AST, and serum creatine, were infrequent. No subject met criteria for Hy's law.

The Applicant's Position:
None of the hematology and chemistry laboratory findings were considered to be clinically consequential.

The FDA's Assessment:
FDA does not agree with the Applicant's conclusion that none of the hematology and chemistry lab finding are clinically consequential.

FDA notes that a Warning and Precaution for neutropenia will be included in the USPI based on the overall incidence of neutropenia (84%) and Grade 3 or 4 neutropenia (56%). FDA also notes that 28% of patients had at least one dose interruption of teclistamab due to a TEAE of neutropenia and febrile neutropenia occurred in 3% of patients.

In addition, FDA determined that addition of a Warning and Precaution for hepatoxicity to the USPI will be needed based on the rates of AST, ALT, and total bilirubin elevation and based on the case of fatal hepatic failure meeting Hy's law criteria, which occurred in a patient treated at the RP2D in the MajesTEC-1 trial, as reported in the 120-Safety Update.

In this case, a 71-year-old woman who had last received teclistamab on cycle 9 day 22 (study day 256), died from hepatic failure on study day 267. The patient received flu vaccine on study day 257 and subsequently developed fever, chills, and malaise. Treatment with teclistamab was interrupted and she received a course of antibiotics but was hospitalized with fever on study day 263 and was noted to have elevated ALT (411 U/L), AST (287 U/L) and GGT (361 U/L). Total bilirubin was 1.2 mg/dL. Respiratory virus panel testing was negative. Over the following days, her hepatic parameters worsened with ALT 1560 U/L, AST 2206 U/L, GGT 545 U/L, alkaline phosphatase 634 U/L, and total bilirubin 1.6 mg/dL on study day 265. Abdominal CT on study day 266 revealed cholecystitis and cholecystolithiasis. The patient received supportive care, including fresh frozen plasma, but died on study day 267. Autopsy findings included lymphocytic myocarditis, nonspecific interstitial pneumonia, and acute
(fulminant) lobular hepatitis.

Hy's law cases usually have three components:

- The drug causes hepatocellular injury, generally defined as an elevated ALT or AST by 3-fold or greater above the upper limit of normal, often with aminotransferases much greater (5-10x) the upper limit of normal.

- Among subjects showing such aminotransferase elevations, they also have elevation of their serum total bilirubin of greater than 2× the upper limit of normal, without findings of cholestasis (defined as serum alkaline phosphatase activity less than 2× the upper limit of normal).
- No other reason can be found to explain the combination of increased aminotransferase and serum total bilirubin, such as viral hepatitis, alcohol abuse, ischemia, preexisting liver disease, or another drug capable of causing the observed injury

FDA notes that the chronology of events and clinical and laboratory findings do not support drug-induced liver injury, as other factors may have contributed to the elevated AST and ALT levels. However, a definitive contribution of teclistamab to the events also cannot be ruled out in the setting of multiple confounding factors.

Vital Signs

Data:
The most frequently reported vital sign abnormalities (≥30% of subjects) included the following for subjects treated at pivotal RP2D:

- Abnormal temperature (defined as >38°C and with ≥1°C increase from baseline): 119 subjects (73.0%)
- Abnormal oxygen saturation (defined as <95%): 102 subjects (61.8%)
- Abnormal respiratory rate (defined as: >20 or <7 breaths/minute): 53 subjects (32.3%).

The Applicant's Position:
Small fluctuations in vital sign values were observed following administration of teclistamab; however, no clinically meaningful trends were observed.

The FDA's Assessment:
FDA notes that changes in vital signs that occur are clinically relevant in the context of patients experiencing CRS following teclistamab administration. Pyrexia, hypoxia, and hypotension were noted as symptoms of CRS (based on AE reporting) in 71%, 13%, and 12% of patients, respectively.

ECGs

Data:
The CSR for MajesTEC-1 provides a comprehensive presentation of triplicate ECG data collected during Phase 1 of the study, including ECG data collected for subjects treated at RP2D in Phase 1. Per protocol, 12-lead ECGs were performed at baseline and if clinically indicated in Phase 2. One subject treated at pivotal RP2D experienced clinically significant abnormal ECG interpretations (sinus tachycardia) that occurred during the event of Grade 3 CRS (for which a symptom of Grade 3 hypotension was reported).

The Applicant's Position:

Mean and median changes from baseline in ECG parameters were not considered clinically meaningful.

The FDA's Assessment:
FDA notes that based on FDA grouping of related preferred terms, cardiac arrhythmias (based on AE reporting) occurred in 16% of patients, including Grade 3 or 4 cardiac arrhythmias in 1.8% of patients, and therefore met the ≥10% threshold for inclusion in the adverse reaction table in Section 6 of the teclistamab USPI.

QT

Data:
No exposure- or time-dependent prolongation of QT intervals corrected using QTcF was observed following IV and SC administration of teclistamab. There were no individual subjects with absolute QTcF >500 msec and change from the baseline >60 msec and no ECG abnormal findings associated with QT prolongation such as torsade de pointe, sudden death, ventricular tachycardia, ventricular fibrillation and flutter, syncope, and seizure.

The Applicant's Position:
These observations are consistent with the physical properties of teclistamab, which is thought to be too large as a monoclonal antibody to directly inhibit the hERG channel and is highly specific to the extracellular epitope of BCMA. As such, teclistamab would not be expected to directly impact cardiac repolarization and result in QTcF prolongation.

Based on data from Phase 1 of MajesTEC-1, a thorough QTc study was not conducted per agreement with FDA at the End-of-Phase 1 meeting.

The FDA's Assessment:
FDA agrees. Per the FDA Clinical Pharmacology team, a dedicated QT assessment was not required and was not conducted as per ICH E14 Q&A (R3).

Immunogenicity

Data:
Among subjects treated at pivotal RP2D, 146 were ADA evaluable with at least 1 postdose ADA sample, and 26 and 4 subjects had evaluable ADA data at ≥6 months and ≥1 year after the first dose of teclistamab, respectively. No subjects treated at the pivotal RP2D were identified as positive for antibodies to teclistamab at any time. Two subjects treated in Phase 1 (1 at a non-RP2D SC dose and 1 treated with IV teclistamab) developed neutralizing antibodies to teclistamab.

The Applicant's Position:
Teclistamab appears to have a low immunogenic response.

The FDA's Assessment:
Refer to the FDA's assessment of immunogenicity performed by the Clinical Pharmacology review team in **Section 6.3.1**.

8.2.5. Analysis of Submission-specific Safety Issues

Targeted reviews were completed for the following specific AEs of clinical interest for teclistamab: CRS, neurotoxicity (including ICANS), sARRs, injection-site reactions, hypogammaglobulinemia , cytopenias, infections, immune-mediated AEs, TLS, and second primary malignancies.

8.2.5.1. Cytokine Release Syndrome

Data:

At least 1 event of any grade CRS was reported in 118 subjects (71.5%) treated at pivotal RP2D (Table 19). Fifty-four subjects (32.7%) experienced multiple CRS events. All events were either Grade 1 or Grade 2 except for 1 Grade 3 event that occurred in the context of concurrent Grade 3 pneumonia. The most common symptom of CRS was pyrexia (117 subjects [70.9%]). Most subjects (109 subjects, [66.1%]) received supportive treatment for CRS, with 86 subjects (52.1%) receiving paracetamol, and 60 subjects (36.4%) receiving tocilizumab. Steroids were administered to treat CRS for 13 subjects (7.9%).

CRS tended to occur early during treatment for most subjects (during step-up dosing or the first treatment dose), and the median time to CRS onset was 2.0 days (range: 1 to 6). The median duration of CRS was 2.0 days (range: 1 to 9), and all events resolved. No subjects treated at pivotal RP2D discontinued teclistamab or required teclistamab dose reduction due to CRS.

Table 19: Summary of Treatment-emergent CRS Events; All Treated Analysis Set (Study 64007957MMY1001; Pivotal RP2D)

	RP2D		
	Phase 1	Phase 2 Cohort A	Total
Analysis set: All Treated	40	125	165
Number of subjects with CRS	28 (70.0%)	90 (72.0%)	118 (71.5%)
Maximum toxicity grade			
Grade 1	19 (47.5%)	63 (50.4%)	82 (49.7%)
Grade 2	9 (22.5%)	26 (20.8%)	35 (21.2%)
Grade 3	0	1 (0.8%)	1 (0.6%)
Grade 4	0	0	0
Grade 5	0	0	0
Number of subjects with CRS leading to discontinuation of study drug	0	0	0
Number of subjects with multiple CRS events	12 (30.0%)	42 (33.6%)	54 (32.7%)
Grade of CRS worsened at any subsequent event	0	4 (3.2%)	4 (2.4%)
Number of subjects with supportive measures to treat CRS[a]	28 (70.0%)	81 (64.8%)	109 (66.1%)
Anti-IL6 receptor tocilizumab	16 (40.0%)	44 (35.2%)	60 (36.4%)
Multiple doses at any time during study	1 (2.5%)	4 (3.2%)	5 (3.0%)
>1 dose for a single CRS event	1 (2.5%)	3 (2.4%)	4 (2.4%)
Corticosteroids	5 (12.5%)	8 (6.4%)	13 (7.9%)
IV Fluids	9 (22.5%)	12 (9.6%)	21 (12.7%)
Vasopressor used	0	1 (0.8%)	1 (0.6%)
Single	0	1 (0.8%)	1 (0.6%)

Multiple	0	0	0
Oxygen used	5 (12.5%)	16 (12.8%)	21 (12.7%)

Table 19: Summary of Treatment-emergent CRS Events; All Treated Analysis Set (Study 64007957MMY1001; Pivotal RP2D)

	RP2D		
	Phase 1	Phase 2 Cohort A	Total
Blow-by	0	0	0
Nasal cannula low flow (≤6L/min)	5 (12.5%)	16 (12.8%)	21 (12.7%)
Nasal cannula high flow (>6L/min)	0	0	0
Face mask	0	0	0
Non-Rebreather mask	0	0	0
Venturi mask	0	0	0
Other	0	0	0
Positive pressure	0	0	0
Continuous Positive Airway Pressure	0	0	0
Bilevel Positive Airway Pressure	0	0	0
Intubation/ Mechanical Ventilation	0	0	0
Other	26 (65.0%)	73 (58.4%)	99 (60.0%)
Occurrence of CRS[b]			
Step-up Dose 1	18 (45.0%)	52 (41.6%)	70 (42.4%)
Step-up Dose 2	13 (32.5%)	44 (35.2%)	57 (34.5%)
Repeat Step-up[c]	0	1 (0.8%)	1 (0.6%)
Cycle 1 Day 1	7 (17.5%)	33 (26.4%)	40 (24.2%)
Cycle 1 Day 8	2 (5.0%)	6 (4.8%)	8 (4.8%)
Cycle 1 Day 15	2 (5.0%)	2 (1.6%)	4 (2.4%)
Cycle 1 Day 22	-	2 (1.6%)	2 (1.2%)
Cycle 2+	2 (5.0%)	3 (2.4%)	5 (3.0%)
Time from last injection of Teclistamab to new onset of CRS, hours[d]			
Number of CRS events		133	
Mean (SD)		34.874 (16.6779)	
Median		31.150	
Range		(3.83; 120.50)	
Time from last injection of Teclistamab to new onset of CRS, days			
Number of CRS events	45	145	190
Mean (SD)	2.2 (0.93)	2.5 (0.78)	2.4 (0.82)
Median	2.0	2.0	2.0
Range	(1; 6)	(1; 6)	(1; 6)
Duration of CRS, hours[d]			
Number of CRS events		127	
Mean (SD)		19.941 (22.3309)	
Median		12.000	
Range		(0.33; 151.05)	
Duration of CRS, days			
Number of CRS events	45	147	192
Mean (SD)	2.4 (1.60)	2.0 (1.22)	2.1 (1.32)
Median	2.0	2.0	2.0

Table 19: Summary of Treatment-emergent CRS Events; All Treated Analysis Set (Study 64007957MMY1001; Pivotal RP2D)

	RP2D		
	Phase 1	Phase 2 Cohort A	Total
Range	(1; 8)	(1; 9)	(1; 9)
Outcome of CRS			
N	45	147	192
Recovered or resolved	45 (100.0%)	147 (100.0%)	192 (100.0%)
Not recovered or not resolved	0	0	0
Recovered or resolved with sequelae	0	0	0
Recovering or resolving	0	0	0
Fatal	0	0	0
Unknown	0	0	0
Missing	0	0	0

Key: CRS = cytokine release syndrome; RP2D = recommended Phase 2 dose
[a] Supportive measures to treat CRS and CRS symptoms are included.
[b] Subjects may appear in more than one category. Occurrence is based on the last treatment visit on or prior to the day in which the TEAE occurred.
[c] Prior to Cycle 1.
[d] Hours only displayed for Phase 2, start and end times of CRS events were not collected uniformly in Phase 1.
Note: Percentages calculated with the number of subjects in the all treated analysis set as denominator, except for the outcome of CRS for which percentages are calculated with the number of CRS events in the all-treated analysis set as denominator.
Note: CRS was originally graded by Lee criteria (Lee 2014) in Phase 1 and by ASTCT consensus grading system (Lee 2019) in Phase 2, with conversion of grade in Phase 1 to ASTCT based on data in eCRF. Toxicity grade by ASTCT is presented in this table, for both Phase 1 and Phase 2.
Note: Adverse events are reported until 100 days (Phase 1) or 30 days (Phase 2) after the last dose of teclistamab or until the start of subsequent anticancer therapy, if earlier.
Note: Day 8 is not applicable for subjects on a biweekly or monthly dosing schedule, Day 15 is not applicable for subjects on a monthly dosing schedule, and Day 22 is not applicable for subjects on a monthly dosing schedule or Phase 1 subjects on a weekly dosing schedule (21-day cycle).
Note: Time from last injection to new onset is defined as date of last dose – start date of CRS +1. Duration is defined as end date of CRS – start date of CRS +1. For calculating in days, the date is used without time. For hours the date and time is used and those with time portion missing will be excluded.

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The Applicant's Position:

CRS was frequently reported in subjects treated at pivotal RP2D, which was expected due to its mechanism of action. Nearly all events were low grade and of short duration and none led to dose reduction or treatment discontinuation, supporting the effective management of these events. The only Grade 3 event occurred in the context of severe infection. No Grade 4 or Grade 5 events were observed. The proposed USPI for teclistamab provides specific guidance in the Dosage and Administration and Warnings and Precautions sections to minimize and manage the risk of CRS.

The FDA's Assessment:

FDA concurs with the data presented by the Applicant regarding CRS, with a few minor exceptions. FDA analysis identified 1 additional patient in phase 2 Cohort A who received multiple doses of

tocilizumab. FDA analysis also showed minor differences regarding the numbers for time from last injection of teclistamab to new onset of CRS in hours and days, and duration of CRS in hours; however, the relevant information that will be included in Section 5 of the USPI regarding median time to onset of CRS (2 days) and range (1 to 6) and median duration of CRS (2 days) and range (1 to 9 days), did not differ. Although CRS was graded according to the Lee 2014 criteria in phase 1 and ASTCT (Lee 2019) criteria in phase 2, the Applicant retrospectively evaluated the phase 1 CRS events according to the ASTCT criteria. FDA reviewed this information and determined the impact of this was small and did not change the overall interpretation of CRS results in the primary safety population.

CRS Incidence and Severity

FDA agrees that CRS was frequent in patients treated at the RP2D, occurring in 72% of patients. Although most CRS was Grade 1 or 2, with only one Grade 3 CRS event, FDA notes that Grade 2 CRS is clinically significant in that interventions such IV fluids and/or supplemental oxygen are needed for management. The overall incidence was high despite consistent use of pre-medications, including corticosteroids in all patients through Cycle 1 Day 1. Most patients experienced CRS following doses in the initial step-up dosing schedule, which includes step-up dose 1, step-up dose 2 and the first full treatment dose, and only 2.4% of patients had a first occurrence of CRS after completion of the step-up dosing schedule (first occurrence was on Cycle 1 Day 8 in 2 patients and on Cycle 1 Day 22 in 2 patients). Recurrent CRS occurred in 33% of patients, though only 2.4% of patients had a subsequent event that was increased in severity.

Hospitalization Requirements

Patients were monitored closely in the MajesTEC-1 trial. For all patients treated at the RP2D, hospitalization was required for at least 48 hours after the start of the injection for each of the step-up doses and the first full treatment dose. The protocol also required hospitalization for at least 48 hours for the next dose of teclistamab in patients with Grade ≥2 neurologic toxicity, Grade ≥2 CRS, or Grade ≥3 infusion-related reactions following the previous dose. FDA did not agree with Applicant's initial proposal in the USPI to "(b) (4) ." Due to the risk of CRS and neurologic toxicity, including ICANS, and considering the absence of data to support outpatient administration and monitoring, FDA had significant concerns with this proposal. Based on the extent of the risk, FDA determined it would be appropriate for the USPI to state that patients "should be hospitalized for 48 hours after administration of all doses within the TECVAYLI step-up dosing schedule," including for repeat step-up dosing after dose delays. In addition, consistent with the protocol, the USPI will also state that patients should be hospitalized for 48 hours following the next dose after occurrence of Grade 2 or limited Grade 3 CRS after the previous dose.

Management of CRS

FDA notes that 66% of patients received supportive therapy for management of CRS, including IV

fluids in 13%, low-flow oxygen in 13%, a single vasopressor in 0.6%, tocilizumab in 36%, and steroids in 8%. While there was one Grade 3 CRS event, for which the patient received a single vasopressor, no patients required multiple vasopressors, intensive oxygen support or mechanical ventilation. While management of CRS, including use of tocilizumab and steroids, was per investigator discretion, the protocol stated that tocilizumab may be considered for Grade 1 CRS and recommended administration of tocilizumab for Grade ≥2 CRS. However, FDA notes that tocilizumab is only approved for the treatment of CAR T-cell induced severe (i.e., Grade 3) or life-threatening (i.e., Grade 4) CRS. Furthermore, after review of more extensive data regarding tocilizumab use in the MajesTEC-1 trial submitted in response to the FDA 26 Jan 2022 and 26 Apr 2022 Clinical Information Requests, FDA determined that the data did not support (b) (4) Overarching issues included that the protocol did not include mechanisms to directly assess the safety and efficacy of tocilizumab use in the trial and there were no overall differences in outcomes (e.g., median duration of CRS, time to next teclistamab dose, rates of dose interruption due to CRS) among patients who received tocilizumab compared to patients who did not receive tocilizumab for management of Grade 1 or Grade 2 CRS events (see Appendix 19.7). The USPI will include recommendations to manage CRS per current practice guidelines.

Guidance for USPI

Overall, based on the high incidence of CRS, including Grade 2 CRS in 21% of patients and Grade 3 CRS in 0.6%, despite all patients receiving pre-medications, and the occurrence of recurrent events, including events that occurred beyond the first cycle of treatment, in addition to inclusion of a boxed warning for CRS in the USPI, as proposed by the Applicant, and other mitigation strategies described in the USPI, FDA determined that a REMS with ETASU is needed to minimize the risk of CRS and ensure the benefits of teclistamab outweigh the risks in the post-marketing setting. Refer to Section 12 for further details regarding the REMS with ETASU.

Data:

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8.2.5.2.

8.2.5.3. Neurotoxicity, Including ICANS

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Twenty-one subjects (12.7%) treated at pivotal RP2D experienced treatment-emergent neurotoxicity. All events had a maximum toxicity of Grade 1 (12 subjects [7.3%]) or 2 (9 subjects [5.5%]) and the most frequently reported neurotoxicity events included headache (14 subjects [8.5%]), ICANS (4 subjects [2.4%]; see also below), encephalopathy (2 [1.2%], including only the preferred term of confusional state), and tremor (2 subjects [1.2%], including only the preferred term of tremor).

Thirty-three of the 36 neurotoxicity events (91.7%) had resolved as of the clinical cutoff, with a median duration of 3.0 days (range: 1 to 37). All events were either Grade 1 or Grade 2, resolved spontaneously or with supportive treatment. Neurotoxicity events did not lead to discontinuation or dose reduction of study treatment for any subject treated at pivotal RP2D.

Five subjects (3.0%) treated at pivotal RP2D experienced Grade 1 (3 subjects [1.8%]) or Grade 2 (2 subjects [1.2%]) ICANS including 1 subject identified using the retrospective Applicant assessment of Phase 1 data. One subject had multiple recurrent ICANS events and no subject discontinued treatment due to ICANS. Seven of the 9 ICANS events (77.8%) occurred concurrently with CRS (during or within 7 days of resolution of CRS).

Any grade symptoms of ICANS included dysgraphia and confusional state (2 subjects [1.2%] each) and the following preferred terms, each reported for 1 subject (0.6%): aphasia, dyscalculia, disorientation, and mental status changes.

The Applicant's Position:
All neurotoxicity events among subjects treated at pivotal RP2D, including ICANS, were low-grade, of short duration, and reversible and none led to dose reduction or treatment discontinuation, supporting the effective management of these events when needed. All events resolved spontaneously or with supportive treatment. Headache was the most common such event. As discussed in Section 8.2.2, note that 1 high-grade neurotoxicity event (Grade 4 delirium, Grade 3 ICANS) were reported in each of Phase 1 and Cohort C in Phase 2.

The proposed USPI for teclistamab provides specific guidance in the Dosage and Administration and Warnings and Precautions sections to minimize and manage the risk of ICANS.

The FDA's Assessment:
FDA does not agree with the Applicant's analysis and assessment of neurologic toxicity and ICANS.

Definition of Neurologic Toxicity

The Applicant defined "neurotoxicity" as events that were both neurologic TEAEs reported in either the Nervous System Disorder or Psychiatric SOCs and that were judged by the investigator to be related to teclistamab. FDA does not agree with the Applicant's use of this approach because in a single arm trial it is not possible to clearly distinguish between AEs due to the underlying disease versus toxicities due to the study treatment. Therefore, FDA considers all treatment-emergent AEs to be relevant and does not agree with investigator attribution of relatedness to teclistamab. The FDA analysis of neurologic toxicity includes all TEAEs within the

Nervous System Disorder and Psychiatric SOCs, and several additional related preferred terms that mapped to other SOCs, with grouping of related terms for encephalopathy, motor dysfunction, and sensory neuropathy as follows:

- Encephalopathy: agitation, apathy, aphasia, confusional state, delirium, depressed level of consciousness, disorientation, dyscalculia, hallucination, lethargy, memory impairment, mental status changes, somnolence
- Motor dysfunction: cogwheel rigidity, dysgraphia, dysphonia, gait disturbance, hypokinesia, muscle rigidity, muscle spasms, muscular weakness, peroneal nerve palsy, psychomotor hyperactivity, tremor, VIth nerve paralysis
- Sensory neuropathy: dysaesthesia, hypoaesthesia, hypoaesthesia oral, neuralgia, paraesthesia, paraesthesia oral, peripheral sensory neuropathy, sciatica, vestibular neuronitis

Incidence and Severity of Neurologic Toxicity

Using the above methodology, FDA analysis showed that neurologic TEAEs occurred in 57% of patients, with Grade 1 neurologic TEAEs in 30% of patients, Grade 2 in 24%, and Grade 3 in 2.4% (headache, vestibular neuronitis, sciatica and spinal cord compression). Based on the FDA grouping of preferred terms, the most common neurologic toxicities (≥10% incidence) were headache (25%), motor dysfunction (16%), sensory neuropathy (15%), and encephalopathy (13%). There were no Grade 4 or 5 events as of the 07 Sep 2021 clinical data cut-off. Serious neurologic TEAEs occurred in 6% of patients. Dose interruption due to neurologic TEAEs occurred in 7% of patients. As of the clinical data cut-off, 13% of patients had neurologic TEAEs that were not recovered/resolved, including sensory neuropathy in 7% of patients and motor dysfunction in 3%.

Incidence and Severity of ICANS

FDA notes that the occurrence of immune effector cell-associated neurotoxicity syndrome (ICANS) was only formally assessed in the phase 2 population (N=125) due to the start of the trial preceding introduction of the ASTCT criteria in 2019. While the Applicant performed a retrospective evaluation for potential ICANS events in the phase 1 population (N=40), FDA does not agree with the Applicant's methodology because it was limited to evaluation of "neurotoxicity" events (which FDA does not agree with as discussed above) and events that occurred within 28 days of the first dose of teclistamab. FDA does not agree with restricting the evaluation to only those events occurring within 28 days of the first dose of teclistamab since teclistamab is a therapy with repeat-dose administration. In addition, some events of ICANS in phase 2 occurred beyond Cycle 1. FDA evaluation for potential ICANS events in phase 1 considered all neurologic TEAEs regardless of investigator attribution of relatedness and regardless of timing with respect to the first dose of teclistamab. Using this methodology and applying the ASTCT 2019 criteria, FDA adjudication identified 6 patients with potential ICANS among the 40 patients in the phase 1 subgroup of the primary safety population (**FDA Table 8**). This included the 1 patient (# (b) (6)) identified by the Applicant in their retrospective assessment of the phase 1 data.

FDA Table 8: FDA Adjudication of ICANS (MajesTEC-1 Safety Population Phase 1 Subpopulation)

Patient ID	Adverse Event Term(s)	Grade (CTCAE)	Onset Relative to Last Dose (in days)	Last Dose	Identified in Applicant's Analysis
(b) (6)	Lethargy Confusional state	1 1	3 3	Priming dose 2 Priming dose 2	N
	Confusional state	2	7	Cycle 1 Day 8	N
	Confusional state	1	4	Cycle 2 Day 8	N
	Confusional state	1	2	Cycle 1 Day 1	Y
	Somnolence	1	2	Priming dose 1	N
	Confusional state	2	3	Cycle 1 Day 8	N
	Confusional state	1	6	Cycle 1 Day 1	N

Source: FDA reviewer's analysis [MMY1001 ADAE dataset and patient narratives]

Therefore, based on FDA analysis, ICANS occurred in 6% of patients treated at the RP2D, with maximum Grade 1 ICANS in 3.6% and Grade 2 in 2.4%. There were no Grade ≥3 ICANS events in the primary safety population. Based on the updated analysis including the additional potential ICANS events from phase 1, 3.6% of patients had first occurrence of ICANS was during the step-up dosing schedule (step-up dose 1, step-up dose 2 or Cycle 1 Day 1) and 2.4% of patients had first occurrence of ICANS after completion of initial step-up doing (Cycle 1 Day 8 in 2 patients, Cycle 2 Day 8, and Cycle 2 repeat step-up dose 2). The median time to onset of ICANS from the last dose of teclistamab was 4 days (range 2 to 8 days) and the median duration of ICANS was 3 days (range 1 to 20 days). Forty-one percent (41%) of ICANS events had concurrent CRS. Recurrent ICANS occurred in 1.8% of patients. Dose interruption due to ICANS occurred in 1.8% of patients. As of the clinical data cut-off, ICANS was reported as recovered/resolved in all but one patient.

FDA does not agree with the Applicant's conclusions regarding neurologic toxicity and ICANS. The incidences of neurologic toxicity and ICANS were substantially higher based on the FDA analysis (57% vs. 12.7% and 6% vs. 3%, respectively). While the events were mostly Grade 1 or 2, there were several Grade 3 neurologic TEAEs, some patients required dose interruptions due to neurologic TEAEs (7%) or ICANS (1.8%), and not all events resolved as of the clinical cut-off. FDA notes that the events of Grade 4 delirium and Grade 3 ICANS referred to by the Applicant occurred in patients in one of the IV cohorts in phase 1 and in phase 2 Cohort C, respectively, which are not part of the primary safety population.

Guidance for USPI

The Applicant initially proposed to include a Warning and Precaution for neurologic toxicity in the USPI, including information regarding "neurotoxicity" events and ICANS. Based on the FDA analyses which considered all neurologic TEAEs regardless of attribution and identified additional cases of potential ICANS in phase 1, there is a greater extent of risk of neurologic toxicity, including ICANS. FDA also notes that these toxicities are unique compared to other approved anti-MM therapies that are available "off-the-shelf," and therefore, prescribers may have limited

experience identifying and managing these toxicities. FDA determined that a boxed warning and a REMS with ETASU are therefore necessary to ensure prescribers are trained how to recognize and manage these risks in the post-market setting to ensure the benefit of teclistamab outweighs the risks. Refer to **Section 12** for further details regarding the REMS with ETASU.

8.2.5.4. Injection-site Reactions and Systemic Administration-related Reactions

Data:
Injection-site reactions were reported for 58 subjects (35.2%) treated at pivotal RP2D and the maximum severity of these TEAEs was Grade 1 (50 subjects [30.3%]) or Grade 2 (8 subjects [4.8%]). Topical steroids were administered for 14 subjects (8.5%) and antihistamines for 6 subjects (3.6%) for injection-site reactions.

Two subjects (1.2%) treated at pivotal RP2D experienced sARRs of tongue swelling and pyrexia, all events were Grade 1; 1 subject received an antihistamine to treat the sARR.

The Applicant's Position:
Injection-site reactions are expected with the SC route of administration and were low grade, generally short in duration, and none led to dose reduction or treatment discontinuation. sARRs were reported rarely, and none led to dose reduction or treatment discontinuation.

The FDA's Assessment:
FDA concurs with the data presented by the Applicant regarding incidence of local injection-site reactions (ISRs) and systemic administration-related reactions (sARRs). Based on the route of administration of teclistamab, incidence of ISRs, and risk for sARRs, FDA determined that a Warning and Precaution was needed in the USPI to communicate the risk and management of these reactions.

8.2.5.5. Hypogammaglobulinemia

Data:
A total of 119 subjects (72.1%) experienced hypogammaglobulinemia based on either TEAE reporting (18 subjects [10.9%]) or clinical laboratory criteria (119 subjects [72.1%]). All hypogammaglobulinemia TEAEs had maximum severity of Grade 1 or Grade 2 for all but 2 subjects (1.2%) with Grade 3 hypogammaglobulinemia. Forty-one subjects received IV or SC immunoglobulin treatment at any time. None of the TEAEs were reported as serious and no subjects discontinued study drug due to hypogammaglobulinemia.

The Applicant's Position:
The majority of hypogammaglobulinemia was observed by laboratory assessment. Although reduction in B cell numbers is expected due to the mechanism of action of teclistamab, its impact on the occurrence of hypogammaglobulinemia is difficult to interpret due to the complexity of confounding factors of the study population including multiple myeloma, older age, and prior therapy (Lancman 2021). (b) (4)

The FDA's Assessment:
FDA does not agree with the Applicant's proposal (b) (4)
Based on AE reporting, the incidence of hypogammaglobulinemia was 11%, with Grade 3 hypogammaglobulinemia in 1.2% of patients. Based on the Applicant's analysis, 72% of patients had an IgG level <500 mg/dL at any time after starting treatment; however, FDA notes that 40% of patients had IgG levels <500 mg/dL at baseline (prior to start of treatment); therefore, it is challenging to interpret these results. In addition, it is challenging in general to interpret trends in Ig levels in patients with MM. Furthermore, the clinical relevance of hypogammaglobulinemia as an isolated laboratory abnormality is unclear in the absence of any clear association with increased risk and/or severity of infection. (b) (4)
, FDA determined it would be appropriate to include the incidence of hypogammaglobulinemia based on AE reporting in Section 6 of the USPI.

8.2.5.6. Cytopenias

Data:
Maximum Grade 3 or 4 neutropenia, anemia, thrombocytopenia, and lymphopenia were reported in 57.0% (n=94), 34.5% (n=57), 21.2% (n=35), and 32.1% (n=53) of subjects, respectively, treated at pivotal RP2D. No subjects experienced Grade 5 cytopenia or discontinued treatment due to cytopenias. Febrile neutropenia was reported in 5 subjects (3.0%).

As discussed in Section 8.2.4, no notable trend in the level of neutrophils was observed over time and other hematology laboratory parameters (platelets, hemoglobin, lymphocytes, and white blood cells) declined during step-up dosing and gradually recovered thereafter.

The Applicant's Position:

Although cytopenias were common and led to dose interruption in approximately one-quarter of subjects, they were not among the most frequently reported serious TEAEs and did not lead to dose reduction or treatment discontinuation. A transient reduction in lymphocytes is consistent with the mechanism of action of teclistamab. The proposed USPI for teclistamab provides specific guidance in the Dosage and Administration and Warnings and Precautions sections to minimize and manage the risk of neutropenia.

The FDA's Assessment:
FDA concurs with the data presented by the Applicant regarding incidence of Grade 3 or 4 cytopenias, and febrile neutropenia based on AE reporting. The incidence of Grade 3 or 4 neutropenia, anemia, and thrombocytopenia were similar between the AE and laboratory datasets; however, FDA notes that the incidences of Grade 3 or 4 lymphopenia and leukopenia were substantially higher based on the laboratory dataset compared to AE reporting (84% vs. 32% and 41% vs. 7%, respectively), and the incidences of all-grade cytopenias were also generally higher based on the laboratory dataset vs. AE reporting. The USPI will include incidences based on the laboratory dataset. Based on the incidence of treatment-emergent Grade 3 to 4

neutropenia, FDA also agreed with inclusion of a Warning and Precaution for neutropenia.

8.2.5.7. *Infection*

Data:
Infections were reported in more than half of all subjects (63.0%) with nearly 31% experiencing Grade 3 or 4 infections. Eight subjects had Grade 5 infections including COVID-19 (7 subjects) and pneumonia (1 subject), none of which were judged by the investigator as related to teclistamab. One subject (0.6%) discontinued study treatment due to infection (Grade 3 adenoviral pneumonia). No specific pathogen trends associated with treatment-emergent infections were observed.

The Applicant's Position:
Since multiple myeloma patients have an increased risk of infections due to underlying disease causing hypogammaglobulinemia (see Section 8.2.5.4) and immunosuppression (Terpos 2015), the occurrence of infection should be noted and monitored. The proposed USPI for teclistamab provides specific guidance in the Dosage and Administration and Warnings and Precautions sections to minimize and manage the risk of infection. Administration of teclistamab may increase the risk of infection due to cytopenias or hypogammaglobulinemia.

The FDA's Assessment:
FDA does not agree with the Applicant's statement regarding investigator determination of relatedness of fatal (Grade 5) infections to teclistamab. In a single arm trial, FDA considers all TEAEs. Based on FDA review of reported (verbatim) terms, two of the fatal events of COVID-19 were reclassified as pneumonia. FDA analysis showed a 30% incidence of serious infections, 35% incidence of Grade 3 or 4 infections, 30% incidence of opportunistic infections, and 4.2% incidence of fatal infections, including fatal pneumonia in 1.8% of patients and fatal COVID-19 in 3%. Serious infections occurring in ≥5% of patients included pneumonia (15%), sepsis (5%), and COVID-19 (5%).

Based on the risk of serious, severe, and fatal infections, including opportunistic infections, FDA agrees with inclusion of a Warning and Precaution for infections in the USPI, which will include the revised incidences as above from the FDA analysis. The Applicant also proposed inclusion of information regarding the occurrence of new onset or reactivated viral infections in (b) (4) ; however, FDA determined that this information should be relocated to the list of other clinically relevant adverse reactions occurring in <10% of patients in Section 6 of the USPI.

8.2.5.8. *Other AEs of Clinical Interest*

Data:
Grade 2 immune-mediated lung disease was reported for 2 subjects (1.2%) treated at pivotal RP2D, both of which were judged by the investigator as related to teclistamab. Both subjects continued study treatment and both events resolved (1 with sequela) as of the clinical cutoff.

TLS (serious, Grade 3; judged by the investigator to be very likely related to teclistamab) was reported for 1 subject (0.6%) treated at pivotal RP2D. The subject had no clinical symptoms and

TLS was diagnosed based on elevated uric acid results only.

Two subjects (1.2%) treated at pivotal RP2D reported a second primary malignancy.

The Applicant's Position:
Immune-mediated AEs will continue to be monitored in the teclistamab clinical development program, but limited events have been observed as of the clinical cutoff.

Only 1 event of TLS was observed following treatment with teclistamab monotherapy.

Second primary malignancies have been identified as a rare but important consideration in the treatment of multiple myeloma, but were observed rarely as of the clinical cutoff in the primary analysis of MajesTEC-1.

The FDA's Assessment:
FDA agrees with the Applicant's assessment regarding the low incidence of TLS and second primary malignancies and the plan to continue to monitor for immune-mediated AEs in the ongoing teclistamab development program.

FDA notes that in the primary safety population, one patient (0.6%) developed Grade 2 basal cell carcinoma. Another patient developed transitional cell carcinoma that was considered a relapse of prior urothelial carcinoma.

The case of TLS reported in a patient in the primary safety population was Grade 3 in severity, based only on elevated uric acid level, and resolved in 7 days.

FDA notes the two serious TEAEs of Grade 2 immune-mediated pneumonitis in patients treated at the RP2D, lasting 33 days (reported in the narrative as possible viral pneumonia vs. pneumonitis) and 160 days (infectious work-up negative and transbronchial biopsy show "lung injury pattern with features of an organizing pneumonia"). However, both cases resolved, and both patients were able to continue treatment with teclistamab. FDA will continue to monitor for cases of immune-mediated pneumonitis in the teclistamab clinical development program and in the post-marketing setting.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/ Tolerability

The Applicant's Position:
Not applicable.

The FDA's Assessment:
FDA notes that patient-reported outcomes (PROs) were collected in phase 2 only and consisted of evaluation of health-related quality of life (HRQoL) using the EORTC QLQ-C30, EQ5D-5L, and PGIS. Based on the limited ability to interpret PROs in a single arm trial, FDA considers the results of these evaluations to be exploratory. Refer to the FDA Assessment under **Efficacy Results – Secondary or Exploratory COA (PRO) Endpoints**.

8.2.7. Safety Analyses by Demographic Subgroups

Data:
Separate analyses of any grade TEAEs, Grade 3 or 4 TEAEs, and serious TEAEs were performed to evaluate potential differences in the safety of teclistamab among subgroups defined by the following intrinsic factors: age (<65, 65 to <75, or ≥75 years), sex (male or female), race (White, Black/African American, Other), baseline renal function (eGFR of <30, 30 to <60, 60 to <90, or ≥90 mL/min/1.73m^2), baseline hepatic function (normal or impaired [mild/moderate, severe]), and baseline bone marrow % plasma cells (≤30%, >30 to <60%, and ≥60%).

The Applicant's Position:
For all intrinsic factors examined, no significant or clinically meaningful differences in rates of TEAEs (overall and by SOC and preferred term), Grade 3 or 4 TEAEs, and serious TEAEs were observed across subgroups for subjects who received pivotal RP2D.

The FDA's Assessment:
FDA's safety analysis based on age, sex, and race subgroups is summarized below in **FDA Table 9** through **FDA Table 14**. FDA reviewed the safety results based on baseline renal function, hepatic function, and % bone marrow plasma cells (BMPCs) in the Applicant's CSR but did not independently verify those results. The clinical relevance of difference in safety based on %BMPCs is unclear since there is not an established threshold for use beyond those used in the IMWG diagnostic criteria (Rajkumar 2014). FDA agrees that there are no significant differences in rates of TEAEs, including CRS and neurologic toxicity. However, the numbers of patients in certain subgroups, particularly in the age ≥75 years subgroup and racial subgroups are too small to draw any conclusions. The USPI will state that there were no overall differences observed between patients 65 to 74 years of age compared to younger patients; however, there is an insufficient number of patients ≥75 years of age to assess whether there are differences in safety or effectiveness. The PMR issued to verify the clinical benefit of teclistamab in a randomized trial in patients with RRMM will state that the trial should enroll sufficient numbers of racial and ethnic minority patients and older patients (ages 65-74 and 75 and above) to enable an evaluation of teclistamab in a study population that better reflects the U.S. population of patients with MM.

FDA Table 9: FDA Analysis of Age Subgroups (MajesTEC-1 Safety Population)

Age Subgroup	Safety Population (N=165) n (%)
<65 years	86 (52)
65 to <75 years	55 (33)
≥75 years	24 (15)

Source: FDA reviewer's analysis [MMY1001 ADSL dataset]

FDA Table 10: FDA Analysis of TEAEs by Age (MajesTEC-1 Safety Population)

Adverse Event Category	Age <65 years (N=86)	Age 65 to <75 years (N=55)	Age ≥75 years (N=24)
All Grade TEAEs	86 (100)	55 (100)	24 (100)
Grade 3 or 4 TEAEs	82 (95)	50 (91)	20 (83)
Serious TEAEs	47 (55)	29 (53)	13 (54)
Fatal TEAEs	11 (13)	5 (9)	2 (8)
CRS (All Grades)	64 (74)	38 (69)	16 (67)
Neurologic TEAEs (All Grades)	50 (58)	30 (55)	14 (58)

Source: FDA reviewer's analysis [MMY1001 ADAE dataset]

FDA Table 11: FDA Analysis of Sex Subgroups (MajesTEC-1 Safety Population)

Sex Subgroup	Safety Population (N=165) n (%)
Male	96 (58)
Female	69 (42)

Source: FDA reviewer's analysis [MMY1001 ADSL dataset]

FDA Table 12: FDA Analysis of TEAEs by Sex (MajesTEC-1 Safety Population)

Adverse Event Category	Male (N=96)	Female (N=69)
All Grade TEAEs	96 (100)	69 (100)
Grade 3 or 4 TEAEs	93 (97)	59 (86)
Serious TEAEs	51 (53)	38 (55)
Fatal TEAEs	7 (7)	11 (16)
CRS (All Grades)	69 (72)	49 (71)
Neurologic TEAEs (All Grades)	50 (52)	44 (64)

Source: FDA reviewer's analysis [MMY1001 ADAE dataset]

FDA Table 13: FDA Analysis of Race Subgroups (MajesTEC-1 Safety Population)

Race Subgroup	Safety Population (N=165) n (%)
White	134 (81)
Black or African American	21 (13)
Asian	3 (1.8)
Other	7 (4.2)

*Other includes "Multiple" (N=1) and "Not Reported" (N=4)

Source: FDA reviewer's analysis [MMY1001 ADSL dataset]

FDA Table 14: FDA Analysis of TEAEs by Race (MajesTEC-1 Safety Population)

Adverse Event Category	White (N=134)	Black (N=21)	Other (N=10)
All Grade TEAEs	134 (100)	21 (100)	10 (100)
Grade 3 or 4 TEAEs	125 (93)	18 (86)	9 (90)
Serious TEAEs	76 (57)	8 (38)	5 (5)
Fatal TEAEs	15 (11)	2 (10)	1 (10)
CRS (All Grades)	95 (71)	15 (71)	8 (80)
Neurologic TEAEs (All Grades)	74 (55)	13 (62)	7 (70)

*Other includes "Asian" (N=3), "Multiple" (N=1) and "Not Reported" (N=4)

Source: FDA reviewer's analysis [MMY1001 ADAE dataset]

8.2.8. Specific Safety Studies/Clinical Trials

Data and Applicant's Position:
Not applicable.

The FDA's Assessment:
Not applicable.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Data and Applicant's Position:
Not applicable.

The FDA's Assessment:
FDA notes that no carcinogenicity studies were conducted as teclistamab is a therapeutic bispecific antibody being developed for oncology indications. The FDA Nonclinical Review Team agreed that carcinogenicity studies are not needed to support the approval of this BLA.

Human Reproduction and Pregnancy

Data and Applicant's Position:
Developmental toxicity, including pregnancy and lactation, was not considered essential to inform risk to pregnant women based on the intended patient population and BCMA target biology including data from genetically modified mice that lack BCMA. Therefore, it was not assessed in nonclinical studies.

Pregnancy and breast-feeding is uncommon in this heavily pretreated patient population, subjects in MajesTEC-1 were required to use contraception, and pregnancy was not reported during the study. Immunoglobulin G antibodies are known to cross the human placenta during pregnancy and have been detected in the serum of infants born to patients treated with therapeutic antibodies (Hyrich 2014).

Not applicable

The FDA's Assessment:
FDA notes that the teclistamab USPI will include a Warning and Precaution for embryo-fetal toxicity.

Pediatrics and Assessment of Effects on Growth

Data and Applicant's Position:
Not applicable.

The FDA's Assessment:
FDA notes that no studies were conducted in pediatric patients and the development of teclistamab is focused on adult patients with MM.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data and Applicant's Position:
Not applicable.

The FDA's Assessment:
Not applicable.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Data and Applicant's Position:
Not applicable as teclistamab is not yet marketed in any region.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

Expectations on Safety in the Postmarket Setting

Data and Applicant's Position:
Routine pharmacovigilence activities conducted for teclistamab will include the collection, follow-up, assessment, and reporting of individual case safety reports from any source; signal detection and evaluation to identify risks; and preparation and submission of aggregate safety reports, such as Developmental Safety Update Reports and Periodic Benefit-Risk Evaluation Reports.

The FDA's Assessment:
Given the risk of CRS and neurologic toxicity, including ICANS, FDA has determined that a REMS with ETASU is needed to ensure these risks associated with teclistamab can be adequately managed in the post-market setting. Teclistamab would be the first bispecific CD3 T-cell engager approved for the treatment of patients with RRMM. FDA notes that there are two BCMA-directed CAR T-cell therapies that are approved for similar populations of patients with RRMM, that also have risks of CRS and neurologic toxicity, including ICANS. However, because the CAR T-

cell products are administered as a single infusion in specialized centers, whereas teclistamab has repeat-dose administration, the risk profile for CRS and ICANS differs. In addition, while the CAR T-cell products have a complex manufacturing process and are only administered at specialized centers, teclistamab is an "off-the-shelf" product with SC administration that is likely to be prescribed to a broader population of patients and a broader range of settings in the post-market setting, including community oncology practices. While MM specialists practicing at academic centers may have some experience with the management of CRS and neurologic toxicity with the use of CAR T-cell products, community-based oncologists may have limited experience in managing these types of toxicities. Refer to Section 12 for further details on the REMS with ETASU.

8.2.11. Integrated Assessment of Safety

Data and Applicant's Position:
Safety data presented in this BLA are derived from a single ongoing study of teclistamab (MajesTEC-1) and thus there was no integration with other Applicant-conducted clinical trial data. As discussed in Section 8.2.2, the Applicant considers that sufficient data to assess the safety profile of teclistamab are available for the proposed indicated population.

The FDA's Assessment:
While FDA agrees that the safety data presented in the BLA are derived from the ongoing MajesTEC-1 trial, with a focus on the primary safety population consisting of the 165 patients treated at the RP2D in phase 1 and phase 2 Cohort A, FDA's integrated assessment of safety presented below considers all of the safety data, including data from the additional patients treated in the MajesTEC-1 trial that were not part of the primary safety population, and data with longer follow-up from the 120-Day Safety Update.

FDA reviewed the Applicant's Summary of Clinical Safety, which included supportive data from an additional 175 patients from the MajesTEC-1 trial who were not part of the pivotal safety population. FDA notes that the safety profile of teclistamab in these patients was generally consistent with the safety profile in the primary safety population and no new safety concerns were identified.

FDA also reviewed the 120-day Safety Update submitted by the Applicant on 27 April 2022 (04 January 2022 data cut-off) with a focus on the primary safety population (N=165). FDA notes that there were 6 additional deaths due to TEAEs (streptococcal pneumonia, hepatic failure, and hypovolemic shock in 1 patient each, and COVID-19 in 3 patients). One additional patient permanently discontinued study treatment due to a TEAE of Grade 4 progressive multifocal leukoencephalopathy. One additional patient experienced CRS (Grade 1). There were no new cases of ICANS. There were 2 new serious TEAEs of Grade 4 seizure and Grade 4 Guillain-Barré syndrome (GBS) reported in 1 patient each. As of the data cut-off date for the 120-day Safety Update, the event of GBS had not resolved. In the Applicant's response to the FDA 07 July 2022 Clinical Information Request, it was noted that the patient had died, and the cause of death was listed as GBS. The USPI will include a statement in the Warning and Precaution for neurologic

toxicity that with longer follow-up, Grade 4 seizure and fatal GBS occurred in 1 patient each.

Overall, CRS and neurologic toxicity, including ICANS, are the key safety concerns for teclistamab. Additional concerns include the risks of hepatoxicity, infections, neutropenia, hypersensitivity, and other administration reactions (including local injection site reactions and systemic administration-related reactions). A Warning and Precaution for each of these safety issues will be included in the USPI.

The incidence of CRS (72%) was high, including Grade 2 CRS in 21% of patients and Grade 3 CRS in 0.6%, despite consistent use of pre-medications and hospitalization of patients for at least 48 hours for administration of all doses in the teclistamab step-up dosing schedule. Therefore, in addition to including a Boxed Warning for CRS in the USPI along with guidance that patients should be hospitalized for 48 hours after administration of all doses within the teclistamab step-up dosing schedule and guidance regarding administration of pre-medications, FDA determined that additional risk management strategies beyond labeling (REMS with ETASU) were needed to ensure the risk of CRS could be adequately managed in the post-market setting.

The incidence of neurologic toxicity was also high (57%), including ICANS in 6% of patients, motor dysfunction in 16%, sensory neuropathy in 15% and encephalopathy in 13%. Grade 3 or 4 neurologic toxicity occurred in 2.4% of patients, with additional TEAEs of Grade 4 seizure and fatal GBS observed with longer follow-up. Based on the overall incidence of neurologic toxicity, the occurrence of serious and fatal neurologic TEAEs, and considering that many of the neurologic TEAEs that were observed are unique toxicities that have not been observed with other approved anti-MM therapies that are available “off-the-shelf” (i.e., ICANS, motor dysfunction including Parkinson-like symptoms, and GBS), and the potential broader use of teclistamab considering its SC route of administration, FDA determined that additional risk management strategies were needed beyond the Warning and Precaution for neurologic toxicity proposed by the Applicant, including addition of a Boxed Warning for the risk of neurologic toxicity, including ICANS, to the USPI and a REMS with ETASU to ensure the risks of neurologic toxicity and ICANS could be adequately managed in the post-market setting.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

There were no major statistical issues identified in this submission; however, the following caveats need to be considered when interpreting the results.

The efficacy was based on ORR, an intermediate endpoint, evaluated in a single arm trial. The study also assessed time to response, PFS, OS and PROs. However, these endpoints have limited interpretability in a single-arm trial and are therefore considered exploratory and will not be reported in the USPI. The clinical benefit of teclistamab will need to be verified in a randomized confirmatory clinical trial.

Study results were based on two clinical cut-offs – the planned primary data cut-off on September 7th, 2021, and an additional data cut-off with longer follow-up on November 9th, 2021. The efficacy results based on the clinical cutoff of November 9th, 2021, will be reported in the USPI to provide longer follow-up data on durability of benefit to prescribers.

FDA's efficacy analysis was based on the 110 patients from Cohort A in phase 2 who received the first dose of study intervention on or before March 18, 2021. The data from phase 1 was not included in the primary efficacy analysis as the sample size estimation and hypothesis testing for efficacy was based on the Cohort A phase 2 portion.

With a median duration of follow-up of 7.4 months among responders, the median DOR for the 68 responders from Cohort A in phase 2 was not reached (95% CI: 6.7, 7.6), as calculated using the reverse KM method. The median duration of follow-up of 7.4 months may not provide a robust estimate of the durability of the effect due to high rates of censoring. Therefore, caution should be taken for the interpretation of DOR.

8.4. Conclusions and Recommendations

The FDA's Assessment:

Based on the observed benefit of teclistamab combined with the REMS with ETASU to mitigate the risks of CRS and neurologic toxicity, including ICANS, the FDA clinical and statistical review teams recommend accelerated approval of teclistamab for the indication: "*TECVAYLI is a bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.*"

X X

Primary Statistical Reviewer	Statistical Team Leader
X	X

Primary Clinical Reviewer	Clinical Team Leader

9. Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

An Advisory Committee Meeting was not held, and no external consultations were requested.

10.Pediatrics

The Applicant's Position:
On 26 July 2021, the FDA provided an agreement letter to the Applicant's iPSP, which includes a plan to request a waiver for pediatric assessments for teclistamab for all age groups. A request for a full pediatric waiver consistent with the agreed iPSP is provided in this BLA.

The FDA's Assessment:
FDA agrees.

11. Labeling Recommendations

Data:

The table below provides a high-level summary of the changes made to the US Prescribing Information (USPI) for Tecvayli (teclistamab-cqyv) BLA 761291.

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
Boxed Warning	Included Boxed Warning for cytokine release syndrome (CRS).	FDA added neurologic toxicity, including ICANS, and information about the Tecvayli REMS.
Indications and Usage 1	TRADENAME is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least (b) (4) prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.	FDA modified the indication to patients who have received at least four prior lines of therapy and added the required accelerated approval language.
Dosage and Administration 2	Included table with step-up dosing schedule with recommendations for weekly dosing and pretreatment medications. Included a 3-column table to describe dosage modifications for adverse reactions (CRS, ICANS, infections, hematologic toxicities, and other adverse reactions). Included 3-column table with recommendations for restarting therapy after dose delays. Included 4-column tables with recommendations to manage severe adverse reactions (CRS and ICANS) Included administration instructions with monitoring guidance and with tables displaying injection volumes for each step-up dose and weekly treatment dose by patient weight.	FDA modified this section to include separate subheadings to focus on CRS, neurologic toxicity, and ICANS, including new tables for management recommendations for CRS, neurologic toxicity, and ICANS. A table for dosage modifications for other adverse reactions was also included. FDA added that patients should be hospitalized for 48 hours after administration of all doses within the step-up dosing schedule. FDA removed (b) (4) added reference to following current practice guidelines for management of CRS.
Contraindications 4	…	There are no contraindications to report.

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
Warnings and Precautions (W&P) 5	Included Warnings and Precautions for cytokine release syndrome, neurologic toxicities, infections, (b) (4), neutropenia (b) (4)	FDA modified this section to add new W&P for the TECVAYLI REMS, hepatoxicity, hypersensitivity and other administration reactions, and embryo-fetal toxicity. FDA deleted the W&P (b) (4). FDA deleted the W&P (b) (4) FDA deleted the W&P (b) (4) moved some of the information to the neurologic toxicity, including ICANS W&P.
Adverse Reactions 6.1 and 6.2	(b) (4)	FDA modified this section to align with current labeling practice for display of adverse reactions from the clinical trial and changed the threshold for the laboratory abnormalities table to 30%. FDA moved (b) (4) FDA modified the section to align with recommendations in the guidance (b) (4)
Drug Interactions 7.1	Included recommendations regarding use CYP450 substrates with a narrow therapeutic index in patients receiving TRADENAME.	FDA edited this section to include the period following CRS as a potential risk for DDI based on the mechanism of the DDI and to increase the duration of highest risk of DDI to 7 days

		after the first treatment dose (b) (4)
Use in Specific Populations 8.1, 8.2, 8.3, 8.4, 8.5	Recommended not to use in women who are pregnant.	FDA agreed but modified the language to reflect the pregnancy risk based on teclistamab's mechanism of action.
	Recommended not to breastfeed during treatment and (b) (4)	FDA modified the recommendations for the duration not to breast feed and to use contraception from 3 months to 5 months based on the product half-life.
	Recommended to use contraception during treatment and (b) (4) months after the last dose for female patients of reproductive potential (b) (4)	Contraception heading revised to remove (b) (4) to align with FDA guidance "*Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations*".
	(b) (4)	FDA generally agreed but removed sections (b) (4) .

(b) (4)

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
Description 11	(b) (4)	FDA modified the description of the product to align with the EPC used in the HL.
Clinical Pharmacology 12.1, 12.2, 12.3	Included details on mechanism of action, pharmacodynamics, and pharmacokinetics.	Section 12.1 was revised based on studies submitted, including adding a statement that teclistamab-cqyv activated T-cells in vitro and caused the release of various proinflammatory cytokines, resulting in the lysis of multiple myeloma cells. In Section 12.2, FDA modified the timing for assessment of cytokine changes to include measurements after administration of step-up dose 1, step-up dose 2, and the first 3 treatment doses. Specific numeric data added to describe the reduction from baseline in soluble BCMA. In Section 12.3, FDA revised the section to align with current guidance and labeling practice. The Elimination heading was edited to include the mean terminal elimination half-life, rather than the alpha half-life because terminal elimination half-life is clinically meaningful in determining the duration of exposure to teclistamab, as well as for understanding the accumulation of teclistamab with repeated dosing. PK parameters reported by the Applicant in Section 12.3 were revised to be based on the population PK model at approximately steady-state (13th treatment dose). A new subsection 12.6 Immunogenicity was added (b) (4) .

Nonclinical Toxicology 13.1	(b) (4)	FDA did not agree (b) (4)
Clinical Studies 14	(b) (4)	FDA modified this section to remove (b) (4)
How Supplied/Storage and Handling 16	Included storage and handling conditions of the 30 mg/3 mL and 153 mg/1.7 mL presentations.	FDA generally agreed but provided minor edits to align with current labeling practice, including adding clarity of the solution.
Patient Counseling Information 17	Included patient counseling information on monitoring requirements, CRS, neurologic toxicities, infections, neutropenia, (b) (4)	FDA modified this section to align with changes made to section 5.
Medication Guide	Medication Guide submitted.	FDA modified the Medication Guide to align with changes made to the USPI.

The FDA's Assessment:

FDA modified sections of the USPI and Medication Guide (MG) as described in the table above; see the USPI and MG attached to the approval letter for final, agreed-upon labeling.

12. Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

The Division of Risk Management (DRM) in the Office of Surveillance and Epidemiology (OSE) reviewed this Application and concurs with the review team that additional risk evaluation mitigation strategies (REMS) are required to ensure the risks of teclistamab can be adequately managed in the post-market setting.

The specific goal of the REMS with elements to assure safe use (ETASU) is to mitigate the risk of CRS and neurologic toxicity, including ICANS, by educating prescribers on the importance of monitoring patients for signs and symptoms of CRS and neurologic toxicity including ICANS.

Components of the REMS for teclistamab will include a Communication Plan, ETASU A (certification of prescribers) and ETASU B (certification of pharmacies and healthcare settings that dispense teclistamab). Under ETASU A, prescribers must obtain certification by enrolling and completing training regarding the risks of CRS and neurologic toxicity, including ICANS, and must counsel patients on the risks and provide them with a Patient Wallet Card. Under ETASU B, pharmacies must be certified and verify that prescribers are certified before dispensing teclistamab.

As part of the REMS, the Sponsor must submit REMS Assessments annually from the date of the initial approval. Depending on the findings from formal assessment of the REMS, FDA may modify the REMS or consider other regulatory actions. In the future, if the REMS assessments and/or data from other sources indicates that prescribers have gained familiarity with the risks of CRS and neurologic toxicity with teclistamab and are taking appropriate actions to reduce and manage the risks, FDA may re-evaluate the REMS to determine if continuation of REMS is necessary.

13. Postmarketing Requirements and Commitments

The FDA's Assessment:

The following accelerated approval PMR will be issued:

Conduct a randomized clinical trial in patients with relapsed or refractory multiple myeloma. The trial should enroll sufficient numbers of racial and ethnic minority patients and older patients (ages 65-74 and 75 and above) to enable an evaluation of teclistamab in a study population that better reflects the U.S. population of patients with multiple myeloma. Patients should be randomized to receive a teclistamab-based regimen compared to standard therapy for relapsed or refractory multiple myeloma. The primary endpoint should be progression-free survival and secondary endpoints should include overall survival, overall response rate, and duration of response.

Draft Protocol Submission:	11/2022
Final Protocol Submission:	01/2023
Trial Completion:	09/2025
Final Report Submission:	03/2026

The following FDAAA PMR will be issued:

Conduct a clinical trial to further characterize and determine the incidence of neurologic toxicities in patients receiving teclistamab, including immune effector cell-associated neurotoxicity syndrome, encephalopathy, peripheral neuropathy including Guillain-Barré syndrome, and motor dysfunction including Parkinsonism. This data may come from Study 64007957MMY3001 (MajesTEC-3) and other clinical trials across the teclistamab development program including long term follow-up from Study 64007957MMY1001 (MajesTEC-1). Include the incidence rates, time to onset, and outcomes in the final report. Also include investigation of associations and temporal relationships between the incidence and severity of neurologic adverse events and potential associated risk factors, such as age and comorbidities.

Draft Protocol Submission (Analysis Plan):	04/2023
Final Protocol Submission (Analysis Plan):	10/2023
Trial Completion:	09/2025
Final Report Submission:	03/2026

The following PMC will be issued:

Complete the MajesTEC-1 trial (Study 64007957MMY1001) to obtain the overall response rate and duration of response in enrolled patients with relapsed or refractory multiple myeloma who have received at least 3 prior lines of therapy including a proteasome inhibitor, immunomodulatory agent, and anti-CD38 monoclonal antibody to further characterize efficacy of teclistamab monotherapy in this population.

Trial Completion:	12/2023
Final Report Submission:	06/2024

Submit the datasets with the final report submission.

14. Division Director (DHOT) (NME ONLY)

X

15. Division Director (OCP)

X

16. Division Director (OB)

X

17. Division Director (Clinical)

X

18. Office Director (or designated signatory authority)

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

19. Appendices

19.1 References

The Applicant's References:
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Moreau P, Weisel K, De Stefano V, et al. LocoMMotion: a prospective, non-interventional, multinational study of real-life current standards of care in patients with relapsed/refractory multiple myeloma who received ≥3 prior lines of therapy. Abstract accepted for presentation at the 63rd American Society of Hematology Annual Meeting & Exposition; 11-14 December 2021; Atlanta, Georgia. Abstract 3057. Available at: https://ash.confex.com/ash/2021/webprogram/Paper146188.html. Accessed 12 Nov 2021.

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immunomodulatory drug (IMiD), or double refractory to a PI and an IMiD. Oncologist. 2016;21(11):1355-1361.

The FDA's References:

Lee, J.I., Zhang, L., Men, A.Y., Kenna, L.A. & Huang, S.M. CYP-mediated therapeutic protein-drug interactions: clinical findings, proposed mechanisms and regulatory implications. Clin. Pharmacokinet. 2010;49:295 310.

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19.2 Financial Disclosure

The Applicant's Position:

As noted in Section 8.1.2, the Applicant has adequately assessed clinical investigators for any financial interest/arrangements as defined in 21 CFR Part 54 and no disclosable financial interests were found.

The FDA's Assessment:

FDA reviewed the submitted financial disclosure form 3454 for the MajesTEC-1 trial and agrees with the Applicant's position.

Covered Clinical Study (Name and/or Number):*

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1362		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		

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: N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in study: N/A Applicant of covered study: N/A		
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) 0		
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.

19.3 Nonclinical Pharmacology/Toxicology

Data and Applicant's Position:

Not applicable.

The FDA's Assessment:
Not applicable.

19.4 OCP Appendices (Technical Documents Supporting OCP Recommendations)

19.4.1 Bioanalytical Methods

The FDA's Assessment:
Teclistamab concentration in human serum samples from MajesTEC-1 were quantified using a validated bioanalytical method as summarized in **FDA Table 6** below.

FDA Table 15: Bioanalytical Method Validation Summary for Teclistamab Quantification

Bioanalytical method review summary	Method validation was adequate to support analysis of samples from MajesTEC-1.		
Method description	Electrochemiluminescent-based immunoassay (ECLIA) to quantitate concentrations of teclistamab in human serum samples.		
Materials used for calibration curve	JNJ-64007957 (teclistamab) Lots P73101A and P73111A		
Validated assay range	0.0005 µg/mL to 0.064 µg/mL (anchor points of 0.00025 µg/mL and 0.128 µg/mL)		
Minimum required dilutions (MRDs)	1/1 (neat)		
Regression model & weighting	5 PL Auto-estimate regression with $1/Y^2$ weighting in Watson LIMS™		
Validation parameters	**Method validation summary**		**Acceptability**
Calibration curve performance during accuracy & precision	No of standard calibrators from LLOQ to ULOQ	8	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-4.0 to 4.0%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	≤3.9%	Yes
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs	-11.7 to -4.3%	Yes
	Inter-batch %CV	2.5 to 6.3%	Yes
	Percent total error (TE)	7.6 to 15.5%	Yes
Selectivity & matrix effect	Healthy: Acceptable recovery in 10 of 10 subjects (bias -12.0 to 12.0%), all results for all un-spiked subjects below LLOQ. Multiple myeloma: Acceptable recovery in 10 of 10 subjects (bias -		Yes

	14.0 to 8.0%), all results for all un-spiked subjects below LLOQ.	
Hemolysis effect	No percentage of hemolysis affects the recovery of teclistamab at the LLOQ concentration (bias -18 to 0%).	Yes
Lipemic effect	Low, medium, or high lipemic levels do affect the recovery of teclistamab at the LLOQ concentration in 4 of the 6 samples tested (bias 28 to 42%).	*Not expected to be of concern due to lack of matrix effect in patient samples
Interference & specificity	Presence of anti-drug anti-CD3 antibody at 200 ng/mL and 500 ng/mL does not affect recovery of teclistamab at MQC and LLOQ concentrations. Presence of anti-drug anti-BCMA antibody at 200 ng/mL and 500 ng/mL does not affect recovery of teclistamab at MQC and LLOQ concentrations. Presence of a non-neutralizing anti-human Fc antibody at 200 ng/mL and 500 ng/mL does not affect recovery of teclistamab at MQC and LLOQ concentrations. Presence of recombinant human BCMA target protein does affect recovery of teclistamab at LLOQ concentrations when tested at molar ratios of 10:1 (recombinant human BCMA: teclistamab) but does not affect recovery at lower molar ratios.	Yes
Dilution linearity & hook effect	Maximum acceptable dilution of 1:25,000. No hook effect at 1:1 dilution of 30 µg/mL spike.	Yes
Bench-top/process stability	Spiked samples stable in whole blood at -70°C up to 24 hrs after collection. QCs stable in human serum at room temperature for up to 7 days, at 4°C up to 4 weeks, at -20°C up to 5 weeks.	Yes
Freeze-Thaw stability	Up to 8 cycles.	Yes
Long-term storage	QCs stable in human serum at -70°C up to 1,468 days (~4 years).	Yes
Parallelism	Six samples were assayed at 3 dilution levels and all 6 sets of samples had %CV ≤30%.	Yes
Method performance in MajesTEC-1		
Assay passing rate	83.6% of assay runs met the method acceptance criteria.	Yes
Standard curve performance	Cumulative bias range: -4.2 to 4.4% Cumulative precision: ≤3.9%	Yes
QC performance	Cumulative bias range: -0.4 to 7.6% Cumulative precision: ≤8.2% TE: ≤15.0%	Yes
Method reproducibility	Incurred sample reanalysis was performed on 174 samples and 144 (82.8%) had results within 30% of the reference value.	Yes
Study sample analysis/ stability	Four samples exceeded the 4°C storage stability; results were not reported for these 4 samples. Maximum duration at -70°C = 1,056 days; at 4°C = 21 days; at room temperature = 7 days.	

19.4.2 Population PK Analysis

19.4.2.1 Executive Summary

The FDA's Assessment:

The population PK analysis supports the proposed dose of 0.06 mg/kg SC, followed 2 to 4 days later by 0.3 mg/kg SC, followed 2 to 4 days later by 1.5 mg/kg SC, followed by weekly administration at 1.5 mg/kg SC thereafter. No clinically relevant differences in exposure according to patient characteristics were identified.

19.4.2.2 PPK Assessment Summary

The Applicant's Position:

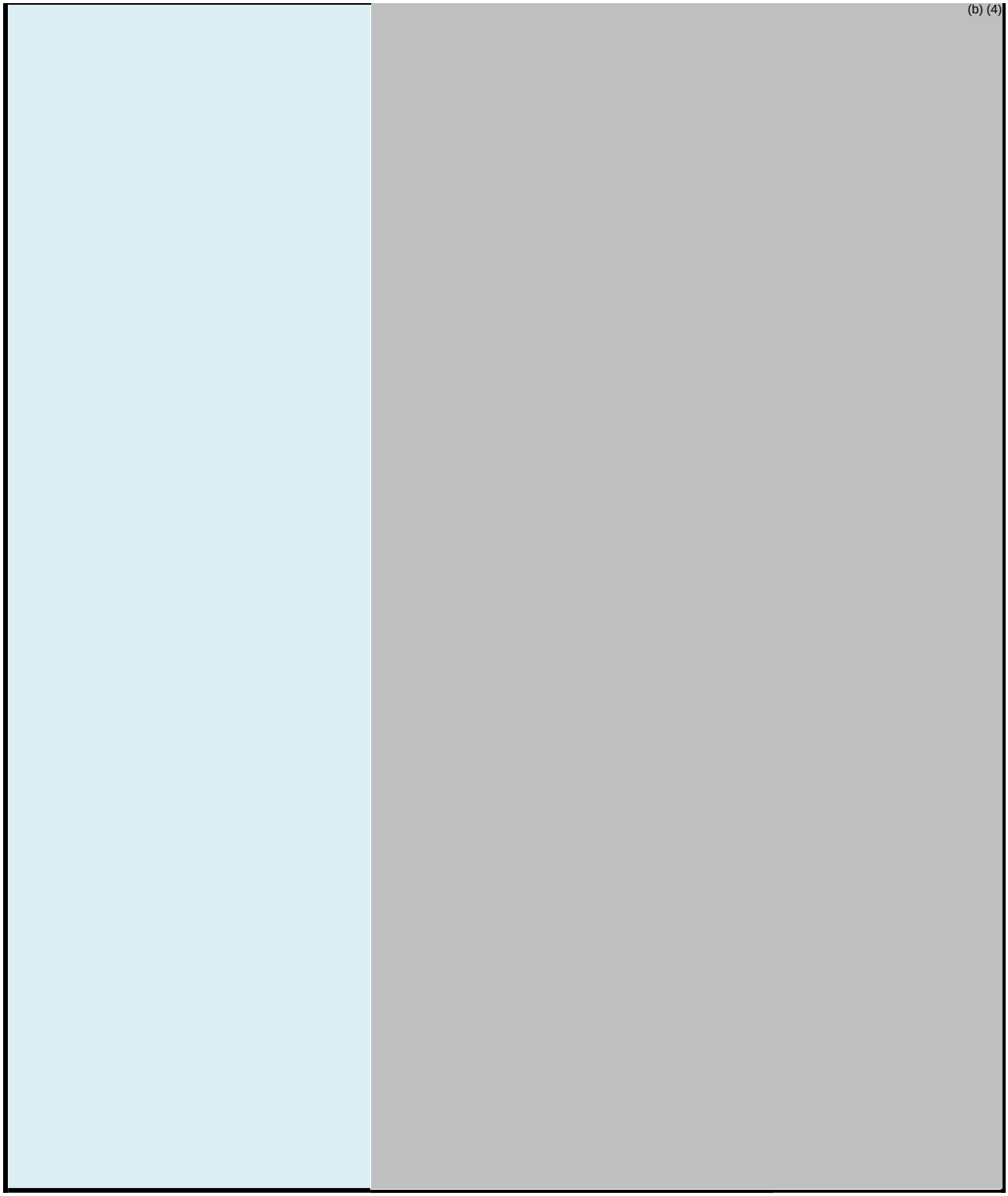
General Information		
Objectives of PPK Analysis		• *To characterize the population pharmacokinetics of teclistamab (IV and SC in subjects with relapsed or refractory multiple myeloma* • *To evaluate the effects of demographic characteristics, disease characteristics, prior treatment, and other intrinsic or extrinsic factors on the PK of teclistamab*
Study Included		*64007957MMY1001 (also known as MajesTEC-1) Part 1 (Phase 1 dose escalation), Part 2 (Phase 1 dose expansion), and Part 3 (Phase 2 dose expansion) with the PK data cutoff on 14 June 2021.*
Dose(s) Included		*Applicant's Population PK and Exposure-Response Analyses Report, Table 1* *-IV from 0.0003 to 0.0192 mg/kg Q2W and from 0.0192 to 0.72 mg/kg weekly* *-SC from 0.08 to 6 mg/kg weekly*
Population Included		*Adult subjects with relapsed or refractory multiple myeloma*
Population Characteristics (Table 21, Table 22)	General	*Age (median 64 yr, range 24-84 yr, 53.9% <65 yr, 33.8% ≥65 yr - <75 yr, 12.3% ≥75 yr)* *Weight (median 74 kg, range 41-139 kg)* *175 (56.8%) male; 133 (43.2%) female* *260 (84.4%) White; 25 (8.1%) Black or African American;* *23 (7.4%) Asian and Other*
	Organ Impairment	*Hepatic (National Cancer Institute Organ Dysfunction Working Group criteria):* *274 (89%) normal ; 34 (11%) mild impairment* *Renal (based on eGFR, mL/min/1.73 m²):* *90 (29.2%) ≥90 mL/min/1.73 m² (normal)* *141 (45.8%) ≥60-<90 mL/min/1.73 m²(mild impairment)* *76 (24.7%) ≥30-<60 mL/min/1.73 m²(moderate impairment)* *1 (0.3%) <30 mL/min/1.73 m² (severe impairment)*
	Pediatrics (if any)	*Not applicable*
No. of Patients, PK Samples, and BLQ		*No. of subjects: 308* *No. of PK samples: 4143* *BLQ post-dose samples: 30 (0.72%)*

Sampling Schedule	Rich Sampling	*Applicant's Population PK and Exposure-Response Analyses Report, Table 1* *<u>Phase1:</u>* *IV cohorts: predose, EOI, 2, 6, 24, 48, 168, and 336 hours (only for Q2W dosing) on Cycle 1 Day 1 and Cycle 3 Day 1. EOI of Cycle 1 Day 8 (QW IV dosing only) and Cycle 1 Day 15; predose for Cycle 2 Day 1, Cycle 2 Day 15, Cycle 3 Day 15, and Cycle 4 Day 1; and if feasible, at EOT and at 4 weeks and 8 weeks posttreatment follow up. Serum samples were also collected up to 24 hours after step up doses.* *SC cohorts: predose, 2, 24, 48, 72, 120, 168, and 336 hours (Q2W SC dosing only) on Cycle 1 Day 1 and Cycle 3 Day 1. Serum samples were collected at predose for step-up doses, Cycle 1 Day 15, Cycle 2 Day 1, Cycle 2 Day 15, Cycle 3 Day 15, Cycle 4 Day 1, and if feasible, at EOT and at 4 weeks and 8 weeks posttreatment follow-up.* *Sparse sampling for other doses and other cycles: most are predose samples.* *<u>Phase 2:</u>* *Sparse sampling only: predose of the first step-up dose, predose of Days 1 and 8 of Cycle 1, predose on Day 1 of Cycles 2, 3, 4, 6, 7, 10, 13, and then every 6 months until EOT*
	In ITT Population	*Not applicable*
Covariates Evaluated	Static	*Applicant's Population PK and Exposure-Response Analyses Report, Table 5* *Body weight, age, sex, race, region, ethnicity, creatinine clearance, albumin, ALT, ALP, renal function based on eGFR, hepatic function, total T cells, soluble BCMA, bone marrow percent plasma cells, extramedullary plasmacytoma, type of myeloma, lesion number, lytic lesion, ECOG status, ISS, revised ISS staging, cytogenetic risk, prior use of the following [anti-CD38 monoclonal antibodies, daratumumab, anti-PD1/anti-PD-L1, anti-BCMA treatment], triple refractory status, penta-refractory status, number of prior lines of therapies, ADA, pivotal vs Phase 1 drug product*
	Time-varying	*Applicant's Population PK and Exposure-Response Analyses Report, Table 5* *Soluble BCMA, ADA, pivotal vs phase 1 drug product*

Final Model	Summary	Acceptability [FDA's comments]
Software and Version	*NONMEM (version 7.3.0)* *Perl-speaks-NONMEM (version 4.6.0)* *R (version 3.4.1)*	
Model Structure	*2-compartment model with first-order absorption and parallel time-independent and time-dependent elimination pathways*	See **FDA Table 8** for Applicant's updated final PPK model parameter estimates. The Applicant's model is generally acceptable for the purpose of characterizing teclistamab PK in patients with relapsed or refractory multiple myeloma.
Model Parameter Estimates	Table 23	
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	*All model parameters were estimated reasonably well with relative standard errors no greater than 30% for all the structural PK and covariate effect parameter estimates with the exception of Q, which had a RSE of 48.5%. The ETA shrinkages of the structural PK parameters were low to moderate (18.0% for CL_1, 36.7% for CL_2, 40.0% for V_1, and 37.9% for K_a); thus, estimates of individual PK parameters were considered to be reasonable.*	
BLQ for Parameter Accuracy	*Since 0.72% postdose PK records were BLQ, exclusion of the postdose BLQ PK observations should not result in appreciable bias in the parameter estimates of the model because of the very few samples with BLQ values (Beal 2001, Ahn 2008). Sensitivity analysis using the likelihood based (M3) method was not deemed necessary and was not performed, as specified in the Analysis Plan.*	
GOF, VPC	Figure 5 *for GOF* Figure 6 *for VPC stratified by cohort*	See **FDA Figure 5** for GOF using linear scale. The GOF and VPC show that the model fit is generally acceptable.
Significant Covariates and Clinical Relevance	Figure 7 *for forest plot of* $C_{ave,1stdose}$ Figure 8 *for forest plot of* $C_{trough,ss}$	No clinically relevant differences in exposure according to patient characteristics were identified.
Analysis Based on Simulation (optional)	Figure 9 *for RP2D Time Profiles*	See **FDA Figure 8** for PK profile on linear scale; **FDA Table 8** for summary of PK parameters; **FDA Table 9** for summary of exposure.

Labeling Language	Description	Acceptability [FDA's comments]
12.3 PK	(b) (4)	

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



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

Table 20: Pharmacokinetic Parameters of Teclistamab-xxxx Following the First and Seventh Recommended Treatment Dose (1.5 mg/kg) in Patients with Relapsed or Refractory Multiple Myeloma (MajesTEC-1)

PK Parameter	The 1st treatment dose of 1.5 mg/kg	The 7th treatment dose of 1.5 mg/kg (steady state)
T_{max} (hours)	72.0 (45.8 – 193) (n=40)	48.9 (0.0 – 166) (n=15)
C_{max} (µg/mL)	8.74 ± 3.65 (n=40)	25.3 ± 11.1 (n=15)
C_{trough} (µg/mL)	7.67 ± 3.52 (n=38)	22.1 ± 10.9 (n=27)
AUC_{tau} (µg·h/mL)	1169 ± 481 (n=38)	3905 ± 1748 (n=13)

T_{max} = Time to reach C_{max}; C_{max} = Maximum observed serum teclistamab-xxxx concentration; C_{trough} = Observed serum teclistamab-xxxx concentration prior to next dose; AUC_{tau} = Area under the concentration-time curve over the weekly dosing interval. Data are presented as mean ± standard deviation, except for T_{max} which is presented as median (minimum, maximum).

Table 21: Demographic and Baseline Characteristics of Pooled Study Dataset (Continuous Covariates) for Population PK Analysis

Phase	Non-RP2D IV (n=83)	Non-RP2D SC (n=39)	RP2D SC (Part 1/2+Part 3A) (n=160)	RP2D SC (Part 3C) (n=26)	Combined IV and SC (n=308)
Age (years)					
Mean (SD)	62.3 (9.79)	63.7 (10.1)	64.1 (9.56)	58.8 (11.3)	63.1 (9.91)
Median	62.0	66.0	64.0	62.0	64.0
IQ	57.0-68.0	56.5-71.5	58.0-71.3	50.5-68.8	57.0-70.0
Range	24.0-82.0	41.0-79.0	33.0-84.0	32.0-74.0	24.0-84.0
Weight (kg)					
Mean (SD)	72.8 (15.4)	75.6 (18.2)	75.0 (16.7)	78.7 (19.9)	74.8 (16.9)
Median	75.0	75.3	73.3	81.0	74.0
IQ	61.5-81.0	59.5-87.8	64.3-86.0	66.3-90.5	62.0-85.5
Range	41.0-124	49.0-117	41.0-139	43.7-125	41.0-139
Serum Creatinine (mmol/L)					
Mean (SD)	82.4 (23.3)	84.8 (24.0)	86.3 (27.5)	84.8 (28.8)	85.0 (26.0)
Median	76.9	77.8	79.3	81.0	78.7
IQ	66.7-94.7	67.5-103	68.8-102	66.1-99.6	67.1-99.9
Range	48.6-168	50.4-147	35.4-197	37.1-150	35.4-197
Creatinine Clearance (mL/min)					
Mean (SD)	83.8 (34.4)	82.0 (29.0)	83.8 (36.9)	94.5 (34.6)	84.5 (35.1)
Median	78.3	79.0	79.2	84.5	79.7
IQ	61.3-100	58.4-99.9	58.8-97.6	70.4-109	60.2-102
Range	28.3-263	41.9-155	24.6-251	50.9-191	24.6-263
Estimated Glomerular Filtration Rate (mL/min/1.73 m^2)					
Mean (SD)	77.7 (22.7)	76.3 (23.2)	78.8 (29.8)	83.3 (25.3)	78.6 (26.8)
Median	75.2	72.8	75.9	88.8	75.9
IQ	61.5-93.5	59.5-94.1	57.3-91.6	66.0-96.6	60.2-93.8
Range	36.0-145	37.9-139	29.5-262	40.0-152	29.5-262
Albumin (g/L)					
Mean (SD)	37.8 (5.52)	38.6 (4.74)	36.7 (6.23)	34.3 (6.95)	37.0 (6.01)
Median	39.0	40.0	37.0	33.6	38.0
IQ	36.0-41.0	36.0-42.0	32.0-42.0	30.6-40.0	33.0-41.0
Range	13.0-48.0	25.0-47.0	14.9-52.0	21.0-48.0	13.0-52.0
Alanine transaminase (U/L)					
Mean (SD)	18.4 (11.5)	17.7 (9.21)	19.4 (13.9)	26.4 (17.6)	19.5 (13.3)
Median	15.6	16.0	17.0	20.3	16.0
IQ	11.5-21.0	11.5-21.0	12.0-22.0	15.7-27.8	12.0-22.0
Range	4.00-62.0	6.00-46.0	5.00-136	11.0-82.0	4.00-136
Aspartate transaminase (U/L)					
Mean (SD)	23.6 (10.1)	21.1 (8.52)	24.9 (13.1)	33.0 (22.4)	24.8 (13.2)
Median	22.0	19.2	21.0	24.5	21.6
IQ	16.0-28.0	15.5-24.5	17.0-28.0	20.3-37.8	17.0-28.0
Range	9.00-57.6	10.0-49.0	10.0-94.4	12.0-115	9.00-115
Alkaline phosphatase (U/L)					
Mean (SD)	66.4 (30.9)	70.1 (34.1)	74.4 (40.3)	87.1 (56.5)	72.8 (39.2)
Median	61.0	60.0	66.1	72.5	64.0
IQ	48.0-74.5	52.0-83.0	51.8-84.0	54.1-89.0	51.0-82.3
Range	24.0-224	24.0-197	10.2-363	40.0-291	10.2-363

Phase	Non-RP2D IV (n=83)	Non-RP2D SC (n=39)	RP2D SC (Part 1/2+Part 3A) (n=160)	RP2D SC (Part 3C) (n=26)	Combined IV and SC (n=308)
Total T cells (/µL)					
Mean (SD)	408 (410)	721 (448)	553 (414)	426 (348)	526 (422)
Median	277	621	419	349	389
IQ	146-467	402-1070	242-796	153-604	220-743
Range	23.5-2370	95.0-1720	16.9-1880	18.0-1520	16.9-2370
Not reported n(%)	5 (6.0)	0 (0)	8 (5.0)	0 (0)	13 (4.2)
Soluble BCMA (ng/mL)					
Mean (SD)	153 (178)	95.3 (103)	153 (195)	165 (189)	147 (181)
Median	82.5	64.1	87.7	96.5	85.3
IQ	30.5-198	26.0-101	33.2-169	21.4-206	29.5-183
Range	5.70-811	10.2-492	0.00100-1030	2.70-748	0.00100-1030
Not reported n(%)	0 (0)	1 (2.6)	3 (1.9)	0 (0)	4 (1.3)
Bone marrow % plasma cells					
Mean (SD)	31.7 (33.3)	31.9 (33.5)	23.8 (26.5)	14.2 (21.8)	26.1 (29.3)
Median	17.8	18.5	14.0	3.50	14.0
IQ	3.30-61.8	4.00-52.5	2.00-40.0	1e-04-16.9	2.00-48.8
Range	1e-04-100	1e-04-100	1e-04-95.0	1e-04-85.0	1e-04-100
Not reported n(%)	3 (3.6)	3 (7.7)	5 (3.1)	0 (0)	11 (3.6)

BCMA=B cell maturation antigen; IQ=interquartile range; IV=intravenous; n=number of subjects; RP2D=recommended Phase 2 dose, which is 1.5 mg/kg teclistamab SC administered weekly, with the first treatment dose preceded by step-up doses of 0.06 and 0.3 mg/kg; SC=subcutaneous; SD=standard deviation.
Note: Statistics were calculated before the imputation of missing values.

Source: Applicant's Population PK and Exposure-Response Analyses Report, Table 2.

Table 22: Demographic and Baseline Characteristics (Categorical Covariates) for Population PK Analysis

Phase	Non-RP2D IV (n=83)	Non-RP2D SC (n=39)	RP2D SC (Part 1/2+Part 3A) (n=160)	RP2D SC (Part 3C) (n=26)	Combined IV and SC (n=308)
Age (years)					
<65	50 (60.2%)	17 (43.6%)	82 (51.2%)	17 (65.4%)	166 (53.9%)
65-<75	25 (30.1%)	16 (41.0%)	54 (33.8%)	9 (34.6%)	104 (33.8%)
≥75	8 (9.6%)	6 (15.4%)	24 (15.0%)	0 (0.0%)	38 (12.3%)
Sex					
Male	42 (50.6%)	20 (51.3%)	95 (59.4%)	18 (69.2%)	175 (56.8%)
Female	41 (49.4%)	19 (48.7%)	65 (40.6%)	8 (30.8%)	133 (43.2%)
Race[a]					
White	71 (85.5%)	31 (79.5%)	134 (83.8%)	24 (92.3%)	260 (84.4%)
African American/ Black	3 (3.6%)	4 (10.3%)	16 (10.0%)	2 (7.7%)	25 (8.1%)
Asian	2 (2.4%)	0 (0.0%)	3 (1.9%)	0 (0.0%)	5 (1.6%)
Other	7 (8.4%)	4 (10.3%)	7 (4.4%)	0 (0.0%)	18 (5.8%)
Region					
USA	38 (45.8%)	23 (59.0%)	53 (33.1%)	8 (30.8%)	122 (39.6%)
Western countries other than USA	45 (54.2%)	16 (41.0%)	107 (66.9%)	18 (69.2%)	186 (60.4%)
Ethnicity (Hispanic)					
Hispanic or Latino	4 (4.8%)	1 (2.6%)	15 (9.4%)	0 (0.0%)	20 (6.5%)
Non-Hispanic or Latino	79 (95.2%)	38 (97.4%)	145 (90.6%)	26 (100.0%)	288 (93.5%)
Ethnicity (Asian)					
Asian	2 (2.4%)	0 (0.0%)	3 (1.9%)	0 (0.0%)	5 (1.6%)
Non-Asian	81 (97.6%)	39 (100.0%)	157 (98.1%)	26 (100.0%)	303 (98.4%)
Renal function (based on eGFR, mL/min/1.73 m^2)					
≥90	23 (27.7%)	11 (28.2%)	45 (28.1%)	11 (42.3%)	90 (29.2%)
≥60-<90	41 (49.4%)	18 (46.2%)	72 (45.0%)	10 (38.5%)	141 (45.8%)
≥30-<60	19 (22.9%)	10 (25.6%)	42 (26.2%)	5 (19.2%)	76 (24.7%)
<30	0 (0.0%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	1 (0.3%)
Hepatic function[b]					
Normal	76 (91.6%)	36 (92.3%)	139 (86.9%)	23 (88.5%)	274 (89.0%)
Impaired[a]	7 (8.4%)	3 (7.7%)	21 (13.1%)	3 (11.5%)	34 (11.0%)
Baseline extramedullary plasmacytoma					
0	75 (90.4%)	36 (92.3%)	133 (83.1%)	19 (73.1%)	263 (85.4%)
≥1	8 (9.6%)	3 (7.7%)	27 (16.9%)	7 (26.9%)	45 (14.6%)
Baseline lytic lesion					
No	16 (19.3%)	5 (12.8%)	20 (12.5%)	4 (15.4%)	45 (14.6%)
Yes	65 (78.3%)	33 (84.6%)	140 (87.5%)	22 (84.6%)	260 (84.4%)
Not reported	2 (2.4%)	1 (2.6%)	0 (0.0%)	0 (0.0%)	3 (1.0%)
Lesion number					
None	16 (19.3%)	5 (12.8%)	20 (12.5%)	4 (15.4%)	45 (14.6%)
1-3	11 (13.3%)	5 (12.8%)	20 (12.5%)	1 (3.8%)	37 (12.0%)
4-10	12 (14.5%)	10 (25.6%)	40 (25.0%)	10 (38.5%)	72 (23.4%)
More than 10	42 (50.6%)	18 (46.2%)	80 (50.0%)	11 (42.3%)	151 (49.0%)
Not reported	2 (2.4%)	1 (2.6%)	0 (0.0%)	0 (0.0%)	3 (1.0%)

Phase	Non-RP2D IV (n=83)	Non-RP2D SC (n=39)	RP2D SC (Part 1/2+Part 3A) (n=160)	RP2D SC (Part 3C) (n=26)	Combined IV and SC (n=308)
Baseline ECOG score					
0	33 (39.8%)	15 (38.5%)	54 (33.8%)	5 (19.2%)	107 (34.7%)
1	50 (60.2%)	24 (61.5%)	105 (65.6%)	21 (80.8%)	200 (64.9%)
3	0 (0.0%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	1 (0.3%)
Baseline ISS[c]					
I	39 (47.0%)	14 (35.9%)	83 (51.9%)	13 (50.0%)	149 (48.4%)
II	23 (27.7%)	18 (46.2%)	55 (34.4%)	6 (23.1%)	102 (33.1%)
III	21 (25.3%)	7 (17.9%)	19 (11.9%)	7 (26.9%)	54 (17.5%)
Not reported	0 (0.0%)	0 (0.0%)	3 (1.9%)	0 (0.0%)	3 (1.0%)
Baseline revised ISS[d]					
I	12 (14.5%)	5 (12.8%)	41 (25.6%)	3 (11.5%)	61 (19.8%)
II	49 (59.0%)	26 (66.7%)	98 (61.2%)	18 (69.2%)	191 (62.0%)
III	13 (15.7%)	4 (10.3%)	12 (7.5%)	4 (15.4%)	33 (10.7%)
Not reported	9 (10.8%)	4 (10.3%)	9 (5.6%)	1 (3.8%)	23 (7.5%)
Cytogenetic risk					
Standard risk	42 (50.6%)	25 (64.1%)	105 (65.6%)	16 (61.5%)	188 (61.0%)
High risk[e]	23 (27.7%)	6 (15.4%)	37 (23.1%)	6 (23.1%)	72 (23.4%)
Not reported	18 (21.7%)	8 (20.5%)	18 (11.2%)	4 (15.4%)	48 (15.6%)
Number of lines of prior therapy					
≤3 lines	13 (15.7%)	5 (12.8%)	40 (25.0%)	2 (7.7%)	60 (19.5%)
>3 lines	70 (84.3%)	34 (87.2%)	120 (75.0%)	24 (92.3%)	248 (80.5%)
Type of myeloma					
IgG	34 (41.0%)	24 (61.5%)	87 (54.4%)	13 (50.0%)	158 (51.3%)
Non-IgG	49 (59.0%)	15 (38.5%)	73 (45.6%)	13 (50.0%)	150 (48.7%)
Bone marrow % plasma cells					
≤30	50 (60.2%)	23 (59.0%)	108 (67.5%)	21 (80.8%)	202 (65.6%)
>30-<60	7 (8.4%)	4 (10.3%)	31 (19.4%)	3 (11.5%)	45 (14.6%)
≥60	23 (27.7%)	9 (23.1%)	16 (10.0%)	2 (7.7%)	50 (16.2%)
Not reported	3 (3.6%)	3 (7.7%)	5 (3.1%)	0 (0.0%)	11 (3.6%)
Prior use of anti-CD38 mAbs					
Yes	79 (95.2%)	37 (94.9%)	160 (100.0%)	26 (100.0%)	302 (98.1%)
Otherwise	4 (4.8%)	2 (5.1%)	0 (0.0%)	0 (0.0%)	6 (1.9%)
Prior use of daratumumab					
Yes	79 (95.2%)	34 (87.2%)	147 (91.9%)	24 (92.3%)	284 (92.2%)
Otherwise	4 (4.8%)	5 (12.8%)	13 (8.1%)	2 (7.7%)	24 (7.8%)
Prior use of anti-PD1/anti-PD-L1					
Yes	10 (12.0%)	4 (10.3%)	7 (4.4%)	1 (3.8%)	22 (7.1%)
Otherwise	73 (88.0%)	35 (89.7%)	153 (95.6%)	25 (96.2%)	286 (92.9%)
Prior use of anti-BCMA					
Anti-BCMA ADC	0 (0.0%)	0 (0.0%)	0 (0.0%)	15 (57.7%)	15 (4.9%)
BCMA CAR-T	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (34.6%)	9 (2.9%)
Both	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (7.7%)	2 (0.6%)
Otherwise	83 (100.0%)	39 (100.0%)	160 (100.0%)	0 (0.0%)	282 (91.6%)
Triple refractory status					
Yes	69 (83.1%)	29 (74.4%)	124 (77.5%)	22 (84.6%)	244 (79.2%)
Other	14 (16.9%)	10 (25.6%)	36 (22.5%)	4 (15.4%)	64 (20.8%)

Phase	Non-RP2D IV (n=83)	Non-RP2D SC (n=39)	RP2D SC (Part 1/2+Part 3A) (n=160)	RP2D SC (Part 3C) (n=26)	Combined IV and SC (n=308)
Penta refractory status					
Yes	33 (39.8%)	15 (38.5%)	47 (29.4%)	9 (34.6%)	104 (33.8%)
Other	50 (60.2%)	24 (61.5%)	113 (70.6%)	17 (65.4%)	204 (66.2%)
Refractory status					
None	0 (0.0%)	0 (0.0%)	3 (1.9%)	0 (0.0%)	3 (1.0%)
PI only	0 (0.0%)	0 (0.0%)	3 (1.9%)	1 (3.8%)	4 (1.3%)
IMiD only	2 (2.4%)	0 (0.0%)	5 (3.1%)	0 (0.0%)	7 (2.3%)
Anti-CD38 antibody only	1 (1.2%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	2 (0.6%)
Both PI and IMiD	4 (4.8%)	4 (10.3%)	5 (3.1%)	0 (0.0%)	13 (4.2%)
Both IMiD and anti-CD38 antibody	6 (7.2%)	5 (12.8%)	14 (8.8%)	3 (11.5%)	28 (9.1%)
Both PI and anti-CD38 antibody	1 (1.2%)	1 (2.6%)	5 (3.1%)	0 (0.0%)	7 (2.3%)
PI+IMiD+anti-CD38 antibody	69 (83.1%)	29 (74.4%)	124 (77.5%)	22 (84.6%)	244 (79.2%)
Antibodies to teclistamab					
Positive	1 (1.2%)	1 (2.6%)	0 (0.0%)	0 (0.0%)	2 (0.6%)
All others	82 (98.8%)	38 (97.4%)	160 (100.0%)	26 (100.0%)	306 (99.4%)
Drug product[f]					
Received pivotal drug product at least for 1 visit	0 (0.0%)	0 (0.0%)	100 (62.5%)	20 (76.9%)	120 (39.0%)
All others	83 (100%)	39 (100%)	60 (37.5%)	6 (23.1%)	188 (61.0%)

ADC=antibody drug conjugate; BCMA=B cell maturation antigen; CAR-T=chimeric antigen receptor T cell therapy; CD38=cluster of differentiation 38; ECOG=Eastern Cooperative Oncology Group; eGFR=estimated glomerular filtration rate based on Modification of Diet in Renal Disease (MDRD) method (Levey 2007); IgG=immunoglobulin G; IMiD=immunomodulatory drug; ISS=International Staging System; IV=intravenous; mAb=monoclonal antibody; n=number of subjects; PD1=programmed cell death protein 1; PD-L1=programmed death ligand 1; PI=proteasome inhibitor; RP2D=recommended Phase 2 dose, which is 1.5 mg/kg teclistamab SC administered weekly, with the first treatment dose preceded by step-up doses of 0.06 and 0.3 mg/kg; SC=subcutaneous; USA=United States of America.

[a] Other race category included Multiple, Other and Not reported.

[b] All subjects with impaired hepatic function were of mild impairment based on National Cancer Institute Organ Dysfunction Working Group criteria (Ramalingam 2010).

[c] Baseline ISS were derived based on the combination of serum β2-microglobulin and albumin.

[d] Baseline revised ISS was derived based on the combination of serum β2-microglobulin and albumin, genetic risk, and level of lactate dehydrogenase level.

[e] High risk is defined by participants having t (4; 14); t (14; 16), or 17p deletion.

[f] Pivotal drug product are available in 10 mg/mL and 90 mg/mL concentration formulations for step-up doses and treatment doses, respectively (Mod2.7.1 and Mod3.2.P.1).

Note: Data are presented as n (%), ie, number of subjects with the observation (percentage).

Source: Applicant's Population PK and Exposure-Response Analyses Report, Table 3.

Table 23: Parameter Estimates of Teclistamab for the Final Population PK Model

Parameters, unit	Estimate	RSE (%)	IIV (%CV)	RSE (%)	Shrinkage (%)
CL_1 (L/day)[a]	0.545	8.37	49.4	17.0	18.0
BWT on CL_1	0.758	20.9			
IISS=II on CL_1	1.35	7.43			
IISS=III on CL_1	1.63	15.0			
TPMM2=Non-IgG on CL_1	0.561	7.98			
CL_2 (L/day)[b]	0.327	24.0	132.9	24.4	36.7
TPMM2=Non-IgG on CL_2	0.401	26.6			
V_1 (L)[c]	4.09	3.83	31.0	20.9	40.0
BWT on V_1	0.462	30.2			
K_{DES} (day^{-1})	0.0328	11.5			
Q (L/day)	0.0473	48.5			
V_2 (L)[d]	1.29	29.9			
BWT on V_2	1.17	27.5			
Ka (day^{-1})	0.140	7.40	52.3	23.7	37.9
F	0.672	6.50			
ADD ERR (%CV)	40.6	4.85			

ADD ERR=additive error term on the log-scale; BWT=baseline body weight in kilograms; CL_1=time-independent clearance; CL_2=clearance associated with time-dependent clearance (CL_t), which decreases over time through a first-order rate (K_{DES}); CV=coefficient of variation; F=subcutaneous bioavailability; IgG=immunoglobulin G; IISS=International Staging System (1=I, 2=II, 3=III); IIV=inter-individual variability; calculated as $(variance)^{1/2}\times 100\%$; Ka=first-order absorption rate constant; K_{DES}=first-order rate constant for CL_2 decrease over time; Q=inter-compartmental clearance; RSE=relative standard error; TPMM2=multiple myeloma type (0=non-IgG,1=IgG); V_1=volume of distribution of the central compartment; V_2=volume of distribution of the peripheral compartment.

[a] $CL_1(L/day) = 0.545 \times \left(\frac{BWT}{74}\right)^{0.758} \times 1.35^{ISS=II} \times 1.63^{ISS=III} \times 0.561^{TPMM=Non-IgG}$

[b] $CL_2(L/day) = 0.327 \times 0.401^{TPMM=Non-IgG}$

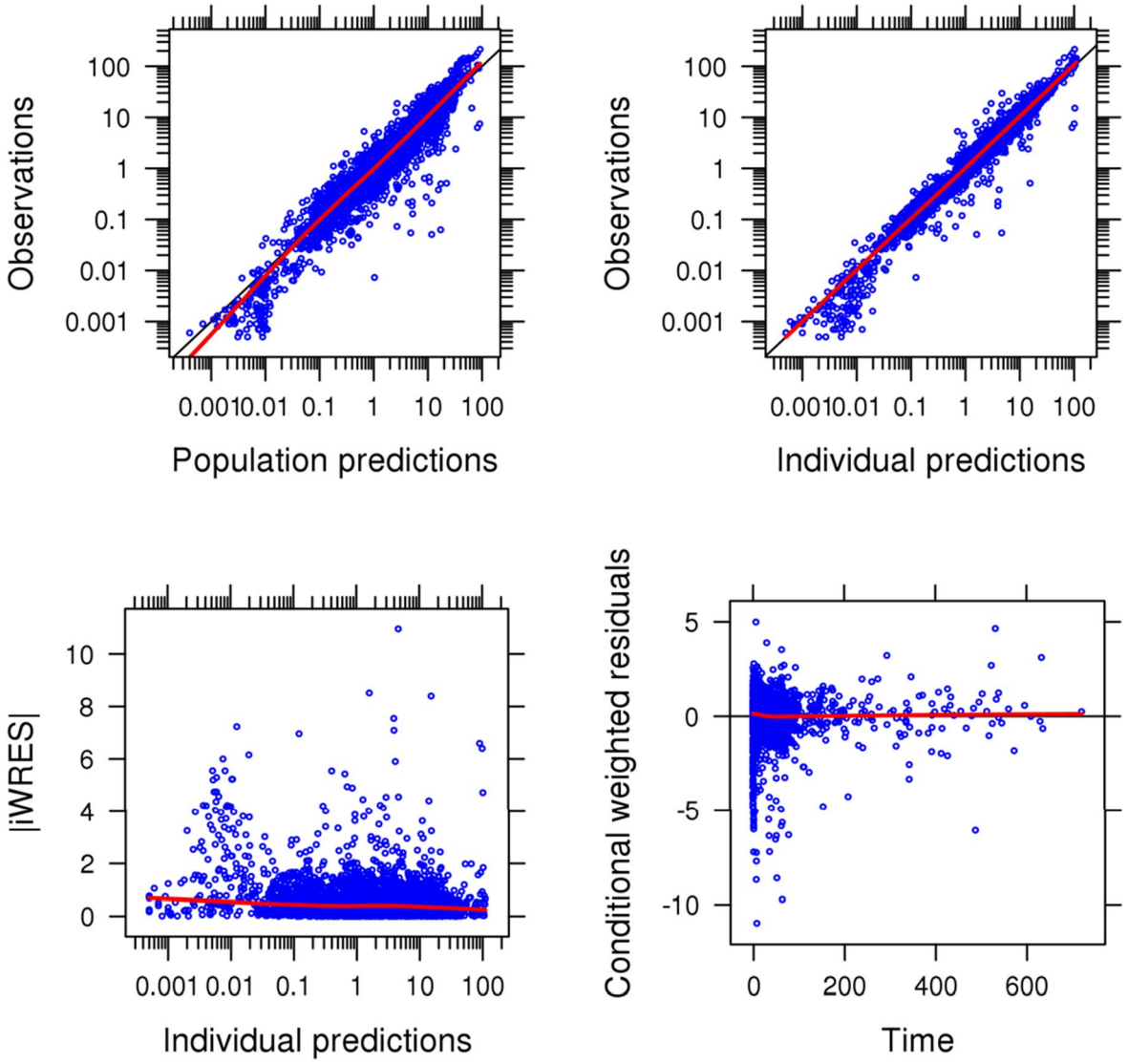
$CL = CL_1 + CL_2 \times e^{-0.0328 \times Time(in\ days)}$

[c] $V_1(L) = 4.09 \times (\frac{BWT}{74})^{0.462}$

[d] $V_2(L) = 1.29 \times (\frac{BWT}{74})^{1.17}$

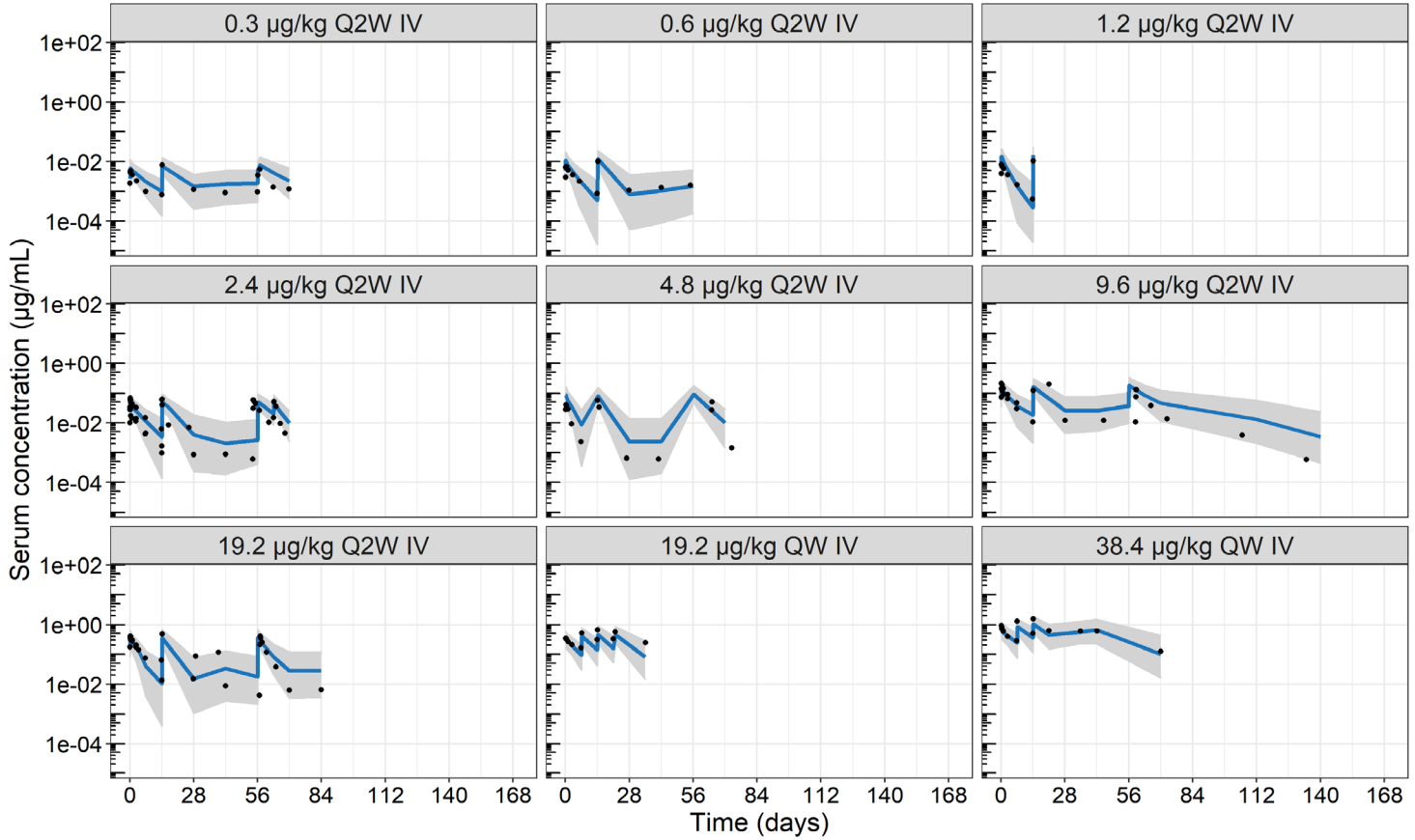
Source: Applicant's Population PK and Exposure-Response Analyses Report, Table 6.

Figure 5: Basic Goodness-of-fit Plots for Final Population PK Model



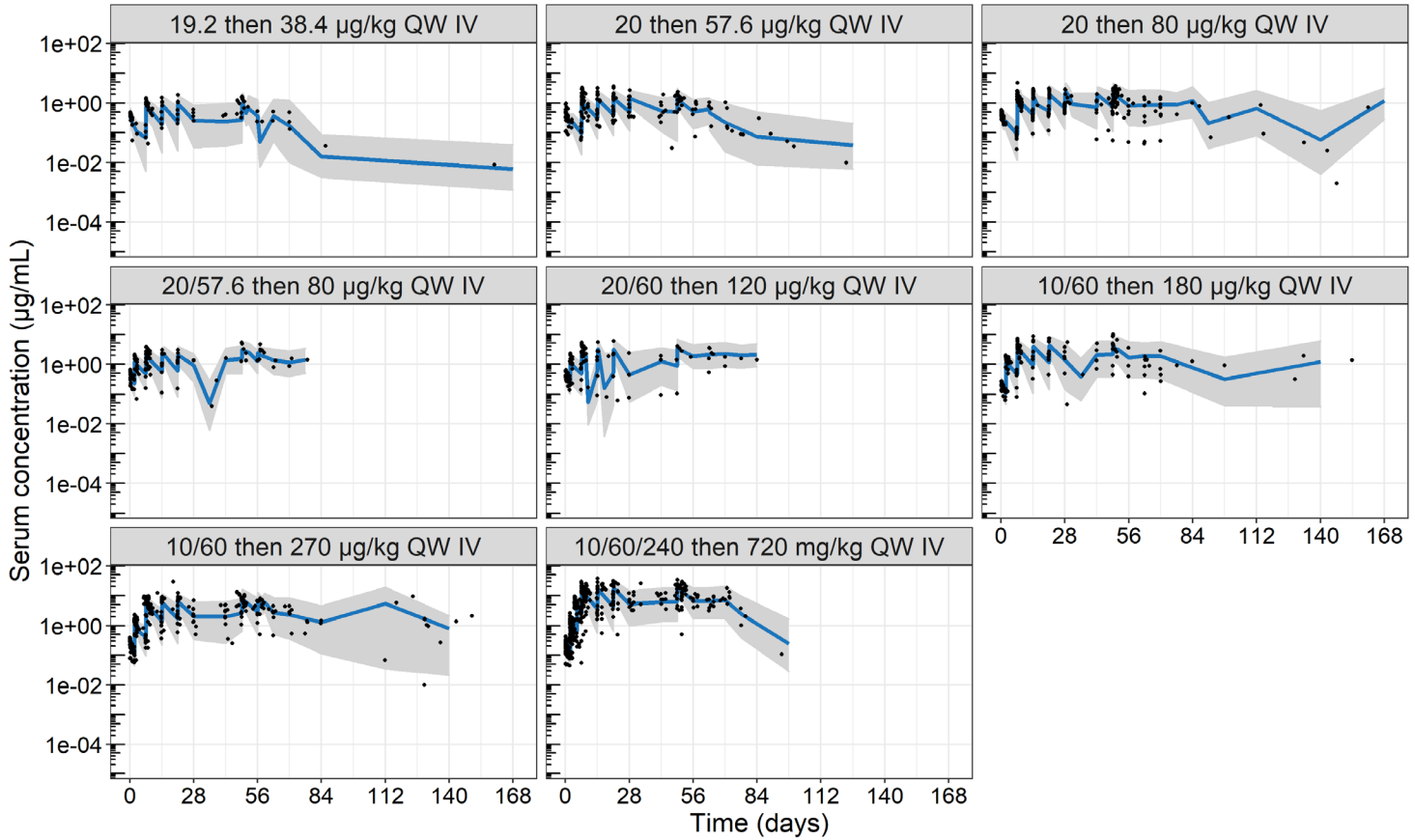
|iWRES|=absolute individual weighted residuals.
Units: Observations or predictions=µg/mL; Time=day
The black solid line is the line of identity or the zero line, and the red solid line is the trend line. The blue circles are the observations.
Source: Applicant's Population PK and Exposure-Response Analyses Report, Figure 3.

Figure 6: Observed versus Simulated Serum Teclistamab Concentration-time Profiles Stratified by Treatment Groups for Final Population PK Model



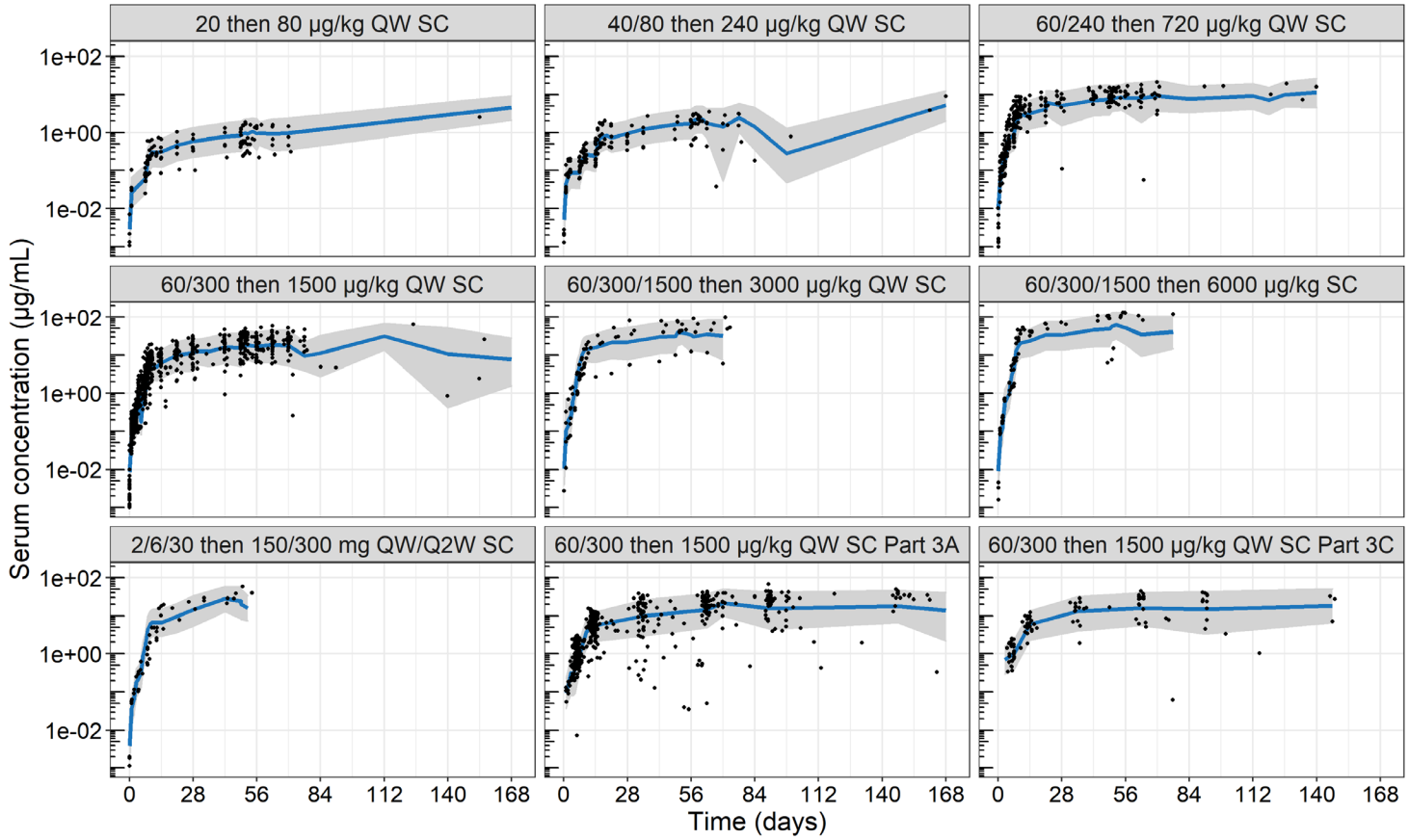
IV=intravenous; n=number of subjects; Q2W=every 2 weeks; QW=weekly.
Blue solid lines represent the median of the simulation. Shaded regions encompass 80% prediction interval of the simulated (n=1000) values. Data points represent the observed data.

Figure 6: Observed versus Simulated Serum Teclistamab Concentration-time Profiles Stratified by Treatment Groups for Final Population PK Model



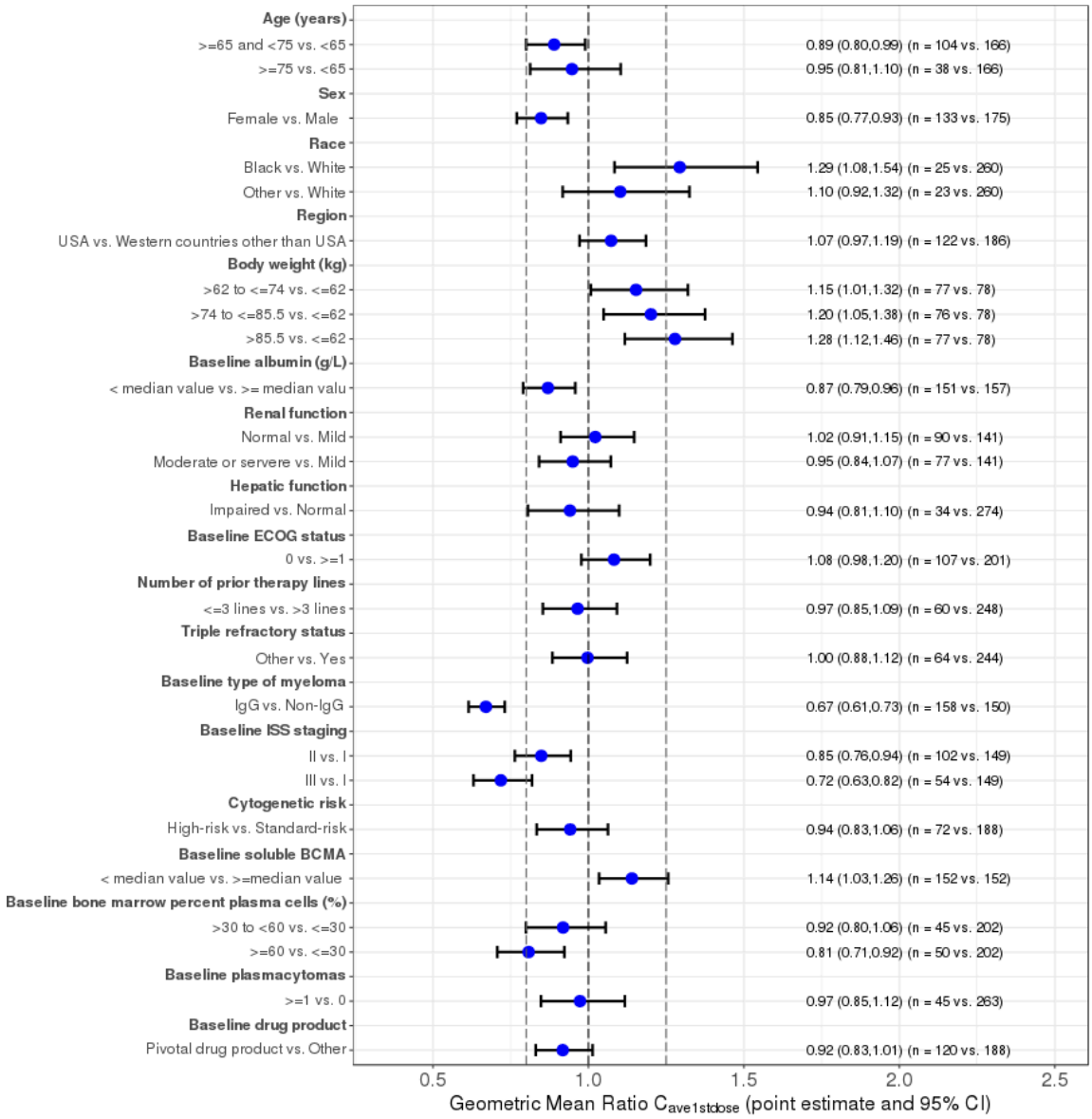
IV=intravenous; n=number of subjects; Q2W=every 2 weeks; QW=weekly.
Blue solid lines represent the median of the simulation. Shaded regions encompass 80% prediction interval of the simulated (n=1000) values. Data points represent the observed data.

Figure 6: Observed versus Simulated Serum Teclistamab Concentration-time Profiles Stratified by Treatment Groups for Final Population PK Model



n=number of subjects; Q2W=every 2 weeks; QW=weekly; SC=subcutaneous.
Blue solid lines represent the median of the simulation. Shaded regions encompass 80% prediction interval of the simulated (n=1000) values. Data points represent the observed data.
Source: Applicant's Population PK and Exposure-Response Analyses Report, Attachment 17.

Figure 7: Forest Plot of Subgroup Analyses of the Predicted Average Concentration of the First Treatment Dose (Cave,1stdose) per the RP2D (Final Population PK Model)



BCMA=B cell maturation antigen; $C_{ave,1stdose}$=predicted average concentration of the first treatment dose; CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; IgG=immunoglobulin G; ISS=International Staging System; RP2D=recommended Phase 2 dose, ie, 1.5 mg/kg teclistamab SC administered weekly, with the first treatment dose preceded by step-up doses of 0.06 and 0.3 mg/kg; SC=subcutaneous; USA=United States of America; vs=versus.

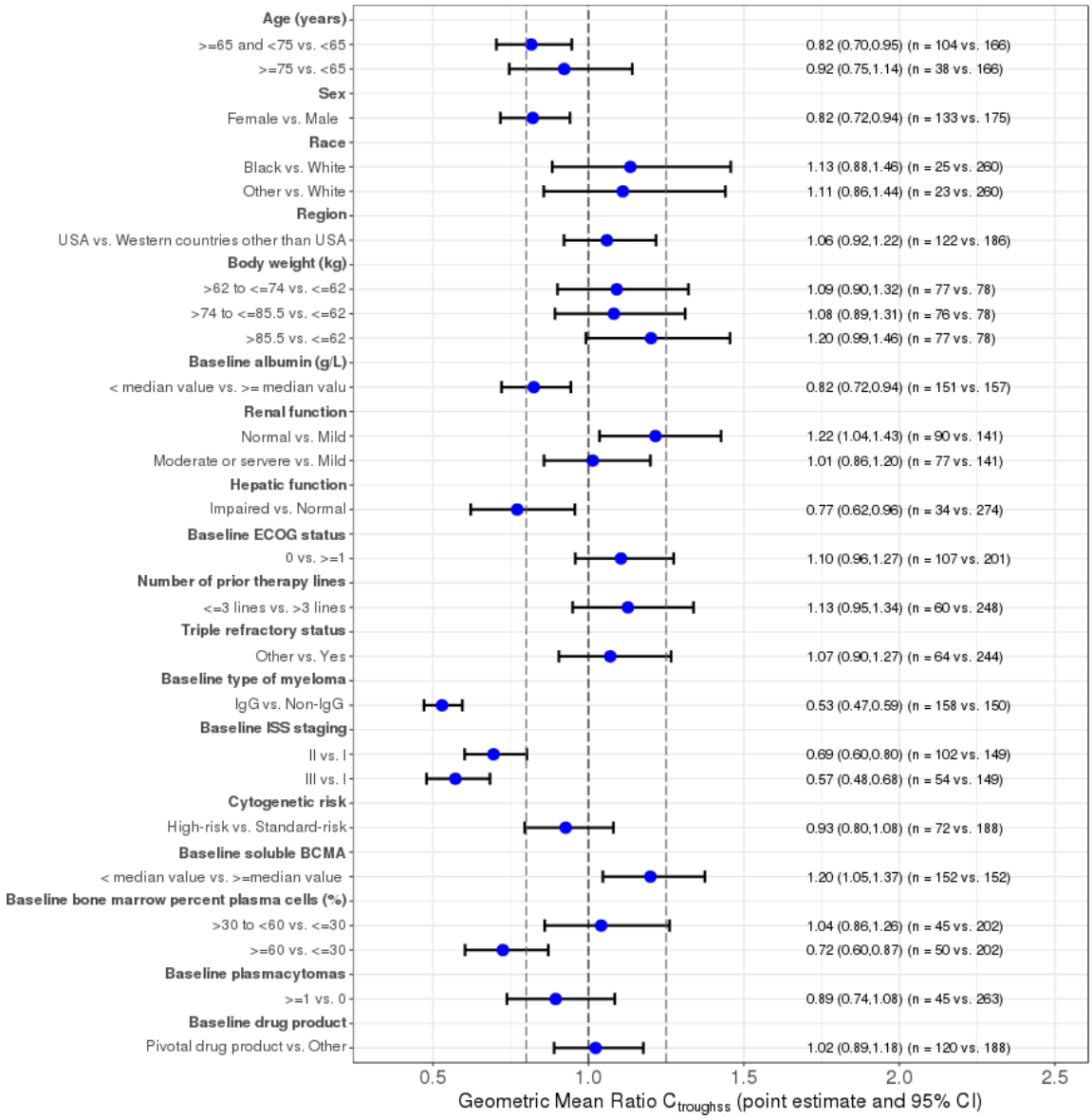
Solid blue circle represents geometric mean ratio and error bar represents 95% CI. Dashed line represents reference value of 1. The associated values are shown on the right column. The dashed vertical lines refer to 0.8 and 1.25.

Note: Subjects in the impaired hepatic function subgroup (n=34) have mild impairment only.

Note: Analyses assumed that all subjects included in the population PK analysis dataset received 1.5 mg/kg teclistamab SC administered weekly, with the first treatment dose preceded by step-up doses of 0.06 and 0.3 mg/kg

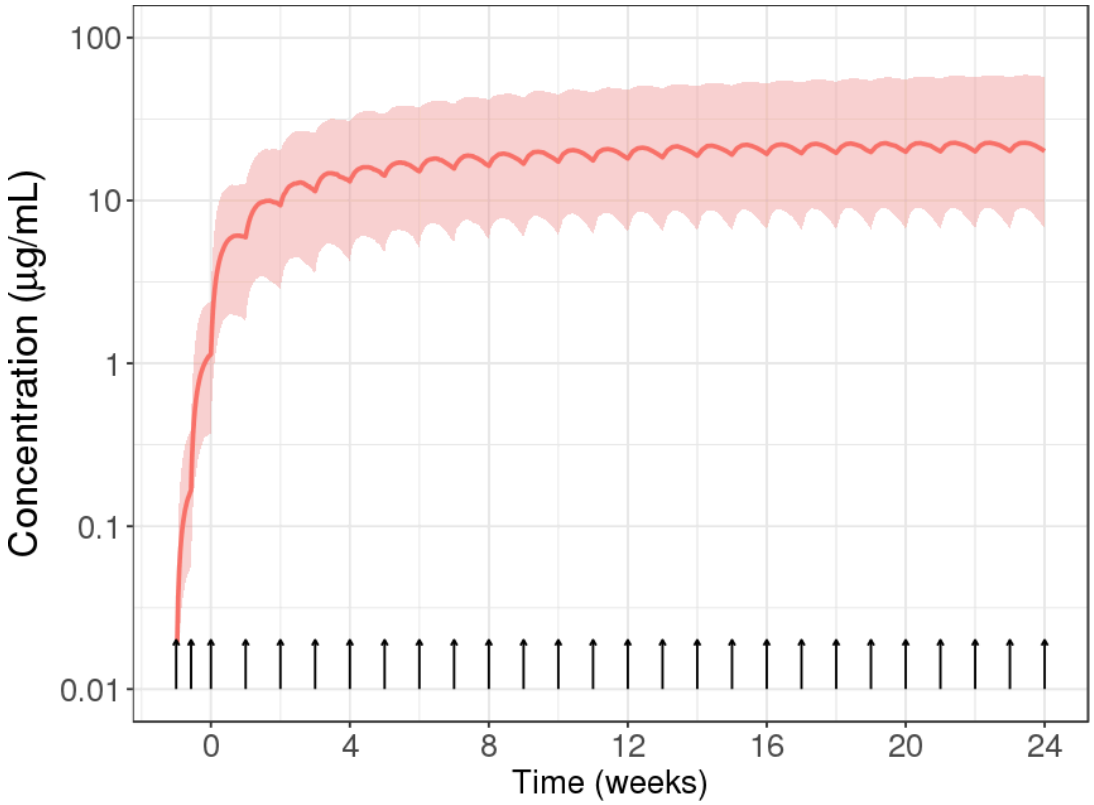
Source: Applicant's Population PK and Exposure-Response Analyses Report, Figure 7.

Figure 8: Forest Plot of Subgroup Analyses of the Predicted Steady-state Trough Concentration (Ctrough,ss) per the RP2D (Final Population PK Model)



BCMA=B cell maturation antigen; CI=confidence interval; $C_{trough,ss}$=predicted steady-state trough concentration; ECOG=Eastern Cooperative Oncology Group; IgG=immunoglobulin G; ISS=International Staging System; RP2D=recommended Phase 2 dose, ie, 1.5 mg/kg teclistamab SC administered weekly, with the first treatment dose preceded by step-up doses of 0.06 and 0.3 mg/kg; SC=subcutaneous; USA=United States of America; vs=versus.
Solid blue circle represents geometric mean ratio and error bar represents 95% CI. Dashed line represents reference value of 1. The associated values are shown on the right column. The dashed vertical lines refer to 0.8 and 1.25.
Note: Subjects in the impaired hepatic function subgroup (n=34) have mild impairment only.
Note: Analyses assumed that all subjects included in the population PK analysis dataset received 1.5 mg/kg teclistamab SC administered weekly, with the first treatment dose preceded by step-up doses of 0.06 and 0.3 mg/kg.
Source: Applicant's Population PK and Exposure-Response Analyses Report, Figure 8.

Figure 9: Simulated Teclistamab Serum Concentration-time Profiles Following RP2D of Teclistamab SC (Final PPK Model)



RP2D=recommended Phase 2 dose, ie, 1.5 mg/kg teclistamab SC administered weekly, with the first treatment dose preceded by step-up doses of 0.06 and 0.3 mg/kg; SC=subcutaneous.
Black arrows represent dosing events.
Simulations were conducted at RP2D (1.5 mg/kg teclistamab SC administered weekly, with the first treatment dose preceded by step-up doses of 0.06 and 0.3 mg/kg) using the final population PK model (n=1000). The solid red line is the simulated median trend and the pink shaded area is the 90% predictive interval.
Source: Applicant's Population PK and Exposure-Response Analyses Report, Figure 5.

The FDA's Assessment:

Overall, the Applicant's population PK (PPK) model is generally acceptable for the purposes of characterizing PK and predicting exposure following subcutaneous (SC) teclistamab administration in patients with relapsed or refractory multiple myeloma. The Reviewer evaluated potential differences in PK and exposure according to intrinsic and extrinsic patient characteristics. No clinically meaningful differences in safety or efficacy are expected due to exposure across patient subgroups.

PPK Data
The PPK analysis utilized PK data from 308 patients with relapsed or refractory multiple myeloma in Study 64007957MMY1001 (MajesTEC-1) who are described in Table 21 and Table 22 above.

Approximately 60% of patients with PK data (186/308 patients total) received the SC

recommended phase 2 dose (RP2D) of 0.06/0.3/1.5 mg/kg SC. The recommended SC dosing regimen is the same as the RP2D. The numbers of patients per route of administration and planned treatment regimen are summarized in **FDA Table 7**.

FDA Table 16: Patient Treatments and Routes of Administration in the PPK Dataset

Route of Administration	Treatment Regimen	n (%)
Intravenous Injection	0.0003 mg/kg Q2W	1 (0.3%)
	0.0006 mg/kg Q2W	1 (0.3%)
	0.0012 mg/kg Q2W	1 (0.3%)
	0.0024 mg/kg Q2W	3 (1%)
	0.0048 mg/kg Q2W	1 (0.3%)
	0.0096 mg/kg Q2W	2 (0.6%)
	0.0192 mg/kg Q2W	2 (0.6%)
	0.0192 mg/kg weekly	1 (0.3%)
	0.0384 mg/kg weekly	1 (0.3%)
	0.0192 mg/kg then 0.0384 mg/kg weekly	4 (1.3%)
	0.02 mg/kg then 0.0576 mg/kg weekly	10 (3.2%)
	0.02 mg/kg then 0.08 mg/kg weekly	12 (3.9%)
	0.01/0.06 mg/kg then 0.18 mg/kg weekly	6 (1.9%)
	0.01/0.06 mg/kg then 0.27 mg/kg weekly	12 (3.9%)
	0.02/0.0576 mg/kg then 0.08 mg/kg weekly	5 (1.6%)
	0.02/0.06 mg/kg then 0.12 mg/kg weekly	6 (1.9%)
	0.01/0.06/0.24 mg/kg then 0.72 mg/kg weekly	15 (4.9%)
Subcutaneous Injection	0.02 mg/kg then 0.08 mg/kg weekly	6 (1.9%)
	0.04/0.08 mg/kg then 0.24 mg/kg weekly	7 (2.3%)
	0.06/0.24 mg/kg then 0.72 mg/kg weekly	15 (4.9%)
	0.06/0.3 mg/kg then 1.5 mg/kg weekly*	186 (60.4%)
	0.06/0.3/1.5 mg/kg then 3 mg/kg weekly	4 (1.3%)
	0.06/0.3/1.5 mg/kg then 6 mg/kg weekly	4 (1.3%)
	2/6/30 mg then 150 mg weekly in Cycle 1 to 2 and then 300 mg Q2W in Cycle 3 and thereafter**	3 (1%)
Total (IV + SC)	**Any Treatment Regimen**	**308 (100%)**

*Recommended SC dosing regimen
**Weight-based (i.e., mg/kg) dosing was used for most patients but 3 out of 308 patients received a flat dose treatment regimen of 2/6/30 mg then 150/300 mg.
IV = intravenous; PPK = population pharmacokinetic; Q2W = every 2 weeks; SC = subcutaneous.
Source: Reviewer Analysis of Applicant's Dataset

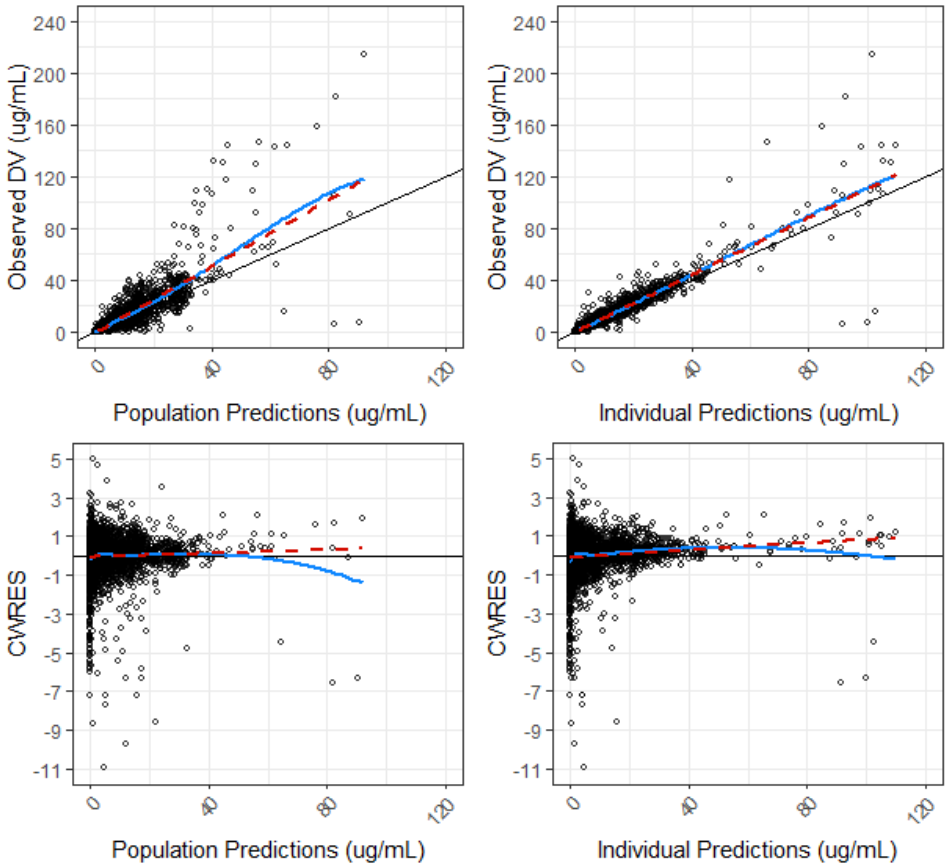
Applicant's PPK Model with PK Cutoff of 14 June 2021

Table 23 summarizes the Applicant's PPK model with a PK data cutoff of 14 June 2021. The Reviewer was able to run the Applicant's PPK model without any significant discrepancies in the final parameter estimates compared to Table 23.

The model includes both time-independent clearance (CL1) and time-dependent clearance (CL2) which decreased over time according to a first-order rate constant (K_{DES}). Intra-individual variability (IIV) for CL2 was relatively high (coefficient of variation [CV%] 132.9%). The CL2 may reflect the decrease in clearance as disease status improves with time, and the variability in baseline disease and treatment response may help explain the large IIV in CL2.

The Applicant's goodness-of-fit plots are displayed in Figure 5 above, and additional goodness-of-fit plots of relevance are provided in **FDA Figure 5**. The PPK model had a tendency to under-predict concentrations above 40 ug/mL, which is apparent in the observed concentration versus individual predicted concentration plot in **FDA Figure 5**. Although this under-prediction may be relevant with further model development or model applications, overall the goodness-of-fit plots indicate that the fit of the model is generally acceptable.

FDA Figure 5: Goodness-of-fit plots for the Population PK Model



Loess in solid blue; Linear regression in dashed red. The lower limit of quantification (LLOQ) was 0.00051 ug/mL according to clinical pharmacology final report titled "csr-cmpl-drug-conc-64007957mmy1001.pdf".
Results are shown for Applicant's PPK model with a PK data cutoff of 14 June 2021.
CWRES = conditional weighted residuals; DV = observed concentration; PK = pharmacokinetic;
PPK = population pharmacokinetic.
Source: Reviewer analysis of Applicant's Final PPK Model

The goodness-of-fit and visual predictive check (VPC) plots indicate that the Applicant's PPK model adequately characterized teclistamab PK in patients with relapsed or refractory multiple myeloma. The model is adequate for the purpose of predicting teclistamab concentrations following SC dosing in patients with relapsed or refractory multiple myeloma. Because of the model's tendency to under-predict higher concentrations, the exposure metrics of trough concentration (C_{trough}) and

average concentration (C_{ave}) may be more accurate than exposure metrics involving higher concentrations (i.e., maximum concentration [C_{max}]) when concentrations exceed 40 ug/mL.

Covariate Effects

The PPK analysis identified that body weight, ISS stage, and myeloma type have statistically significant effects on PK. The predicted impacts of these covariates on average concentration following the first treatment dose ($C_{ave,1stdose}$) and trough concentration following the 7th treatment dose ($C_{trough,7thdose}$) are displayed in Figure 7 and Figure 8, respectively, following the recommended SC dosage regimen.

Geometric mean exposures ($C_{ave,1stdose}$ and $C_{trough,7thdose}$) were numerically higher in patients with higher body weight (Figure 7 and Figure 8), although the differences between weight quartiles were less than 30% and individual predicted exposure overlapped across weight quartiles. In the submitted RP2D efficacy dataset (n=150), Overall Response Rate (ORR) generally increased as body weight increased in patients weighing up to 55 kg, patients weighing >55 to <85 kg, and patients weighing 85 kg and greater. However, subgroup analyses of efficacy did not show this trend to be statistically significant (see **Section 19.4.3.2**; see Applicant's Figure 12). The association between ORR and body weight may also be confounded by other patient factors such as baseline disease status. Current evidence does not indicate that difference in exposure according to body weight has a clinically relevant impact on ORR.

The PPK analysis also indicated that worse ISS stage was associated with higher clearance and lower exposure (Figure 7 and Figure 8). Multivariate E-R analyses (**Section 19.4.3.2**) did not identify any statistically significant differences in efficacy according to ISS stage. However, the clinical subgroup analyses of the 150 patients in the RP2D efficacy dataset (**Section 8.1.2**, Applicant's Figure 3) found that patients with baseline ISS stage I tended to have higher ORR (ISS stage I ORR = 59/79 [74.7%]) compared to stage II or stage III (ORR = 27/52 [51.9%] and ORR = 7/17 [41.2%], respectively). The ORR did not differ significantly between ISS stage II and III. ISS stage I may be associated with both higher exposure and higher ORR, but it is unclear if these are causally related or if there are additional factors that may confound the association between ISS stage, exposure, and ORR.

IgG myeloma (versus non-IgG myeloma) was associated with higher clearance and lower exposure (Figure 7 and Figure 8). However, ORR did not significantly differ by myeloma type according to the clinical efficacy subgroup analyses (**Section 8.1.2**, Applicant's Figure 3) or the multivariate E-R analyses (**Section 19.4.3.2**). No clinically relevant impacts on efficacy are expected from the differences in exposure between IgG myeloma and non-IgG myeloma.

Black and African American patients (n=25) patients have 29% higher $C_{ave,1stdose}$ (Figure 7) and 13% higher $C_{trough,7thdose}$ (Figure 8) following RP2D compared to White patients (n=260). However, the PPK model did not identify a statistically significant difference in clearance or any other PK parameter for Black and African American patients compared to White patients or patients of races other than White, Black, or African American. This suggests that the apparent difference in exposure according to race may be due to confounding with other patient characteristics or due to

the relatively small number of Black and African American patients in MajesTEC-1 (25/308 [8.1]%). Additionally, subgroup analyses of safety did not identify higher risk of safety events in patients who were Black or African American (see **Section 8.2.7 - Safety Analyses by Demographic Subgroups**). Black or African American patients are not expected to have clinically relevant differences in exposure compared to White patients.

Applicant's Updated Final PPK Model with PK Cutoff of 01 December 2021

The Applicant provided an updated PPK dataset and updated PPK model which were used to calculate population PK parameters and teclistamab exposure. The updated PPK dataset included all PK data from the 14 June 2021 PPK dataset (**FDA Table 6**) as well as PK data from 30 additional patients who were assigned to the following dose regimens:

- ☐ 1 patient with 0.06/0.3/1.5 then 3.0 mg/kg QW SC in Phase 1
- ☐ 5 patients with 0.06/0.3/1.5 then 6.0 mg/kg QW SC in Phase 1
- ☐ 7 patients with 0.03/0.09/0.3/1.5 then 6.0 mg/kg monthly SC in Phase 1
- ☐ 5 patients with 0.06/0.3/1.5 then 1.5 mg/kg QW SC in Phase 2 Cohort A
- ☐ 12 patients with 0.06/0.3/1.5 then 1.5 mg/kg QW SC in Phase 2 Cohort C

The updated PPK model had the same structure as the PPK model developed from the 14 June 2021 PPK dataset. The Reviewer was able to run the Applicant's updated final PPK model without any significant discrepancies compared to the Applicant's final parameter estimates summarized in **FDA Table 8**. Overall, PPK trends and conclusions did not appear to change significantly with the updated model. Relevant differences in PK parameters for the updated 01 Dec 2021 model (**FDA Table 8**) compared to the 14 Jun 2021 model (Table 23) are summarized below:

- ☐ Population time-independent clearance (CL1) decreased from 0.545 L/day to 0.449 L/day.
- ☐ Population CL1 was ~30% of total clearance in the original model but it is now 41% in the updated model.
- ☐ Population time-dependent clearance (CL2) increased from 0.327 L/day to 0.547 L/day.
- ☐ Population total clearance at baseline increased from 0.872 L/h to 0.996 L/h.
- ☐ C_{max} after 13th treatment dose increased from ~231 ug/mL to 271 ug/mL.

FDA Table 17: Parameter Estimates of Teclistamab for the Updated Final Population Pharmacokinetic Model using a Population PK Data Cutoff of 01 December 2021

Parameters, unit	Estimate	RSE (%)	IIV (%CV)	RSE (%)	Shrinkage (%)
CL_1 (L/day)[a]	0.449	8.87	53.6	14.3	14.4
BWT on CL_1	0.704	21.8			
IISS=II on CL_1	1.31	7.83			
IISS=III on CL_1	1.67	11.1			
TPMM2=Non-IgG on CL_1	0.689	7.76			
CL_2 (L/day)[b]	0.547	15.6	107	20.5	33.8
TPMM2=Non-IgG on CL_2	0.295	21.6			
V_1 (L)[c]	4.13	4.40	48.8	50.6	29.5
BWT on V_1	0.358	60.9			
K_{DES} (day^{-1})	0.0292	13.0			
Q (L/day)	0.0390	55.5			
V_2 (L)[d]	1.34	26.1			
BWT on V_2	1.40	25.5			
Ka (day^{-1})	0.133	7.73	45.2	32.1	44.3
F	0.718	7.38			
ADD ERR (%CV)	41.7	4.35			

ADD ERR=additive error term on the log-scale; BWT=baseline body weight in kilograms; CL_1=time-independent clearance; CL_2=clearance associated with time-dependent clearance (CL_t), which decreases over time through a first order- rate (K_{DES}); CV=coefficient of variation; F=subcutaneous bioavailability; IgG=immunoglobulin G; IISS=International Staging System (1=I, 2=II, 3=III); IIV=inter-individual variability; calculated as $(\text{variance})^{1/2} \times 100\%$; Ka=first-order absorption rate constant; K_{DES}=first-order rate constant for CL_2 decrease over time; Q=inter-compartmental clearance; RSE=relative standard error; TPMM2=multiple myeloma type (0=Non-IgG,1=IgG); V_1=volume of distribution of the central compartment; V_2=volume of distribution of the peripheral compartment.

[a] $CL_1(L/day) = 0.449 \times \left(\frac{BWT}{74}\right)^{0.704} \times 1.31^{ISS=II} \times 1.67^{ISS=III} \times 0.689^{TPMM=Non-IgG}$

[b] $CL_2(L/day) = 0.547 \times 0.295^{TPMM=Non-IgG}$

$CL = CL_1 + CL_2 \times e^{-0.0292 \times Time(in\ days)}$

[c] $V_1(L) = 4.13 \times (\frac{BWT}{74})^{0.358}$

[d] $V_2(L) = 1.34 \times (\frac{BWT}{74})^{1.40}$

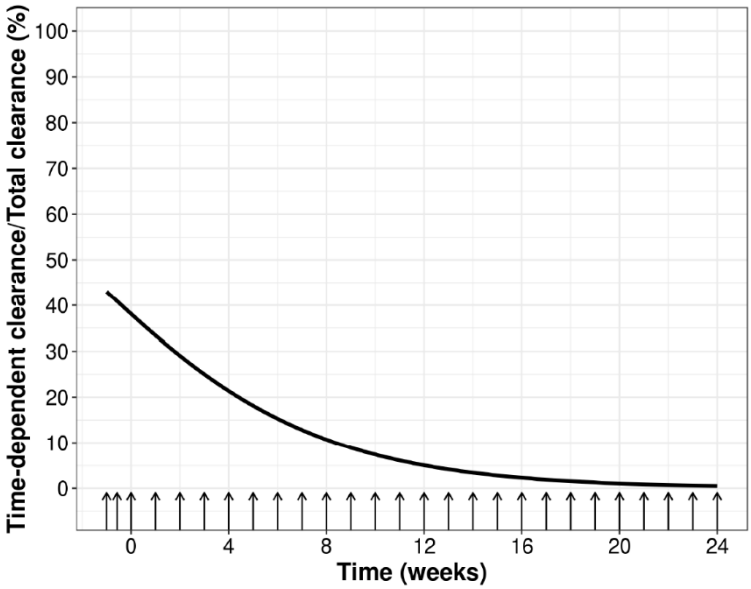
PK data cutoff = 01 December 2021.
Source: Table 1 in Applicant's Response to FDA Information Request issued 19 July 2022

PK Parameters and Predicted Exposure

The PPK model summarized in **FDA Table 7** with PK data cutoff of 01 Dec 2021 is preferred over the PPK model with PK cutoff of 14 June 2021 (Table 23) for summarizing PK parameters and predicting exposure because of the greater number of patients included as data.

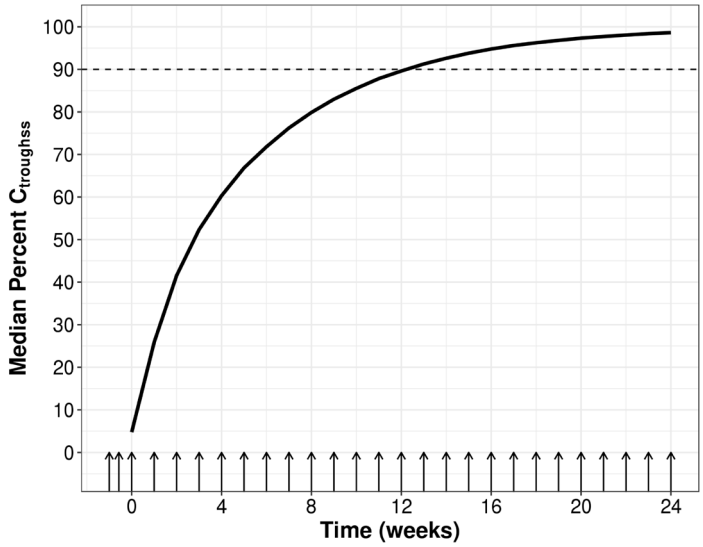
The simulated PK profile based on the Applicant's updated PPK model using PK data cutoff of 01 Dec 2021 indicates patients will achieve 90% of steady-state exposure after 12 weekly treatment doses (i.e., at the 13th weekly treatment dose). The decrease in time-dependent clearance (CL2) over time is presented in ***FDA Figure 6***. The change in median C_{trough} concentration over time following the proposed dosage is presented in **FDA Figure 7**.

FDA Figure 6: Median Percent of Time-dependent Clearance Versus Time Profiles Following the Recommended Subcutaneous Teclistamab Dosage Regimen



Simulations were conducted at the recommended SC teclistamab dosage regimen (0.06 mg/kg SC on Day -7, then 0.3 mg/kg SC on Day -4, then 1.5 mg/kg SC on Day 1 and once weekly thereafter) using the final population pharmacokinetic model (n=1,000). The solid line is the simulated median. Black arrows represent dosing events. Results are shown for Applicant's PPK model with a PK data cutoff of 01 December 2021.
PK = pharmacokinetic; PPK = population pharmacokinetic; SC = subcutaneous.
Source: Figure 2 in Applicant's Response to FDA Information Request issued 19 July 2022

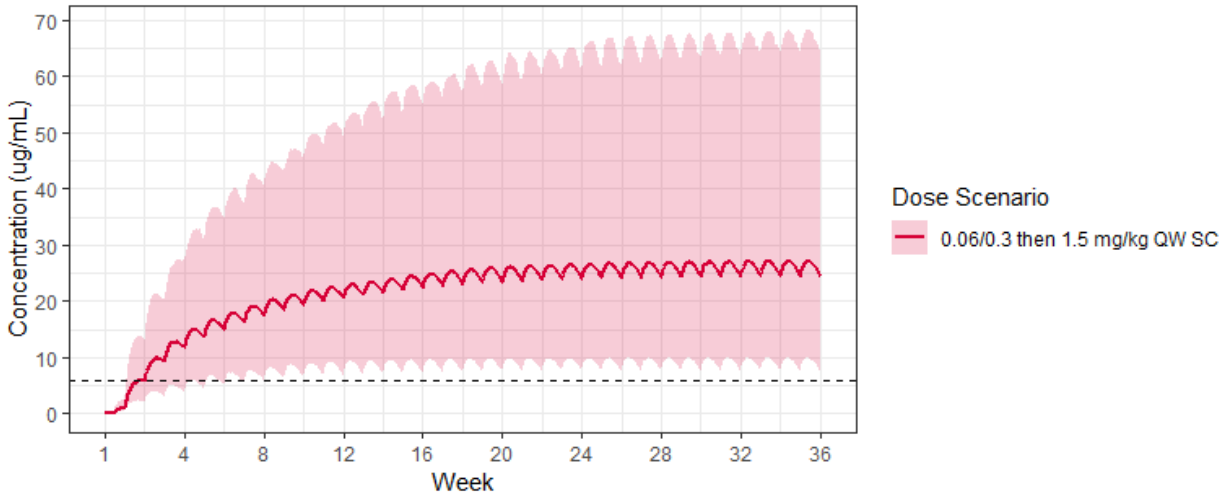
FDA Figure 7: Median Percent $C_{trough,ss}$ Versus Time Profiles Following the Recommended Subcutaneous Teclistamab Dosage Regimen



Simulations were conducted at the recommended SC teclistamab dosage regimen (0.06 mg/kg SC on Day -7, then 0.3 mg/kg SC on Day -4, then 1.5 mg/kg SC on Day 1 and once weekly thereafter) using the final population pharmacokinetic model (n=1,000). The solid line is the simulated median ratio of C_{trough} to $C_{trough,ss}$ expressed as percent. The dashed line is drawn at 90% to visualize that the steady-state was considered achieved after 12 weekly treatment doses.
Results are shown for Applicant's PPK model with a PK data cutoff of 01 December 2021.
C_{trough} = Serum teclistamab concentration prior to next dose; $C_{trough,ss}$ = Serum teclistamab concentration prior to next dose at-steady state; PK = pharmacokinetic; PPK = population pharmacokinetic; SC = subcutaneous.
Source: Figure 1 in Applicant's Response to FDA Information Request issued 19 July 2022

Following administration of 12 weekly treatment doses of teclistamab 1.5 mg/kg SC, the mean of individual simulated accumulation ratios was 4.2-fold for C_{max}, 4.1-fold for C_{trough}, and 5.3-fold for area under the concentration-time curve over the weekly dosing interval (AUC_{tau}). The predicted PK profile of teclistamab is displayed in **FDA Figure 8**. Predicted exposure and PK parameters are summarized in **FDA Table 9** and **FDA Table 10**, respectively.

FDA Figure 8: Median Teclistamab Serum Concentration over Time Predicted using the Applicant's Updated Final Population PK Model



Solid lines = median predicted concentration. Shaded region = 5th to 95th percentile.
Horizontal dashed line = Applicant's estimated EC90 from ex vivo cytotoxicity assay (6.0391 ug/mL).
Following administration of teclistamab in a virtual population of 1000 patients resampled with replacement from the 338 MajesTEC-1 patients with relapsed or refractory multiple myeloma in the 01 December 2021 PPK dataset. All patients were simulated to receive teclistamab 0.06 mg/kg SC on Day 1, 0.3 mg/kg SC on Day 4, and then 1.5 mg/kg SC on Day 7 and once weekly thereafter.
Results are shown for Applicant's PPK model with a PK data cutoff of 01 December 2021.
EC90 = 90% maximal effective concentration; PK = pharmacokinetic; PPK = population pharmacokinetic; QW = once weekly; SC = subcutaneous.
Source: Reviewer analysis of Applicant's updated PPK model and virtual patient dataset provided in response to the FDA Information Request issued 19 July 2022.

FDA Table 18: Predicted Exposure with Applicant's Proposed Dosing in Patients with Relapsed or Refractory Multiple Myeloma (MajesTEC-1)

	Teclistamab Geometric Mean (CV%)	
Exposure Parameter	**The 1st treatment dose of 1.5 mg/kg SC**	**The 13th treatment dose of 1.5 mg/kg once weekly SC (90% of steady state exposure)**
C_{max} (ug/mL)	6.34 (60%)	23.8 (55%)
C_{trough} (ug/mL)	5.77 (63%)	21.1 (63%)
AUC_{tau} (ug·h/mL)	836 (61%)	3838 (57%)

Following administration of teclistamab in a virtual population of 1000 patients resampled with replacement from the 338 MajesTEC-1 patients with relapsed or refractory multiple myeloma in the 01 December 2021 PPK dataset. All patients were simulated to receive teclistamab 0.06 mg/kg SC on Day 1, 0.3 mg/kg SC on Day 4, and then 1.5 mg/kg SC on Day 7 and once weekly thereafter.
AUC_{tau} = Area under the concentration-time curve over the weekly dosing interval; C_{max} = Maximum serum teclistamab concentration; C_{trough} = Serum teclistamab concentration prior to next dose; CV = coefficient of variation; PK = pharmacokinetic; PPK = population pharmacokinetic; SC = subcutaneous; SD = standard deviation.
Results are shown for Applicant's PPK model with a PK data cutoff of 01 December 2021.
Source: Reviewer analysis of Applicant's updated PPK model and virtual patient dataset provided in response to the FDA Information Request issued 19 July 2022.

FDA Table 19: Predicted Total Clearance and Half-life with Applicant's Proposed Dosing in Patients with Relapsed or Refractory Multiple Myeloma (MajesTEC-1)

PK Parameter	Statistic	The 1st treatment dose of 1.5 mg/kg SC	The 13th treatment dose of 1.5 mg/kg QW SC	1.5 mg/kg QW SC Steady State
Total Clearance	geometric mean (CV%)	0.7861 L/day (67.7%)	0.4741 L/day (56.6%)	0.4351 L/day (59.3%)
Distribution half-life ($t_{1/2\alpha}$)	mean (SD)	3.9 days (2.0)	5.7 days (2.4)	6.1 days (2.6)
Elimination half-life ($t_{1/2\beta}$)	mean (SD)	26.3 days (8.2)	27.7 days (8.2)	28.2 days (8.7)

Following administration of teclistamab in 338 MajesTEC-1 patients with relapsed or refractory multiple myeloma in the 01 December 2021 PPK dataset. All patients were simulated to receive teclistamab 0.06 mg/kg SC on Day 1, 0.3 mg/kg SC on Day 4, and then 1.5 mg/kg SC on Day 7 and once weekly thereafter.
Results are shown for Applicant's PPK model with a PK data cutoff of 01 December 2021.
CV = coefficient of variation; PK = pharmacokinetic; PPK = population pharmacokinetic; QW = once weekly; SC = subcutaneous; SD = standard deviation.
Source: Reviewer analysis of Applicant's updated PPK model and virtual patient dataset provided in response to the FDA Information Request issued 19 July 2022.

The median time to first response with the recommended SC dosing regimen was 1.2 months (**FDA Table 4**) which is less than the time to reach steady-state. Therefore, patients may have higher exposure after achieving first response compared to exposure before first response. The expected increase in exposure may be related to disease improvement over time.

Following discontinuation of teclistamab after the 13th treatment dose, teclistamab concentration is expected to decrease by 50% of 13th treatment dose C_{max} at a median (5th to 95th percentile) of 15.1 days (7.1 to 33 days) after the time of maximum concentration (T_{max}). Teclistamab concentration is expected to decrease by 97% of 13th treatment dose C_{max} at a median (5th to 95th percentile) of 69 days (32 to 163 days) after T_{max} (**FDA Table 11**).

FDA Table 20: Simulated Teclistamab Decrease from Cmax Following Subcutaneous Teclistamab Recommended Dosage Regimen Assuming the 4th or the 13th dose of 1.5 mg/kg as the Last Dose Given

	Mean (SD)	Median	5th-95th Percentiles
After the 4th treatment dose			
Time (days) post-T_{max} to reach			
50% of C_{max}	15.1 (8.5)	13.3	(6.4, 29.6)
90% of C_{max}	42.5 (28)	35.9	(16.4, 87.9)
% decrease from C_{max} at			
2 weeks post-T_{max}	53 (19.3)	52.6	(21.7, 85.4)
3 weeks post-T_{max}	69.4 (18.3)	71.6	(35.5, 94.7)
4 weeks post-T_{max}	79.3 (15.9)	82.9	(48.0, 97.6)
After the 13th treatment dose			
Time (days) post-T_{max} to reach			
50% of C_{max}	17 (9.5)	15.1	(7.1, 33)
90% of C_{max}	48.3 (30.9)	40.6	(18.9, 102.5)
% decrease from C_{max} at			
2 weeks post-T_{max}	48.2 (19.4)	46.4	(4.6, 95.3)
3 weeks post-T_{max}	64.8 (19.1)	66.3	(9.1, 98.3)
4 weeks post-T_{max}	75.3 (17)	78.6	(14.3, 98.9)

Following administration of teclistamab in a virtual population of 1000 patients resampled with replacement from the 338 MajesTEC-1 patients with relapsed or refractory multiple myeloma in the 01 December 2021 PPK dataset. All patients were simulated to receive teclistamab 0.06 mg/kg SC on Day 1, 0.3 mg/kg SC on Day 4, and then 1.5 mg/kg SC on Day 7 and once weekly thereafter.
C_{max} = Maximum serum teclistamab concentration; PPK = population pharmacokinetic; SC = subcutaneous; SD = standard deviation; T_{max} = time of maximum serum teclistamab concentration.
Source: Applicant's Draft USPI (Received 04 August 2022) response dated 09 August 2022

19.4.3 Exposure-Response Analysis

19.4.3.1 E-R Efficacy Executive Summary

The FDA's Assessment:

Higher ORR was associated with higher exposure (first treatment dose C_{ave} and 4th treatment dose C_{ave}) in MajesTEC-1 Phase 1 patients who received SC teclistamab at multiple different dose levels. The ORR appeared to plateau above the median exposure for the proposed treatment dose of 1.5 mg/kg SC QW.

When E-R efficacy analyses were conducted in patients who all received the same 1.5 mg/kg SC QW treatment dose, no clear exposure-efficacy associations were identified. This may be due to the relatively narrow range of exposures in a dataset containing only one dose level.

Overall, the E-R analysis of efficacy supports the proposed treatment dose of 1.5 mg/kg SC QW.

19.4.3.2 E-R Efficacy Assessment Summary

The Applicant's Position:

General Information			
Goal of ER analysis		*Explore the E-R relationship for selected efficacy endpoints, focusing on the primary endpoint of ORR, and other efficacy endpoints including DOR, PFS, and OS*	
Study Included		*64007957MMY1001*	
Endpoint		*Primary: RP2D ORR* *Secondary: Phase 1 ORR and RP2D PFS, DOR, and OS*	
No. of Patients (total, and with individual PK)		*-Efficacy Analysis Set for pivotal RP2D: 150 patients (IRC assessment based on IMWG 2016 criteria)* *-Phase 1 ORR: 72 patients (investigator assessment based on IMWG 2011 criteria)*	
Population Characteristics (Table 24)	General	*-Age median (range): 64.5 (33-84) years* *-Weight median (range): 72.5 (41-139) kg* *-88 (58.7%) male; 62 (41.3%) female* *-134 (89.3%) White; 6 (4.0%) Black or African American*	
	Pediatrics (if any)	*Not applicable*	
Dose(s) Included		*-RP2D: 1.5 mg/kg SC administered weekly, with the first treatment dose preceded by step-up doses of 0.06 and 0.3 mg/kg* *-Phase 1: SC from 0.08 mg/kg to 3 mg/kg weekly*	
Exposure Metrics Explored (range)		• *Predicted average concentration of the first treatment dose ($C_{ave,1stdose}$)* • *Predicted trough concentration after the first 4 weekly treatment doses ($C_{trough,4doses}$), ie, predose concentration of the fifth weekly treatment dose*	
Covariates Evaluated		*Body weight, type of myeloma [IgG versus non IgG], ISS, cytogenetic risk, bone marrow percent plasma cells, extramedullary plasmacytoma, soluble BCMA, total T cells, CD4+ T cells, CD8+ T cell, PD1 expression, and CD25 expression*	
Final Model Parameters		**Summary**	**Acceptability [FDA's comments]**
Model Structure		*Logistic Regression Analysis*	
Model Parameter Estimates		Table 26 *for RP2D ORR* Table 27 *for RP2D PFS, DOR and OS (for primary and major secondary endpoints)*	Multivariate analysis of ORR in patients who received the RP2D (n=150) indicated that baseline sBCMA and baseline PD1 expression may be associated with ORR (Table 26).
Model Evaluation		• *An E-R trend was observed for ORR assessed by the investigator based on IMWG 2011 criteria in SC subjects in Phase 1 (Phase 1 ORR) where ORR increased with teclistamab exposure across SC doses ranging from 0.08 to 3 mg/kg weekly, approaching plateau at the RP2D.* • *Near flat E-R trend for ORR assessed by IRC based on IMWG 2016 criteria in subjects who received the RP2D regimen (RP2D ORR). Responders and*	

	non responders had comparable and overlapping exposure range. • *The Cox proportional hazard regression of DOR, PFS, and OS versus exposure also resulted in 95% CIs containing 1, indicating no significant difference in these efficacy endpoints across the exposure tertile groups.*	
Covariates and Clinical Relevance	*The prognostic factors that were significantly associated with the ORR response in the multivariate analysis were baseline soluble BCMA and baseline PD1 expression ($p<0.05$).*	
Simulation for Specific Population	*Not applicable*	
Visualization of E-R relationships	Figure 10 *for Phase ORR logistic regression and boxplot* Figure 11 *for RP2D ORR logistic regression and boxplot* Figure 12 *for RP2D ORR forest plot* Figure 13 *for Kaplan-Meier RP2D PFS, DOR and OS* Table 25 *for baseline characteristics stratified by exposure tertiles*	In Phase 1 patients who received SC teclistamab (n=72), Cave for 1st treatment dose and Cave for 4th treatment dose were associated with improved ORR with an effect plateau at higher concentrations (Figure 10). No E-R associations were identified with secondary endpoints of PFS, DOR, or OS.
Overall Clinical Relevance for ER	A positive E-R relationship was observed for ORR assessed by investigator based on IMWG 2011 criteria in Phase 1 across the teclistamab exposure range associated with SC doses from 0.08 to 3 mg/kg weekly, and the response at the concentration range of RP2D is approaching the ORR plateau (ie, maximum response). At RP2D, responders and non responders had comparable and overlapping exposure range. In addition, duration of response, progression-free survival, and overall survival were not significantly correlated with teclistamab exposures at the RP2D dose.	Overall, the E-R efficacy analyses appear to support the proposed treatment dose of 1.5 mg/kg QW SC.

Labeling Language	Description	Acceptability [FDA's comments]
12.2 Pharmacodynamics	(b) (4)	(b) (4)

Table 24: Summary of Baseline Characteristics and Laboratory Values in the Phase 1 and RP2D ER Efficacy Analysis

	Phase 1 ORR (n=72)	Efficacy Analysis Set for Pivotal RP2D (n=150)
Age (years)		
Mean (SD)	62.7 (9.92)	64.3 (9.44)
Median	64	64.5
IQ	56.0-69.0	58.3-71.0
Range	39.0-84.0	33.0-84.0
Sex		
Female	29 (40.3%)	62 (41.3%)
Male	43 (59.7%)	88 (58.7%)
Race		
Asian	0 (0.0%)	3 (2.0%)
Black or African American	4 (5.6%)	6 (4.0%)
White	59 (81.9%)	134 (89.3%)
Other[a]	9 (12.5%)	7 (4.7%)
Weight (kg)		
Mean (SD)	77.0 (16.6)	74.3 (16.7)
Median	75.7	72.5
IQ	65.3-91.0	62.0-85.3
Range	49.0-117	41.0-139

	Phase 1 ORR (n=72)	Efficacy Analysis Set for Pivotal RP2D (n=150)
Renal Function (mL/min/1.73m^2)		
>=90	22 (30.6%)	41 (27.3%)
>=60-<90	34 (47.2%)	68 (45.3%)
>=30-<60	16 (22.2%)	40 (26.7%)
<30	0 (0.0%)	1 (0.7%)
Hepatic Function		
Normal	69 (95.8%)	130 (86.7%)
Mild impairment	3 (4.2%)	20 (13.3%)
Type of Myeloma		
IgG	36 (50.0%)	81 (54.0%)
Non-IgG	36 (50.0%)	69 (46.0%)
Baseline ISS		
I	36 (50.0%)	79 (52.7%)
II	24 (33.3%)	52 (34.7%)
III	11 (15.3%)	17 (11.3%)
Not reported	1 (1.4%)	2 (1.3%)
Cytogenetic Risk		
Standard risk	46 (63.9%)	97 (64.7%)
High risk	17 (23.6%)	36 (24.0%)
Not reported	9 (12.5%)	17 (11.3%)

	Phase 1 ORR (n=72)	Efficacy Analysis Set for Pivotal RP2D (n=150)
Baseline Bone Marrow % Plasma Cells		
<= 30	47 (65.3%)	103 (68.7%)
>30 - <60	8 (11.1%)	28 (18.7%)
>= 60	12 (16.7%)	14 (9.3%)
Not reported	5 (6.9%)	5 (3.3%)
Baseline Extramedullary Plasmacytoma		
0	61 (84.7%)	123 (82.0%)
>=1	11 (15.3%)	27 (18.0%)
Baseline Soluble BCMA (ng/mL)		
Mean (SD)	149 (187)	156 (198)
Median	85.4	93.2
IQ	33.8-160	31.9-170
Range	3.59-1030	0.00100-1030
Not reported n(%)	3 (4.2%)	3 (2.0%)
Baseline PD1 Expression (%)		
Mean (SD)	25.5 (16.9)	24.4 (14.0)
Median	22.5	22.1
IQ	10.1-34.9	13.2-32.6
Range	0.400-66.1	3.00-76.2
Not reported n(%)	5 (6.9%)	7 (4.7%)
Baseline CD25 Expression (%)		
Mean (SD)	12.0 (9.24)	11.6 (7.25)
Median	8.2	9.50
IQ	5.00-17.6	6.35-15.8
Range	1.20-39.5	1.20-38.9
Not reported n(%)	5 (6.9%)	7 (4.7%)
Baseline CD4+ T Cells (/µL)		
Mean (SD)	221 (194)	222 (166)
Median	167	168
IQ	109-262	105-282
Range	16.2-1180	11.2-739
Not reported n(%)	8 (11.1%)	72 (48.0%)
Baseline CD8+ T Cells (/µL)		
Mean (SD)	356 (318)	253 (260)
Median	260	165
IQ	125-436	83.0-330
Range	6.40-1380	1.10-1360
Not reported n(%)	4 (5.6%)	7 (4.7%)
Baseline Total T Cells (/µL)		
Mean (SD)	666 (434)	554 (419)
Median	539	418
IQ	328-879	242-793
Range	44.2-1830	16.9-1880
Not reported n(%)	4 (5.6%)	7 (4.7%)

BCMA=B cell maturation antigen; CD=cluster of differentiation; IgG=immunoglobulin G; IQ=interquartile range; ISS=International Staging System; n=number of subjects; PD1=programmed cell death protein 1

[a] Other race category included Multiple, Other and Not reported.

Table 25: Covariate Distribution over Cave,1d Tertiles for All Subjects Included in the RP2D ER Efficacy Analysis

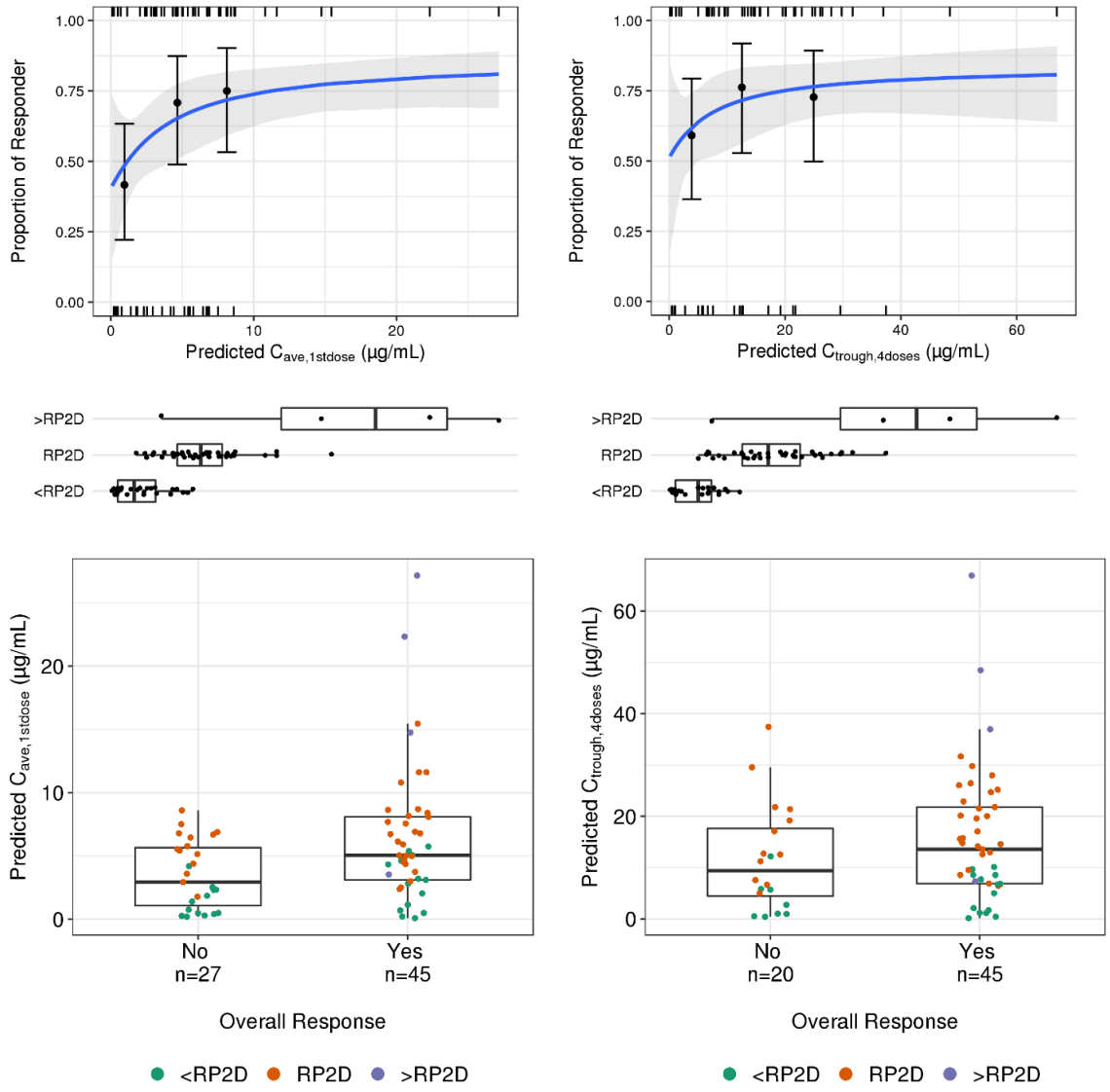
	$C_{ave,1stdose}$			$C_{trough,4doses}$		
	Tertile 1 (n=50)	Tertile 2 (n=50)	Tertile 3 (n=50)	Tertile 1 (n=45)	Tertile 2 (n=44)	Tertile 3 (n=44)
Age (years)						
Mean (SD)	66.2 (8.40)	63.2 (9.10)	63.4 (10.6)	64.4 (9.82)	63.0 (10.3)	65.2 (8.69)
Median	67	62	64	64	64.5	65.5
IQ	62.0-72.0	58.0-70.8	57.5-71.0	58.0-72.0	58.0-68.0	59.0-72.3
Range	47.0-82.0	40.0-80.0	33.0-84.0	39.0-82.0	33.0-84.0	49.0-80.0
Sex						
Female	27 (54.0%)	21 (42.0%)	14 (28.0%)	25 (55.6%)	17 (38.6%)	15 (34.1%)
Male	23 (46.0%)	29 (58.0%)	36 (72.0%)	20 (44.4%)	27 (61.4%)	29 (65.9%)
Race						
Asian	1 (2.0%)	0 (0.0%)	2 (4.0%)	1 (2.2%)	1 (2.3%)	1 (2.3%)
Black or African American	0 (0.0%)	3 (6.0%)	3 (6.0%)	1 (2.2%)	1 (2.3%)	4 (9.1%)
White	47 (94.0%)	46 (92.0%)	41 (82.0%)	40 (88.9%)	40 (90.9%)	37 (84.1%)
Other	2 (4.0%)	1 (2.0%)	4 (8.0%)	3 (6.7%)	2 (4.5%)	2 (4.5%)
Weight (kg)						
Mean (SD)	68.8 (14.2)	74.2 (16.4)	79.9 (17.7)	70.3 (15.7)	76.5 (15.4)	76.8 (18.7)
Median	67.7	73.5	76	68.2	74.9	73
IQ	60.0-74.4	61.3-86.7	70.9-88.5	60.2-76.5	65.8-90.0	64.3-85.5
Range	46.0-118	41.0-107	49.0-139	44.9-118	41.0-104	49.0-139
Renal Function (mL/min/1.73m^2)						
>=90	13 (26.0%)	13 (26.0%)	15 (30.0%)	11 (24.4%)	12 (27.3%)	16 (36.4%)
>=60-<90	24 (48.0%)	22 (44.0%)	22 (44.0%)	23 (51.1%)	18 (40.9%)	18 (40.9%)
>=30-<60	13 (26.0%)	14 (28.0%)	13 (26.0%)	10 (22.2%)	14 (31.8%)	10 (22.7%)
<30	0 (0.0%)	1 (2.0%)	0 (0.0%)	1 (2.2%)	0 (0.0%)	0 (0.0%)
Hepatic Function						
Normal	43 (86.0%)	44 (88.0%)	43 (86.0%)	38 (84.4%)	39 (88.6%)	42 (95.5%)
Mild impairment	7 (14.0%)	6 (12.0%)	7 (14.0%)	7 (15.6%)	5 (11.4%)	2 (4.5%)
Type of Myeloma						
IgG	42 (84.0%)	30 (60.0%)	9 (18.0%)	39 (86.7%)	28 (63.6%)	5 (11.4%)
Non-IgG	8 (16.0%)	20 (40.0%)	41 (82.0%)	6 (13.3%)	16 (36.4%)	39 (88.6%)
Baseline ISS						
I	22 (44.0%)	24 (48.0%)	33 (66.0%)	17 (37.8%)	27 (61.4%)	29 (65.9%)
II	22 (44.0%)	18 (36.0%)	12 (24.0%)	23 (51.1%)	9 (20.5%)	12 (27.3%)
III	5 (10.0%)	8 (16.0%)	4 (8.0%)	5 (11.1%)	6 (13.6%)	3 (6.8%)
Not reported	1 (2.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)	2 (4.5%)	0 (0.0%)
Cytogenetic Risk						
Standard risk	32 (64.0%)	29 (58.0%)	36 (72.0%)	30 (66.7%)	29 (65.9%)	26 (59.1%)
High risk	12 (24.0%)	13 (26.0%)	11 (22.0%)	7 (15.6%)	11 (25.0%)	13 (29.5%)
Not reported	6 (12.0%)	8 (16.0%)	3 (6.0%)	8 (17.8%)	4 (9.1%)	5 (11.4%)
Baseline Bone Marrow % Plasma Cells						
<= 30	31 (62.0%)	34 (68.0%)	38 (76.0%)	31 (68.9%)	32 (72.7%)	34 (77.3%)
>30 - <60	12 (24.0%)	8 (16.0%)	8 (16.0%)	8 (17.8%)	8 (18.2%)	5 (11.4%)
>= 60	7 (14.0%)	5 (10.0%)	2 (4.0%)	5 (11.1%)	3 (6.8%)	2 (4.5%)

	$C_{ave,1stdose}$			$C_{trough,4doses}$		
	Tertile 1 (n=50)	Tertile 2 (n=50)	Tertile 3 (n=50)	Tertile 1 (n=45)	Tertile 2 (n=44)	Tertile 3 (n=44)
Not reported	0 (0.0%)	3 (6.0%)	2 (4.0%)	1 (2.2%)	1 (2.3%)	3 (6.8%)
Baseline Extramedullary Plasmacytoma						
0	42 (84.0%)	37 (74.0%)	44 (88.0%)	39 (86.7%)	36 (81.8%)	39 (88.6%)
>=1	8 (16.0%)	13 (26.0%)	6 (12.0%)	6 (13.3%)	8 (18.2%)	5 (11.4%)
Baseline Soluble BCMA (ng/mL)						
Mean (SD)	148 (207)	156 (177)	164 (213)	132 (148)	109 (153)	141 (147)
Median	101	95.2	87.4	106	71.7	97.2
IQ	40.9-148	34.4-179	23.4-203	47.9-151	25.1-105	26.1-197
Range	5.78-1030	8.27-818	0.00100-969	10.0-818	5.78-842	3.59-589
Not reported n(%)	1 (2.0%)	2 (4.0%)	0 (0%)	0 (0%)	2 (4.5%)	1 (2.3%)
Baseline PD1 Expression (%)						
Mean (SD)	24.7 (14.7)	25.0 (13.8)	23.6 (13.8)	23.4 (13.7)	23.8 (10.6)	22.7 (16.2)
Median	22	24.2	21	22.4	22.8	18.1
IQ	13.7-31.3	13.5-32.9	13.3-34.1	12.5-30.8	15.2-32.5	10.5-31.9
Range	5.90-66.1	4.10-76.2	3.00-54.5	4.10-64.1	6.50-46.5	3.20-76.2
Not reported n(%)	1 (2.0%)	4 (8.0%)	2 (4.0%)	1 (2.2%)	3 (6.8%)	2 (4.5%)
Baseline CD25 Expression (%)						
Mean (SD)	10.9 (6.57)	11.2 (5.80)	12.7 (8.99)	11.8 (6.94)	9.80 (6.68)	11.8 (7.33)
Median	8.6	9.65	9.95	8.8	8.6	9.8
IQ	6.40-13.9	6.88-15.0	5.55-18.2	6.35-15.9	5.60-10.6	6.40-17.3
Range	2.30-25.4	1.20-24.5	1.70-38.9	3.10-25.4	2.60-38.9	1.20-29.0
Not reported n(%)	1 (2.0%)	4 (8.0%)	2 (4.0%)	1 (2.2%)	3 (6.8%)	2 (4.5%)
Baseline CD4+ T Cells (/µL)						
Mean (SD)	247 (191)	239 (179)	191 (130)	259 (200)	205 (135)	212 (159)
Median	181	167	136	180	170	190
IQ	123-342	106-293	100-264	116-398	110-259	98.4-265
Range	13.6-739	21.3-606	11.2-489	13.6-739	48.8-606	21.3-586
Not reported n(%)	24 (48.0%)	29 (58.0%)	19 (38.0%)	19 (42.2%)	26 (59.1%)	18 (40.9%)
Baseline CD8+ T Cells (/µL)						
Mean (SD)	242 (237)	262 (274)	255 (273)	250 (243)	280 (275)	268 (274)
Median	171	176	152	186	224	138
IQ	91.5-313	82.8-336	71.0-319	81.5-335	91.5-338	88.6-369
Range	6.00-968	16.0-1360	1.10-1180	6.00-1090	18.8-1360	18.3-1180
Not reported n(%)	1 (2.0%)	4 (8.0%)	2 (4.0%)	1 (2.2%)	3 (6.8%)	3 (6.8%)
Baseline Total T Cells (/µL)						
Mean (SD)	537 (407)	586 (409)	540 (445)	575 (453)	561 (374)	582 (459)
Median	409	539	362	413	441	422
IQ	216-751	266-778	232-790	236-858	266-714	241-836
Range	44.2-1620	21.0-1880	16.9-1830	44.2-1880	95.5-1750	71.0-1830
Not reported n(%)	1 (2.0%)	4 (8.0%)	2 (4.0%)	1 (2.2%)	3 (6.8%)	3 (6.8%)

BCMA=B cell maturation antigen; CD=cluster of differentiation; IgG=immunoglobulin G; IQ=interquartile range; ISS=International Staging System; n=number of subjects; PD1=programmed cell death protein 1

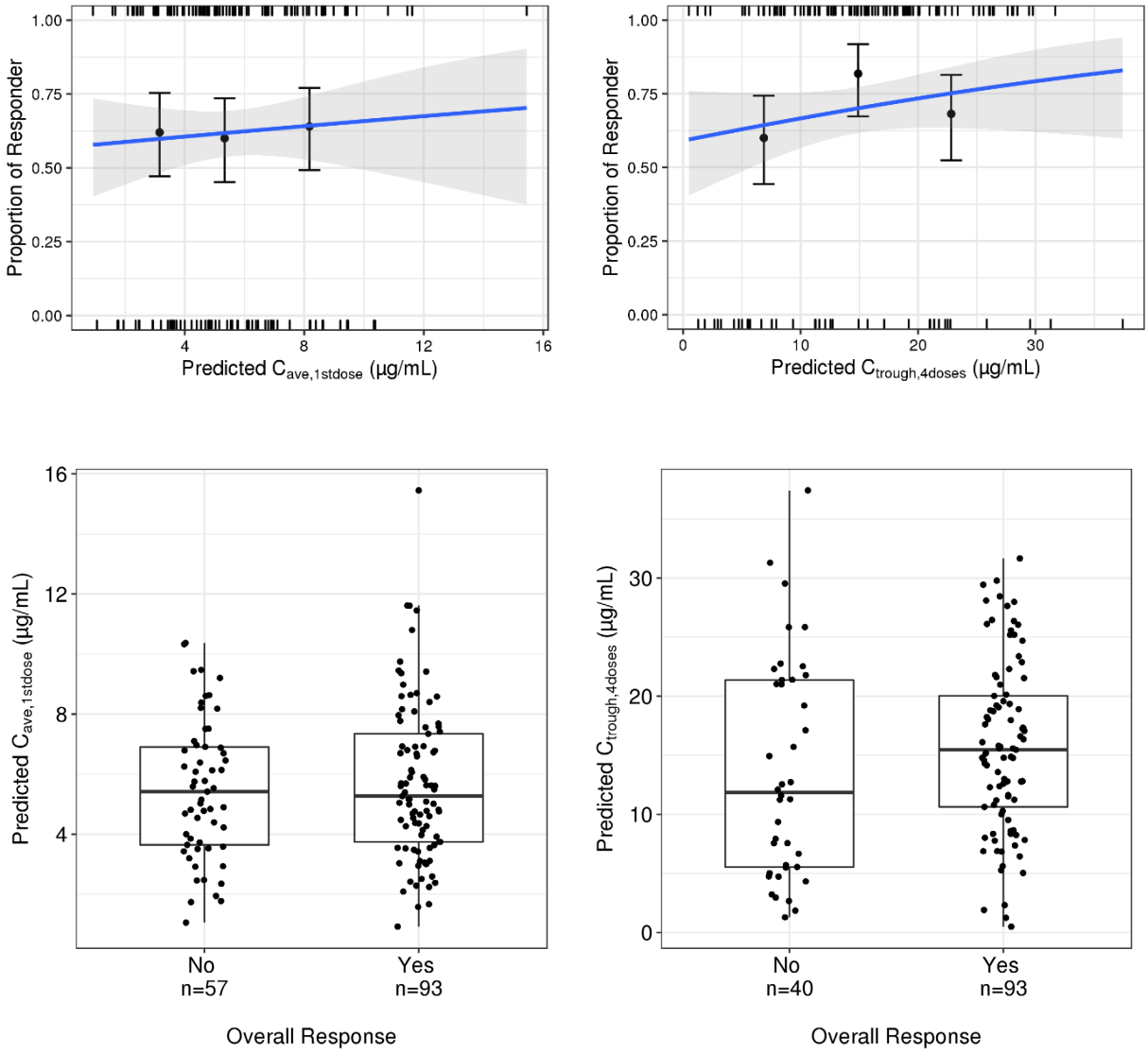
[a] Other race category included Multiple, Other and Not reported.

Figure 10: E-R Relationship of the Overall Response in the Phase 1 SC Subjects (Phase 1 ORR; R2PD and non-RP2D) Versus the Predicted Cave,1stdose and Ctrough,4doses (Investigator Assessment, 2011 IMWG)



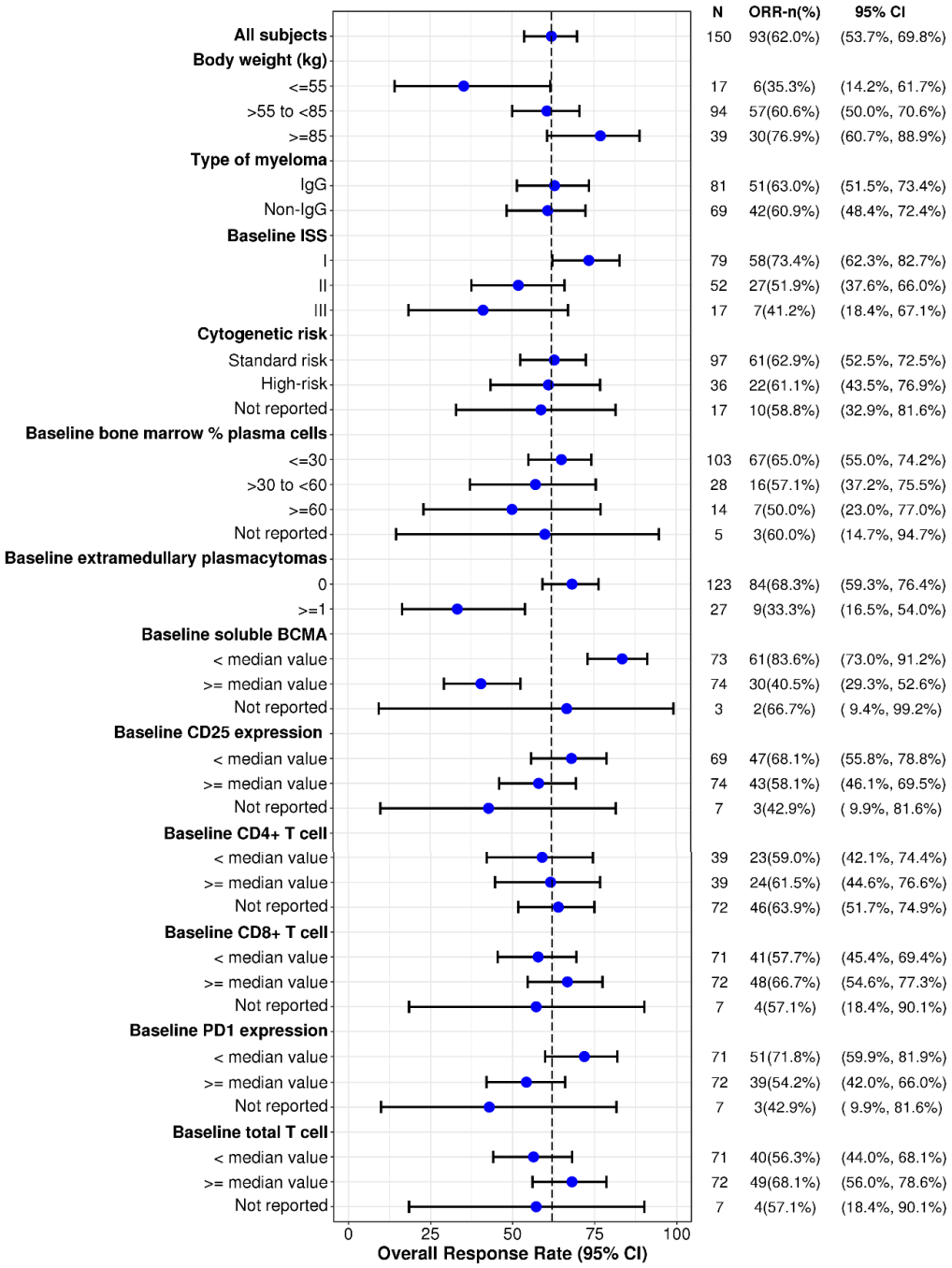
$C_{ave,1stdose}$=average concentration during the first treatment dose; CI=confidence interval; $C_{trough,4doses}$=trough concentration after the first 4 weekly treatment doses, ie, predose concentration of the fifth weekly treatment dose; E-R=exposure-response; IMWG=International Myeloma Working Group; n=number of subjects; ORR=overall response rate; RP2D=recommended Phase 2 dose, which is 1.5 mg/kg teclistamab SC administered weekly, with the first treatment dose preceded by step-up doses of 0.06 and 0.3 mg/kg; SC=subcutaneous.
Top panel: Error bars are the 95% CI of ORR in the respective exposure tertile groups. Shaded areas of the logistic regression plots represent the 95% CI of the predicted ORR. Short vertical lines at the lower and upper part of the plotting area represents the exposure metrics in non-responders and responders, respectively. Bottom panel: dots are the individual exposure metrics predicted based on actual dosing and individual population pharmacokinetic model parameter estimates.
Source: Applicant's Population PK and Exposure-Response Analyses Report, Figure 13.

Figure 11: E-R Relationship of the Overall Response in the Pooled RP2D Subjects (RP2D ORR) Versus the Predicted Cave,1stdose and Ctrough,4doses (IRC Assessment, 2016 IMWG)



$C_{ave,1stdose}$=average concentration during the first treatment dose; CI=confidence interval; $C_{trough,4doses}$=predicted trough concentration after the first 4 weekly treatment doses ie, predose concentration of the fifth weekly treatment dose; E-R=exposure-response; IMWG=International Myeloma Working Group; IRC=Independent Review Committee; ORR=overall response rate; RP2D=recommended Phase 2 dose, which is 1.5 mg/kg teclistamab SC administered weekly, with the first treatment dose preceded by step-up doses of 0.06 and 0.3 mg/kg; SC=subcutaneous.
Top panel: Error bars are the 95% CI of ORR in the respective exposure tertile groups. Shaded areas of the logistic regression plots represent the 95% CI of the predicted ORR. Short vertical lines at the lower and upper part of the plotting area represents the exposure metrics in non-responders and responders, respectively. Bottom panel: black dots are the individual exposure metrics predicted based on actual dosing and individual population PK model parameter estimates.
Source: Applicant's Population PK and Exposure-Response Analyses Report, Figure 9.

Figure 12: Forest Plot of Subgroup Analysis on RP2D ORR Versus Baseline Characteristics



BCMA=B cell maturation antigen; CD=cluster of differentiation; CI=confidence interval; IgG=immunoglobulin G; ISS=International Staging System; N=number of subjects; ORR=overall response rate; PD1=programmed cell death protein 1; RP2D=recommended Phase 2 dose, which is 1.5 mg/kg teclistamab SC administered weekly, with the first treatment dose preceded by step-up doses of 0.06 and 0.3 mg/kg; SC=subcutaneous.

Solid blue circle represents geometric mean ratio and error bar represents 95% CI. The dashed vertical line shows the overall RP2D ORR of 62%.

Source: Applicant's Population PK and Exposure-Response Analyses Report, Figure 10.

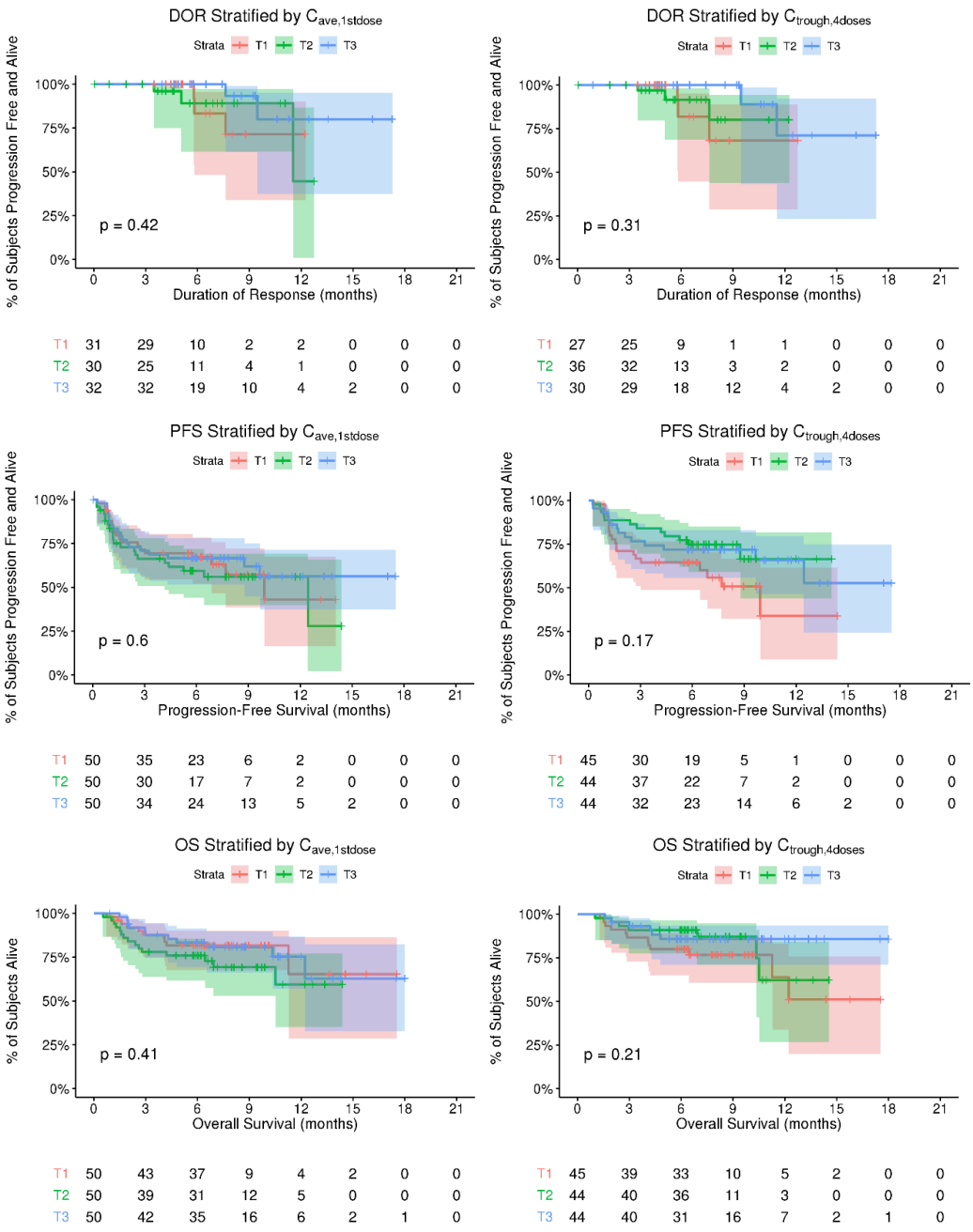
Table 26: Results of the Logistic Regression Analyses for RP2D ORR

Univariate Analyses with $C_{ave,1stdose}$		Odds Ratio	95% CI	p-value
$C_{ave,1stdose}$ (per µg/mL)		1.04	0.91-1.19	0.58
Univariate Analyses with $C_{trough,4doses}$		Odds Ratio	95% CI	p-value
$C_{trough,4doses}$ (per µg/mL)		1.03	0.98-1.09	0.19
Multivariate Analyses (significant predictors only, as continuous endpoint)		Odds Ratio	95% CI	p-value
Baseline soluble BCMA (per ng/mL)		0.99	0.99-0.996	**<0.001**
Baseline PD1 expression (per %T cell)		0.96	0.93-0.99	**0.016**
Multivariate Analyses (significant predictors only, as categorical endpoint)	N	Odds Ratio	95% CI	p-value
Baseline soluble BCMA				
≥ median value vs < median value	74 vs 73	0.12	0.05-0.27	**<0.001**
Not reported vs < median value	3 vs 73	0.29	0.02-7.42	0.36
Baseline PD1 expression				
≥ median value vs < median value	72 vs 71	0.37	0.16-0.82	**0.016**
Not reported vs < median value	7 vs 71	0.44	0.07-2.42	0.35

BCMA=B cell maturation antigen; $C_{ave,1stdose}$=average concentration during the first treatment dose; CI=confidence interval; $C_{trough,4doses}$=predicted trough concentration after the first 4 weekly treatment doses, ie, predose concentration of the fifth weekly treatment dose; N=number of subjects; ORR=overall response rate; PD1=programmed cell death protein 1; RP2D=recommended Phase 2 dose, which is 1.5 mg/kg teclistamab SC administered weekly, with the first treatment dose preceded by step-up doses of 0.06 and 0.3 mg/kg; SC=subcutaneous; vs=versus.

Source: Applicant's Population PK and Exposure-Response Analyses Report, Table 7.

Figure 13: Kaplan-Meier Curves for DOR, PFS, and OS Stratified by Predicted Cave,1stdose and Ctrough,4doses Tertiles for Pivotal RP2D



$C_{ave,1stdose}$=average concentration during the first treatment dose; $C_{trough,4doses}$=predicted trough concentration after the first 4 weekly treatment doses, ie, predose concentration of the fifth weekly treatment dose; DOR=duration of response; OS=overall survival; PFS=progression-free survival; RP2D=recommended Phase 2 dose, which is 1.5 mg/kg teclistamab SC administered weekly, with the first treatment dose preceded by step-up doses of 0.06 and 0.3 mg/kg; SC=subcutaneous; T1=lowest exposure tertile group; T2=middle exposure tertile group; T3=highest exposure tertile group.
Numbers below the plots represent the number of subjects at risk at each timepoint.
Source: Applicant's Population PK and Exposure-Response Analyses Report, Figure 11.

Table 27: RP2D DOR, PFS, and OS Kaplan-Meier and Cox Proportional Hazards Estimates

RP2D Efficacy Variables		Number of Subjects	Median Time (95% CI)	Hazard Ratio[a] (95% CI)	p-value	Concordance
DOR	Overall	150	NE (11.5-NE)			
	Stratified by $C_{ave,1stdose}$				0.427	0.697
	T1 [0.923,4.39]	50	NE (5.82-NE)	-		
	T2 (4.39,6.62]	50	11.5 (11.5-NE)	0.487 (0.136-1.74)		
	T3 (6.62,15.4]	50	NE (9.46-NE)	0.652 (0.2-2.13)		
	Stratified by $C_{trough,4doses}$				0.31	0.67
	T1 [0.492,11.2]	45	NE (5.82-NE)	-		
	T2 (11.2,18.7]	44	NE (7.62-NE)	0.385 (0.105-1.41)		
	T3 (18.7,37.4]	44	NE (9.46-NE)	0.784 (0.241-2.55)		
PFS	Overall	150	12.5 (8.77-NE)			
	Stratified by $C_{ave,1stdose}$				0.593	0.536
	T1 [0.923,4.39]	50	9.92 (6.87-NE)	-		
	T2 (4.39,6.62]	50	12.5 (4.17-NE)	0.928 (0.587-1.47)		
	T3 (6.62,15.4]	50	NE (8.77-NE)	0.805 (0.519-1.25)		
	Stratified by $C_{trough,4doses}$				0.168	0.564
	T1 [0.492,11.2]	45	9.92 (3.02-NE)	-		
	T2 (11.2,18.7]	44	NE (8.77-NE)	0.698 (0.428-1.14)		
	T3 (18.7,37.4]	44	NE (9.66-NE)	1.33 (0.774-2.29)		
OS	Overall	150	NE (12.2-NE)			
	Stratified by $C_{ave,1stdose}$				0.406	0.564
	T1 [0.923,4.39]	50	NE (11.3-NE)	-		
	T2 (4.39,6.62]	50	NE (10.5-NE)	0.995 (0.542-1.83)		
	T3 (6.62,15.4]	50	NE (12.2-NE)	0.692 (0.403-1.19)		
	Stratified by $C_{trough,4doses}$				0.208	0.571
	T1 [0.492,11.2]	45	NE (11.3-NE)	-		
	T2 (11.2,18.7]	44	NE (10.3-NE)	0.562 (0.28-1.13)		
	T3 (18.7,37.4]	44	NE (NE-NE)	1.11 (0.538-2.31)		

$C_{ave,1stdose}$=average concentration during the first treatment dose; CI=confidence interval; $C_{trough,4doses}$=trough concentration after the first 4 weekly treatment doses, ie, predose concentration of the fifth weekly treatment dose; DOR=duration of response; NE=not estimable; RP2D=recommended Phase 2 dose, ie, 1.5 mg/kg teclistamab SC administered weekly with the first treatment dose preceded by step-up doses of 0.06 and 0.3 mg/kg; OS=overall survival; PFS=progression-free survival; p-val=p-value from log rank test; SC=subcutaneous; T1=lowest exposure tertile group; T2=middle exposure tertile group; T3=highest exposure tertile group. The concentration ranges for each tertile group are in the units of µg/mL.

[a] Hazard ratio were calculated with T1 as the reference.

Source: Applicant's Population PK and Exposure-Response Analyses Report, Attachment 29.

The FDA's Assessment:

E-R efficacy analyses were performed separately for two different E-R datasets:

- MajesTEC-1 Phase 1 patients with SC dosing (n=72).
- MajesTEC-1 Phase 1 patients with SC dosing + Phase 2 Cohort A patients (n=150).

The reviewer also compared ORR across exposure quartiles in the primary efficacy dataset of Phase 2 Cohort A patients (n=110). The selection of the primary efficacy dataset is discussed in **Section 8.1.1 – 64007957MMY1001(MajesTEC-1**).

In all E-R efficacy analyses, individual exposure was predicted using the PPK model developed from PK data with cutoff of 14 June 2021 (**Section 19.4.2.2**) and actual dosing information for each patient.

MajesTEC-1 Phase 1 Patients with SC Dosing Regimens

The Applicant's Phase 1 ORR dataset included 72 patients who received SC treatment doses from 0.08 mg/kg up to 3 mg/kg once weekly. Baseline characteristics for patients in the Phase 1 ORR sample are summarized in Table 24.

Higher average concentration following the first weekly treatment dose ($C_{ave,1stdose}$) and higher trough concentration following the 4th weekly treatment dose ($C_{trough,4doses}$) were both associated with higher ORR (investigator assessment, IMWG 2011 criteria) in patients who received SC teclistamab in Phase 1 (see Figure 10). The ORR appeared to plateau above the median exposure in Phase 1 patients who received the SC RP2D (n=40).

Although E-R efficacy data is limited at higher exposures, the Phase 1 E-R analysis suggests that treatment doses above the RP2D will not result in higher ORR.

MajesTEC-1 Pooled SC RP2D Phase 1 Patients + Phase 2 Cohort A Patients

The RP2D E-R efficacy dataset included 150 patients who received the RP2D in Phase 1 or in Phase 2 Cohort A. Baseline characteristics for patients in the RP2D E-R efficacy sample are summarized overall in Table 24 and by exposure tertile in Table 25.

The E-R analysis did not identify any clear associations between exposure ($C_{ave,1stdose}$ or $C_{trough,4doses}$) and IRC-assessed ORR (Figure 11), progression-free survival, duration of response, or overall survival (Figure 13 and Table 27) in the pooled RP2D E-R dataset.

The subgroup analysis in Figure 12 shows that lower baseline soluble B cell maturation antigen (sBCMA) and lower baseline PD-1 expression may be associated with higher ORR. This was supported by the multivariate logistic regression analysis which found statistically significant associations between ORR and sBCMA as well as PD-1 expression while individual exposure did not have any associations with ORR (Table 26).

The E-R efficacy analysis may not have identified any clear associations between exposure and ORR due to the relatively limited exposure range, as all patients in the dataset received the same treatment regimen (RP2D). Additionally, the Applicant's analysis of the RP2D E-R efficacy sample pools MajesTEC-1 phase 1 and phase 2 patients together when efficacy results for phase 1 and

phase 2 should be separated [see **Section 8.1.1 – 64007957MMY1001(MajesTEC-1**)]. Differences between study phases may act as confounding factors and impact the E-R efficacy results.

MajesTEC-1 Phase 2 Cohort A Patients

In the primary efficacy dataset of patients in Phase 2 Cohort A (n=120), E-R data was available for a total of 110/120 patients. There were no clear trends in IRC-assessed ORR across $C_{ave,1stdose}$ quartiles, as shown in **FDA Table 12**. The lack of identifiable E-R associations may be due to the limited exposure range, as all patients in the dataset received the same treatment regimen (i.e., the RP2D).

FDA Table 21: ORR versus Cave,1stdose Quartile in the MajesTEC-1 Phase 2 Cohort A E-R Efficacy Dataset

Response	$C_{ave,1stdose}$ Q1 (n=28) n (%)	$C_{ave,1stdose}$ Q2 (n=27) n (%)	$C_{ave,1stdose}$ Q3 (n=27) n (%)	$C_{ave,1stdose}$ Q4 (n=28) n (%)
Best Response is Partial Response or better	18 (64.3%)	16 (59.3%)	19 (70.4%)	15 (53.6%)
Best Response worse than Partial Response	9 (32.1%)	11 (40.7%)	8 (29.6%)	9 (32.1%)
Not evaluable or Not applicable	1 (3.6%)	0	0	4 (14.3%)

Q1 = 0.92 to <3.551 ug/mL; Q2 = 3.55 to <5.031 ug/mL; Q3 = 5.03 to <6.911 ug/mL; Q4 = 6.91 to 11.451 ug/mL.
Individual $C_{ave,1stdose}$ was predicted using the Applicant's final PPK model and actual dosing information for each patient in the Phase 2 Cohort A dataset.
For patients in MajesTEC-1 Phase 2, ORR was assessed by IRC based on IMWG 2016 criteria. Efficacy data cutoff date was 09 November 2021.
$C_{ave,1stdose}$ = average concentration following the first weekly treatment dose (i.e., after step-up doses have been administered) up until the second weekly treatment dose; E-R = exposure-response; IMWG = International Myeloma Working Group; ORR = overall response rate; PPK = population pharmacokinetic; Q = Quartile.
Source: Reviewer analysis of Applicant's E-R Dataset

Overall, the E-R efficacy analyses appear to support the proposed treatment dose of 1.5 mg/kg QW SC.

19.4.3.3 E-R Safety Executive Summary

The FDA's Assessment:

The E-R safety analysis did not identify any safety concerns with the proposed 1.5 mg/kg QW SC treatment dose.

The reviewer also conducted exploratory E-R analysis of CRS occurring with step-up dose 1 or step-up dose 2, and no safety concerns were identified for the proposed 0.06/0.3/1.5 mg/kg SC step-up dosing regimen. The exploratory E-R analysis of CRS supported the need for a step-up dosing regimen prior to the weekly treatment dosing in order to mitigate the risk of CRS. Additionally, multivariate analyses suggest that tocilizumab administration to treat CRS with step-up dose 1 may impact the CRS rate with step-up dose 2.

19.4.3.4 E-R Safety Assessment Summary

The Applicant's Position:

General Information		
Goal of ER analysis		*Explore the E-R relationship for selected AEs, including Grade ≥3 anemia, neutropenia, lymphopenia, thrombocytopenia, and infection in subjects who received teclistamab SC*
Study Included		*64007957MMY1001*
Population Included		*Adult subjects with relapsed or refractory multiple myeloma*
Endpoint		*Grade ≥3 TEAE of anemia, neutropenia, lymphopenia, thrombocytopenia, and infection*
No. of Patients (total, and with individual PK)		*199*
Population Characteristics (Table 28)	General	*-Age median (range): 65 (33-84) years* *-Weight median (range): 74 (41-139) kg* *-115 (57.8%) male; 84 (42.2%) female* *-165 (82.9%) White; 20 (10.1%) Black or African American*
	Organ impairment	*-Hepatic (National Cancer Institute Organ Dysfunction Working Group criteria):* *175 (87.9%) normal ; 24 (12.1%) mild impairment* *-Renal (based on eGFR, mL/min/1.73 m^2):* *56 (28.1%) >=90 mL/min/1.73 m^2 (normal)* *90 (45.2%) >=60-<90 mL/min/1.73 m^2(mild impairment)* *52 (26.1%) >=30-<60 mL/min/1.73 m^2(moderate impairment)* *1 (0.5%) < 30 mL/min/1.73 m^2 (severe impairment)*
	Pediatrics (if any)	*Not applicable*
	Geriatrics (if any)	*-Age median (range): 71.5 (65-84)* *100 (50.3%) subj >=65 yr; 30 (15.1%) subj >=75 yr)* *-43 (43%) male; 57 (57%) female*
Dose(s) Included		*SC 0.08 to 3 mg/kg weekly*
Exposure Metrics Explored (range)		• *Predicted maximum concentration following the first treatment dose ($C_{max,1stdose}$).* • *Predicted maximum concentration following the first 4 weekly treatment doses ($C_{max,4doses}$)*
Covariates Evaluated		*Body weight, soluble BCMA, ISS, type of myeloma (IgG vs Non-IgG)*

Final Model Parameters	Summary	Acceptability [FDA's comments]
Model Structure	*Quartile analyses*	Rates of selected safety events were compared across exposure quartiles, and no E-R safety modeling was performed for teclistamab treatment dosing.
Model Parameter Estimates	Table 30 *for Grade ≥3 TEAE occurrence rates by exposure quartiles*	
Model Evaluation	*No apparent increase in the Grade ≥3 TEAE occurrence rates with increasing exposure ($C_{max,1stdose}$ and $C_{max,4doses}$) within the studied teclistamab dose range in Study MajesTEC-1. Teclistamab exposure, were overall comparable between subjects with or without of TEAEs, indicating no apparent E-R trend.*	
Covariates and Clinical Relevance	*ISS and type of myeloma imbalance across the exposure quartile groups may contribute as confounding factors (*Table 29 *and* Figure 15*).*	Worse ISS stage tended to have higher rates of Grade ≥3 anemia and thrombocytopenia which may confound the associations between cytopenia rates, ISS stage, and exposure. The higher cytopenia rates with higher ISS stage is not likely due to exposure differences between ISS stages.
Simulation for Specific Population	*Not applicable*	
Visualization of E-R relationships	Figure 14 *for quartile analyses* Table 29 *for baseline characteristics stratified by exposure quartiles* Figure 15 *for composition of ISS and type of myeloma in the Grade ≥3 TEAE occurrence rate* Figure 16 *for boxplot comparison of exposure in subjects without vs with Grade ≥3 TEAE*	No clear associations between exposure (C_{ave} for 1st treatment dose and C_{ave} for 4th treatment dose) and the selected safety events were identified. **FDA Table 14** for comparison of cytopenia rates derived from the lab dataset across exposure quartiles; **FDA Table 15** for rates of TEAE leading to dose modifications across exposure quartiles; **FDA Table 16** for comparison of neurologic toxicity

		rates across exposure quartiles.
Overall Clinical Relevance for ER	*No positive ER safety trend was apparent for Grade ≥3 TEAE anemia, neutropenia, lymphopenia, thrombocytopenia and infection across teclistamab ezposure quartile groups.*	E-R safety analyses did not identify any safety concerns with the 1.5 mg/kg QW SC treatment dose.
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	(b) (4)	See Reviewer comments under "The Applicant's Position" in **Section 19.4.3.2**.

Table 28: Summary of Baseline Characteristics in the ER Safety Analysis

	ER Safety Analysis (n=199)
Age (years)	
Mean (SD)	64.1 (9.63)
Median	65.0
IQ	58.0-71.5
Range	33.0-84.0
Sex	
Female	84 (42.2%)
Male	115 (57.8%)
Race	
Asian	3 (1.5%)
Black or African American	20 (10.1%)
White	165 (82.9%)
Other[a]	11 (5.5%)
Weight (kg)	
Mean (SD)	75.1 (17.0)
Median	74.0
IQ	62.1-86.6
Range	41.0-139
Renal Function (mL/min/1.73m^2)	
>=90	56 (28.1%)
>=60-<90	90 (45.2%)
>=30-<60	52 (26.1%)
<30	1 (0.5%)
Hepatic Function	
Normal	175 (87.9%)
Mild impairment	24 (12.1%)
Type of Myeloma	
IgG	111 (55.8%)
Non-IgG	88 (44.2%)
Baseline ISS	
I	97 (48.7%)
II	73 (36.7%)
III	26 (13.1%)
Not reported n(%)	3 (1.5%)
Cytogenetic Risk	
Standard risk	130 (65.3%)
High risk	43 (21.6%)
Not reported n(%)	26 (13.1%)
Baseline Bone Marrow % Plasma Cells	
<= 30	131 (65.8%)
>30 - <60	35 (17.6%)
>= 60	25 (12.6%)
Not reported n(%)	8 (4.0%)
Baseline Extramedullary Plasmacytoma	
0	169 (84.9%)
>=1	30 (15.1%)

	ER Safety Analysis (n=199)
Baseline Soluble BCMA (ng/mL)	
Mean (SD)	142 (182)
Median	84.8
IQ	29.3-157
Range	0.00100-1030
Not reported n(%)	4 (2.0%)

BCMA=B cell maturation antigen; CD=cluster of differentiation; IgG=immunoglobulin G; IQ=interquartile range; ISS=International Staging System; n=number of subjects

[a] Other race category included Multiple, Other and Not reported.

Table 29: Covariate Distribution over Cmax,1stdose and Cmax,4doses Quartiles for All Subjects Included in the ER Safety Analysis

Based on $C_{max,1stdose}$	Q1 (n=50)	Q2 (n=50)	Q3 (n=49)	Q4 (n=50)	Combined (n=199)
Weight (kg)					
Mean (SD)	70.0 (16.2)	72.1 (14.0)	77.8 (16.3)	80.6 (19.3)	75.1 (17.0)
Median	67.9	71.5	80.5	76.0	74.0
IQ	57.3-79.3	61.3-80.0	63.0-89.7	69.5-89.2	62.1-86.6
Range	46.0-118	41.0-101	44.9-107	49.0-139	41.0-139
Soluble BCMA (ng/mL)					
Mean (SD)	144 (171)	133 (194)	166 (203)	127 (161)	142 (182)
Median	99.6	79.5	89.3	82.6	84.8
IQ	55.9-154	34.0-135	27.9-212	27.3-155	29.3-157
Range	10.2-1030	5.78-1000	7.99-969	0.00100-842	0.00100-1030
Not reported n(%)	0 (0%)	2 (4.0%)	2 (4.1%)	0 (0%)	4 (2.0%)
Baseline ISS					
I	13 (26.0%)	28 (56.0%)	26 (53.1%)	30 (60.0%)	97 (48.7%)
II	25 (50.0%)	16 (32.0%)	17 (34.7%)	15 (30.0%)	73 (36.7%)
III	11 (22.0%)	6 (12.0%)	5 (10.2%)	4 (8.0%)	26 (13.1%)
Not reported	1 (2.0%)	0 (0.0%)	1 (2.0%)	1 (2.0%)	3 (1.5%)
Type of Myeloma					
IgG	40 (80.0%)	37 (74.0%)	25 (51.0%)	9 (18.0%)	111 (55.8%)
Non-IgG	10 (20.0%)	13 (26.0%)	24 (49.0%)	41 (82.0%)	88 (44.2%)

Based on $C_{max,4doses}$	Q1 (n=44)	Q2 (n=45)	Q3 (n=42)	Q4 (n=44)	Combined (n=175)
Weight (kg)					
Mean (SD)	70.9 (16.9)	75.7 (14.0)	76.0 (17.3)	79.1 (19.7)	75.4 (17.2)
Median	67.4	74.4	75.0	75.0	74.0
IQ	59.4-79.9	68.3-86.0	62.3-89.1	65.3-87.5	62.6-86.8
Range	46.0-118	49.0-101	41.0-121	49.0-139	41.0-139
Soluble BCMA (ng/mL)					
Mean (SD)	118 (117)	102 (139)	151 (183)	102 (111)	117 (139)
Median	90.1	69.5	78.0	65.9	78.6
IQ	31.2-128	29.3-113	36.5-179	18.1-150	26.2-148
Range	10.2-492	5.78-818	8.27-842	3.59-461	3.59-842
Not reported n(%)	0 (0%)	2 (4.4%)	2 (4.8%)	0 (0%)	4 (2.3%)

Based on $C_{max,4doses}$	Q1 (n=44)	Q2 (n=45)	Q3 (n=42)	Q4 (n=44)	Combined (n=175)
Baseline ISS					
I	17 (38.6%)	23 (51.1%)	24 (57.1%)	27 (61.4%)	91 (52.0%)
II	20 (45.5%)	15 (33.3%)	13 (31.0%)	15 (34.1%)	63 (36.0%)
III	7 (15.9%)	5 (11.1%)	5 (11.9%)	2 (4.5%)	19 (10.9%)
Not reported	0 (0.0%)	2 (4.4%)	0 (0.0%)	0 (0.0%)	2 (1.1%)
Type of Myeloma					
IgG	37 (84.1%)	33 (73.3%)	22 (52.4%)	6 (13.6%)	98 (56.0%)
Non-IgG	7 (15.9%)	12 (26.7%)	20 (47.6%)	38 (86.4%)	77 (44.0%)

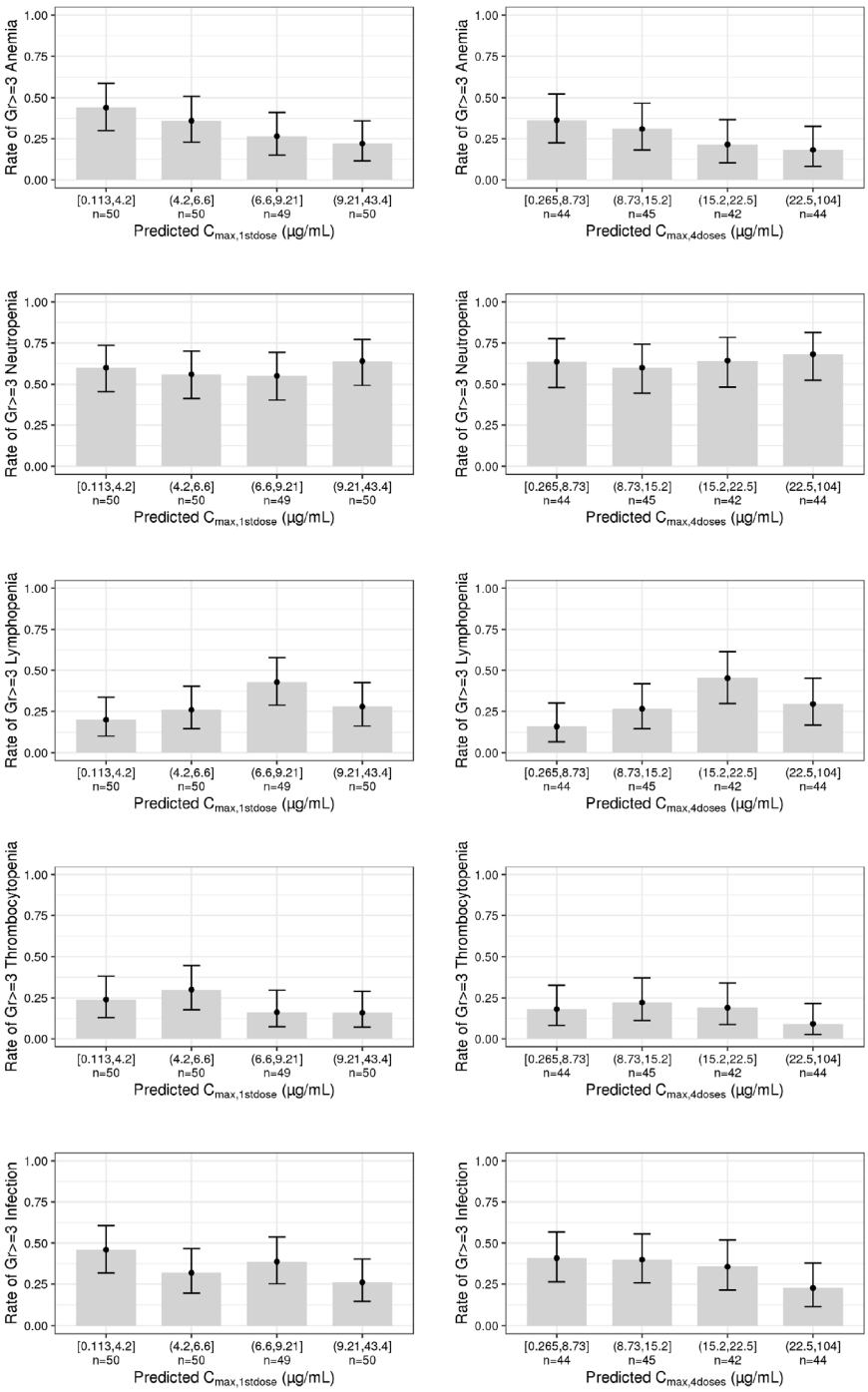
BCMA=B cell maturation antigen; $C_{max,4doses}$=maximum concentration following the first 4 weekly treatment doses; IgG=immunoglobulin G; IQ=interquartile range; ISS=International Staging System; n=number of subjects; Q1=lowest exposure quartile group; Q2=second exposure quartile group; Q3=third exposure quartile group; Q4=highest exposure quartile group; SD=standard deviation.
The E-R safety dataset (n=199) was used as basis. The quartile groups Q1, Q2, Q3, and Q4 are associated with $C_{max,1stdose}$ ranges of [0.113, 4.2], (4.2, 6.6], (6.6, 9.21], and (9.21, 43.4] µg/mL, respectively.
$C_{max,4doses}$ were available only in 175 subjects who received at least 4 treatment doses. The quartile groups Q1, Q2, Q3, and Q4 are associated with $C_{max,4doses}$ ranges of [0.265, 8.73], (8.73,15.2], (15.2, 22.5], and (22.5, 104] µg/mL, respectively.
Source: Applicant's Population PK and Exposure-Response Analyses Report, Attachment 24.

Table 30: Summary of Grade ≥3 TEAE Occurrence Rates and 95% CI Overall and Stratified by Cmax,1stdose and Cmax,4doses Quartile Groups

		Anemia		Neutropenia		Lymphopenia		Thrombocytopenia		Infection	
		N_{event}/ $N_{subject}$	AE rate (95% CI)	N_{event}/ $N_{subject}$	AE rate (95% CI)	N_{event}/ $N_{subject}$	AE rate (95% CI)	N_{event}/ $N_{subject}$	AE rate (95% CI)	N_{event}/ $N_{subject}$	AE rate (95% CI)
Overall		64/199	32.2 (25.7-39.1)	117/199	58.8 (51.6-65.7)	58/199	29.1 (22.9-36.0)	43/199	21.6 (16.1-28.0)	71/199	35.7 (29.0-42.8)
Stratified by $C_{max,1stdose}$											
Q1	[0.113,4.2]	22/50	44.0 (30.0-58.7)	30/50	60.0 (45.2-73.6)	10/50	20.0 (10.0-33.7)	12/50	24.0 (13.1-38.2)	23/50	46.0 (31.8-60.7)
Q2	(4.2,6.6]	18/50	36.0 (22.9-50.8)	28/50	56.0 (41.3-70.0)	13/50	26.0 (14.6-40.3)	15/50	30.0 (17.9-44.6)	16/50	32.0 (19.5-46.7)
Q3	(6.6,9.21]	13/49	26.5 (14.9-41.1)	27/49	55.1 (40.2-69.3)	21/49	42.9 (28.8-57.8)	8/49	16.3 (7.3-29.7)	19/49	38.8 (25.2-53.8)
Q4	(9.21,43.4]	11/50	22.0 (11.5-36.0)	32/50	64.0 (49.2-77.1)	14/50	28.0 (16.2-42.5)	8/50	16.0 (7.2-29.1)	13/50	26.0 (14.6-40.3)
Stratified by $C_{max,4doses}$											
Q1	[0.265,8.73]	16/44	36.4 (22.4-52.2)	28/44	63.6 (47.8-77.6)	7/44	15.9 (6.6-30.1)	8/44	18.2 (8.2-32.7)	18/44	40.9 (26.3-56.8)
Q2	(8.73,15.2]	14/45	31.1 (18.2-46.6)	27/45	60.0 (44.3-74.3)	12/45	26.7 (14.6-41.9)	10/45	22.2 (11.2-37.1)	18/45	40.0 (25.7-55.7)
Q3	(15.2,22.5]	9/42	21.4 (10.3-36.8)	27/42	64.3 (48.0-78.4)	19/42	45.2 (29.8-61.3)	8/42	19.0 (8.6-34.1)	15/42	35.7 (21.6-52.0)
Q4	(22.5,104]	8/44	18.2 (8.2-32.7)	30/44	68.2 (52.4-81.4)	13/44	29.5 (16.8-45.2)	4/44	9.1 (2.5-21.7)	10/44	22.7 (11.5-37.8)

AE=adverse event; CI=confidence interval; $C_{max,1stdose}$=maximum concentration following the first treatment dose; $C_{max,4doses}$=maximum concentration following the first 4 weekly treatment doses; N_{event}=number of events; $N_{subject}$=number of subjects overall or in the respective exposure quartile groups; Q1=lowest exposure quartile group; Q2=second exposure quartile group; Q3=third exposure quartile group; Q4=highest exposure quartile group; TEAE=treatment-emergent adverse event.
The concentration ranges for each quartile group inside square brackets are in the units of µg/mL.
Source: Applicant's Population PK and Exposure-Response Analyses Report, Attachment 35.

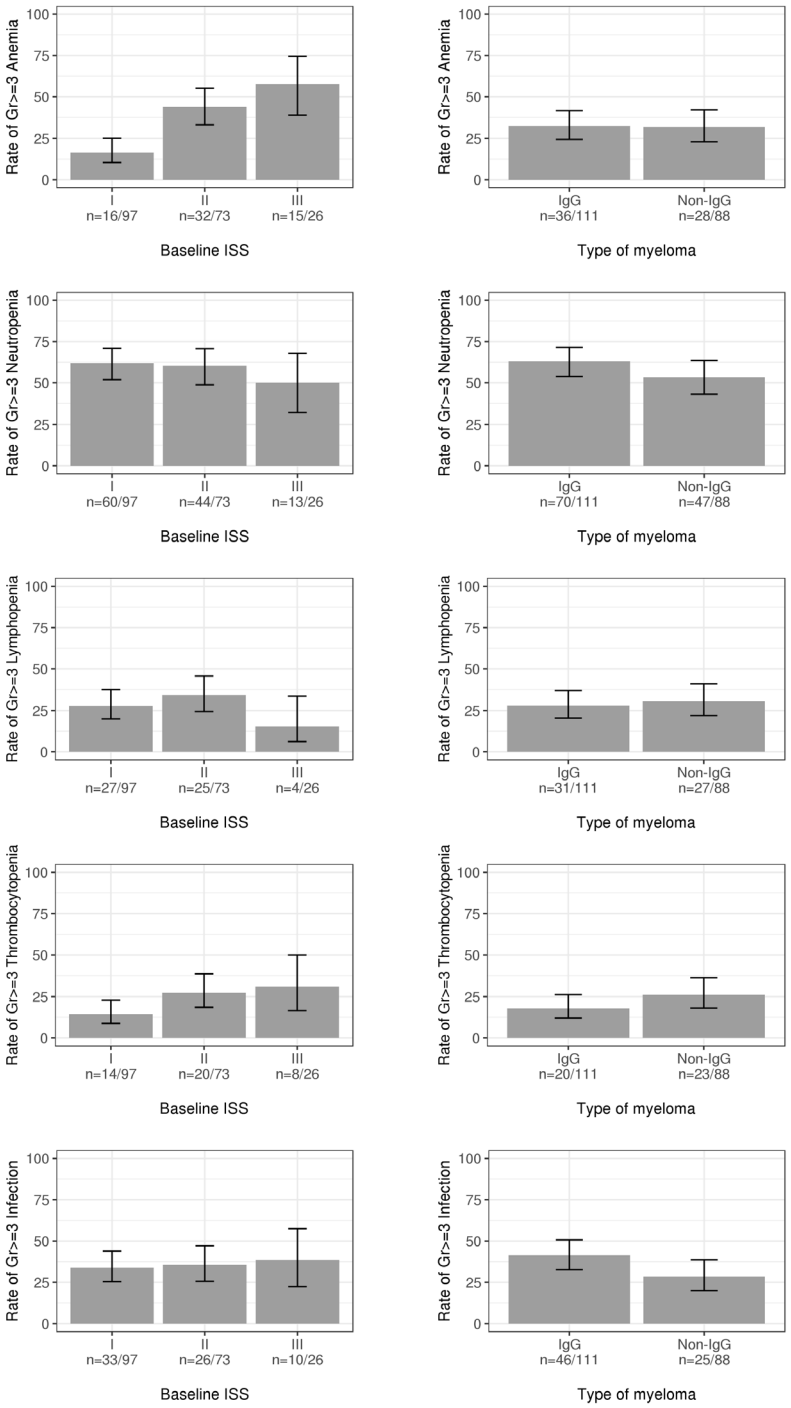
Figure 14: Comparison of Grade ≥3 TEAE Occurrence Rates by the Predicted Cmax,1stdose and Cmax,4doses Quartiles



AE=adverse event; CI=confidence interval; $C_{max,1stdose}$=maximum concentration following the first treatment dose; $C_{max,4doses}$=maximum concentration following the first 4 weekly treatment doses; Gr=Grade; n=number of subjects. Error bars are the 95% CI of AE occurrence rates in the respective exposure quartile groups.
Source: Applicant's Population PK and Exposure-Response Analyses Report, Figure 14.

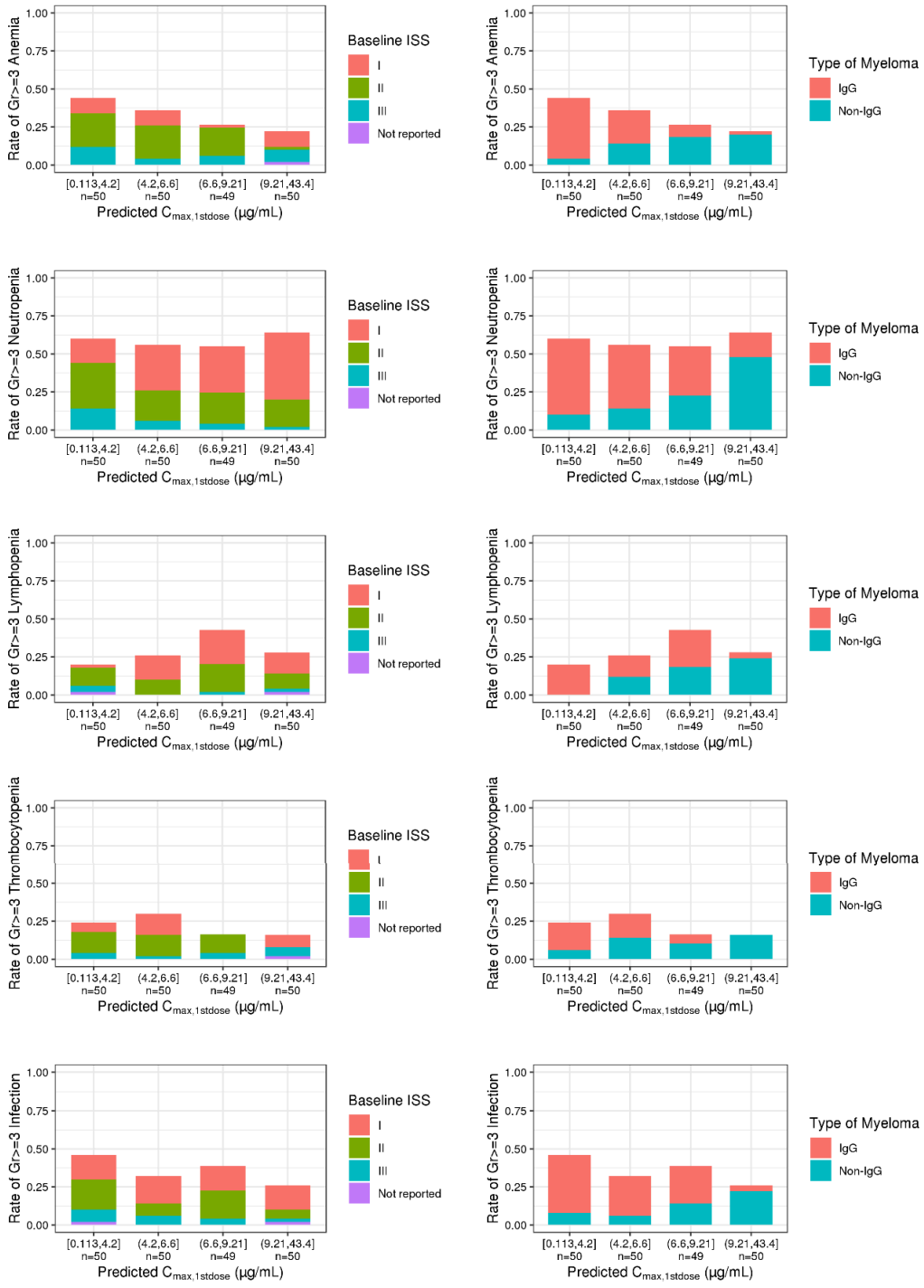
Figure 15: Composition of ISS and Type of Myeloma in the Grade ≥3 TEAE Occurrence Rates and Across the Predicted $C_{max,1stdose}$ and $C_{max,4doses}$ Quartiles

A



AE=adverse event; $C_{max,1stdose}$=maximum concentration following the first treatment dose; $C_{max,4doses}$=maximum concentration following the first 4 weekly treatment doses; Gr=Grade; IgG=immunoglobulin G; ISS=International Staging System; n=number of subjects.

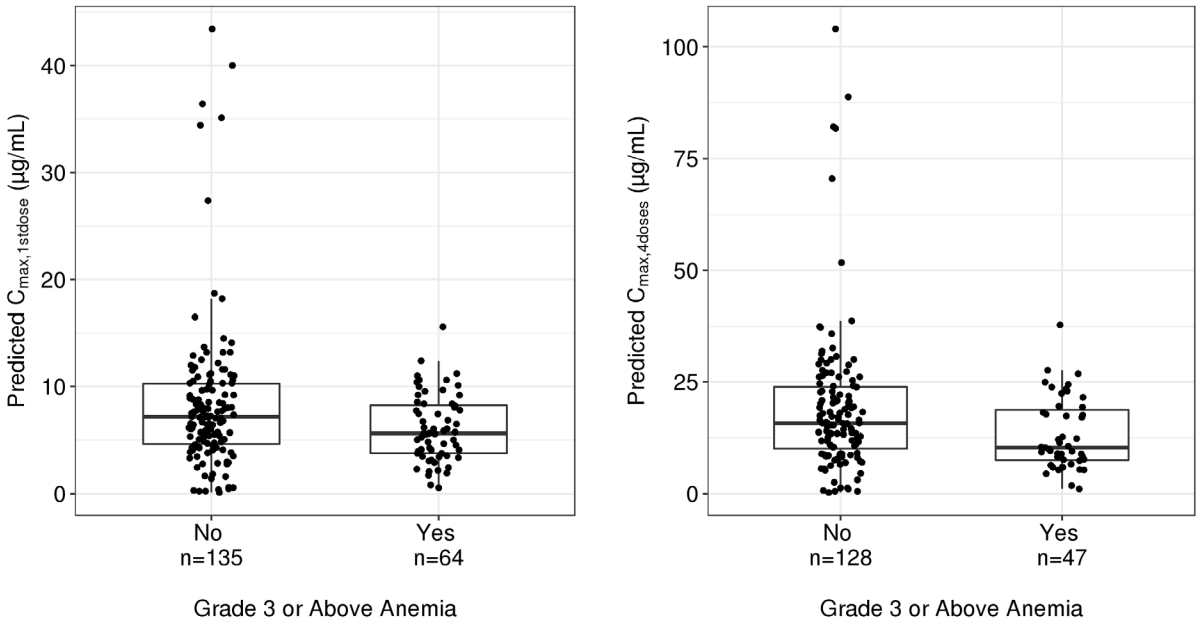
B



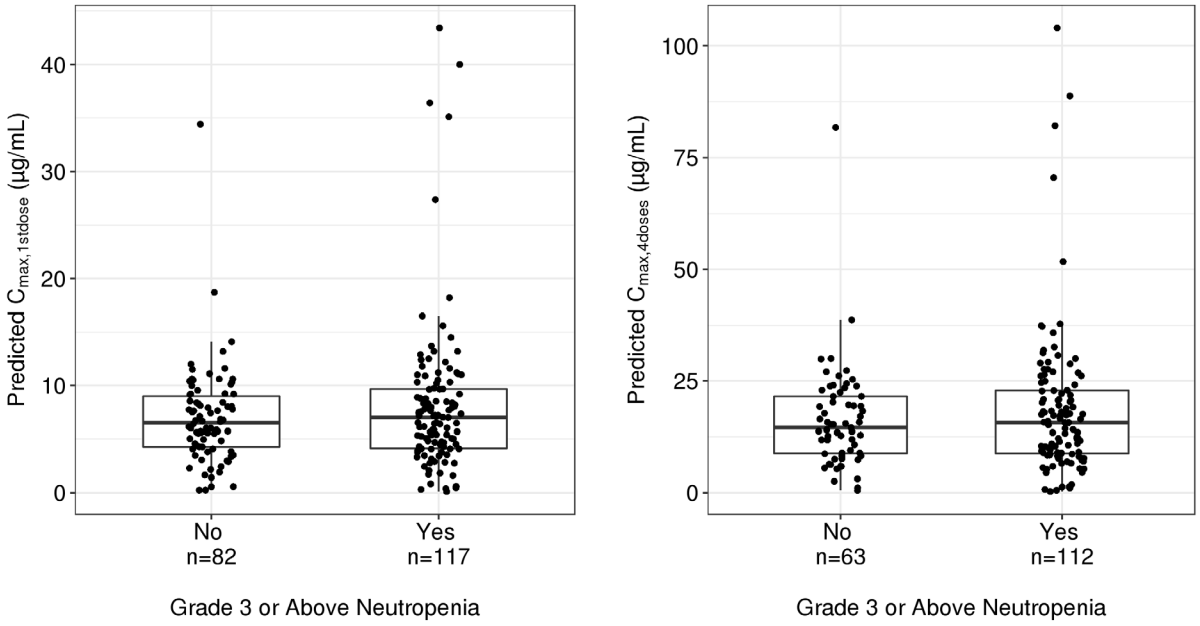
AE=adverse event; $C_{max,1stdose}$=maximum concentration following the first treatment dose; $C_{max,4doses}$=maximum concentration following the first 4 weekly treatment doses; Gr=Grade; IgG=immunoglobulin G; ISS=International Staging System; n=number of subjects.
Source: Applicant's Population PK and Exposure-Response Analyses Report, Attachment 36.

Figure 16: Comparison of Predicted Exposure Metrics Between Subjects With and Without Grade ≥3 Anemia, Neutropenia, Lymphopenia, Thrombocytopenia and Infection

A)

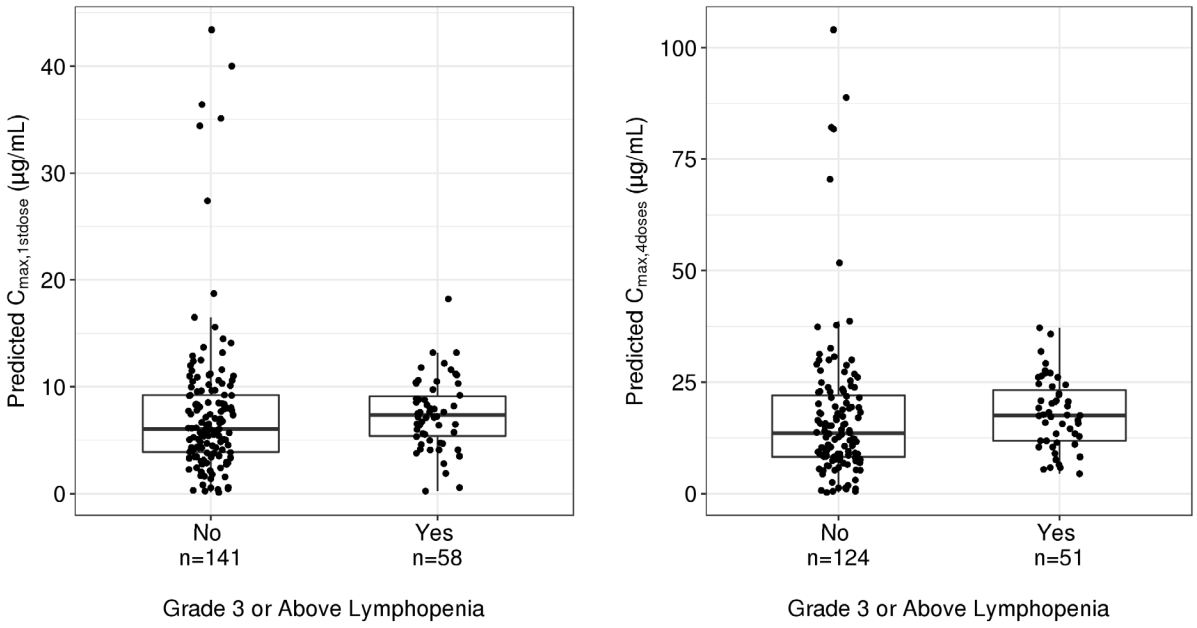


B)

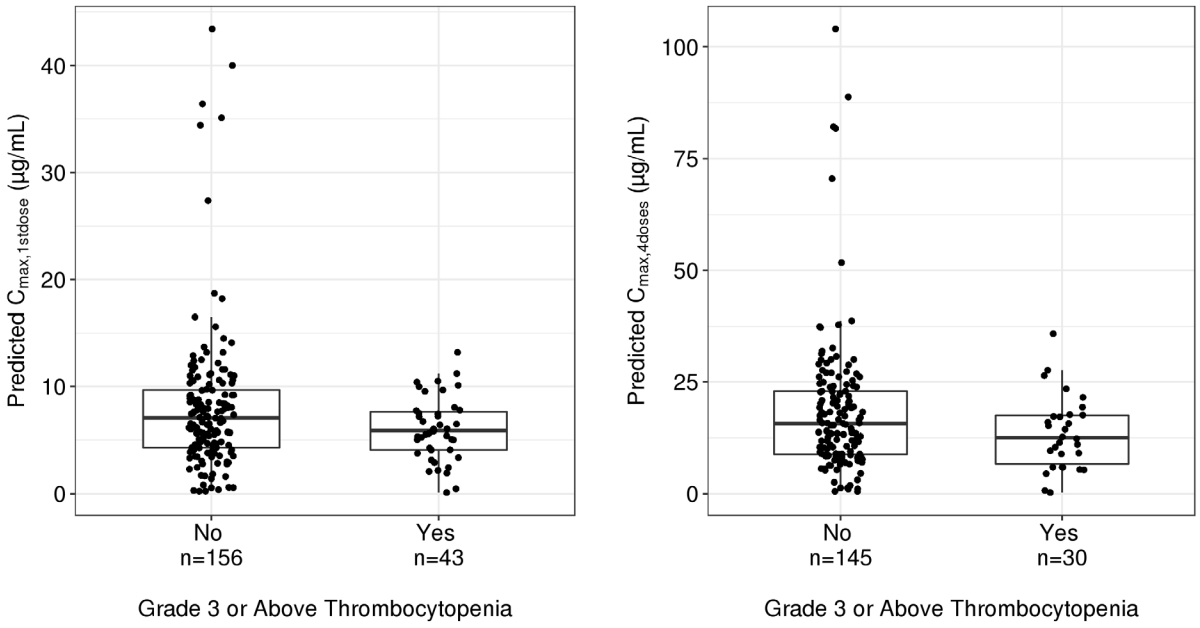


$C_{max,1stdose}$=maximum concentration following the first treatment dose; $C_{max,4doses}$=maximum concentration following the first 4 weekly treatment doses; n=number of subjects.

C)

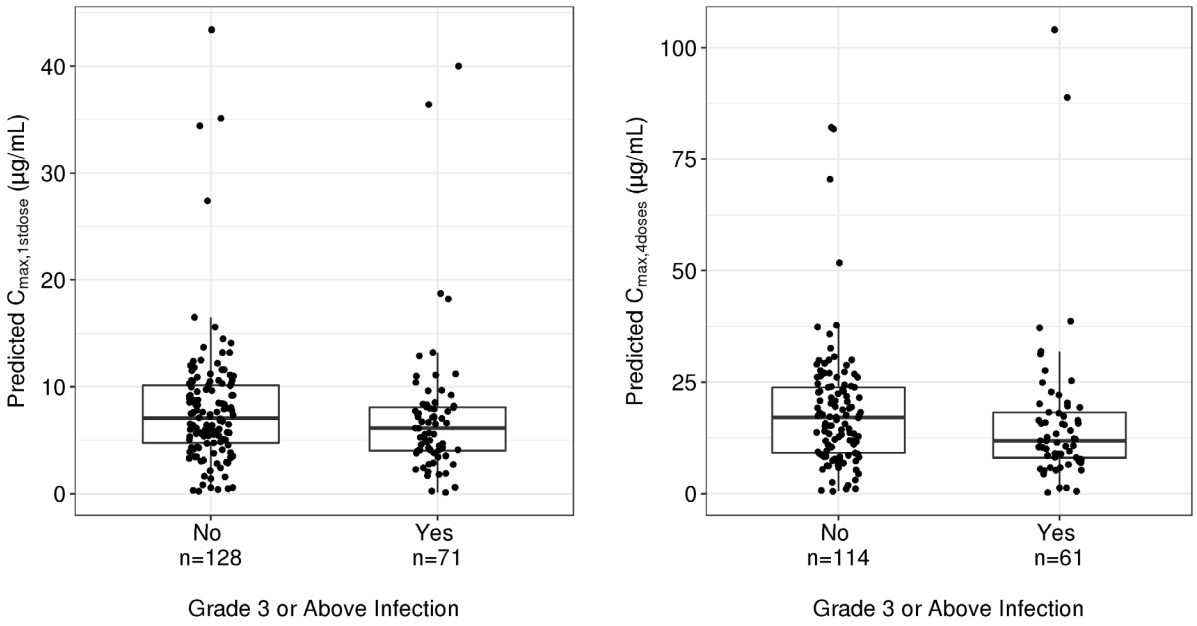


D)



$C_{max,1stdose}$=maximum concentration following the first treatment dose; $C_{max,4doses}$=maximum concentration following the first 4 weekly treatment doses; n=number of subjects.

E)



$C_{max,1stdose}$=maximum concentration following the first treatment dose; $C_{max,4doses}$=maximum concentration following the first 4 weekly treatment doses.
Source: Applicant's Population PK and Exposure-Response Analyses Report, Attachment 37.

The FDA's Assessment:

The E-R safety dataset contained data from 199 total patients who received SC teclistamab from the Phase 1 (n=79) or Phase 2 Cohort A (n=120) in Study MajesTEC-1. The majority of patients in the E-R safety dataset were assigned to the RP2D (160/199 [80.4%]). The number of patients per treatment regimen is displayed in **FDA Table 13**. Table 28 summarizes baseline patient characteristics for the E-R safety sample.

FDA Table 22: Subject Disposition of Safety E-R Analysis Dataset

TRT	Treatment	Category	Number of Subjects	Number of Subjects with $C_{max,1stdose}$	Number of Subjects with $C_{max,4doses}$
18	20 then 80 µg/kg QW SC	<RP2D	6	6	5
19	40/80 then 240 µg/kg QW SC	<RP2D	7	7	6
20	60/240 then 720 µg/kg QW SC	<RP2D	15	15	12
21	60/300 then 1500 µg/kg QW SC	RP2D	40	40	38
22	60/300/1500 then 3000 µg/kg QW SC	>RP2D	4	4	4
23	60/300/1500 then 6000 µg/kg SC	>RP2D	4	4	4
24	2/6/30 then 150/300 mg QW/Q2W SC	Flat dose	3	3	3
301	60/300 then 1500 µg/kg QW SC Part 3A	RP2D	120	120	103
Total number of subjects			199	199	175

$C_{max,1stdose}$=maximum concentration following the first treatment dose; $C_{max,4doses}$=maximum concentration following the first 4 weekly treatment doses; E-R=exposure-response; Q2W=every 2 weeks; QW=weekly; RP2D=recommended Phase 2 dose, which is 0.06 mg/kg SC, followed 2 to 4 days later by 0.3 mg/kg SC, followed 2 to 4 days later by 1.5 mg/kg SC and then 1.5 mg/kg SC QW thereafter; SC=subcutaneous; TRT=treatment code in the E-R dataset.
Source: Attachment 1 in Applicant's Response to FDA 01 July 2022 Information Request

The exploratory E-R safety analyses did not identify any clear associations between higher maximum concentration following first treatment dose ($C_{max,1stdose}$) and maximum concentration following fourth treatment dose ($C_{max,4doses}$) and increased risk of any of the following TEAEs:

- ☐ Grade ≥3 anemia worse than baseline derived from lab dataset (***FDA Table 14***)
- ☐ Grade ≥3 neutropenia worse than baseline derived from lab dataset (***FDA Table 14***)
- ☐ Grade ≥3 lymphopenia worse than baseline derived from lab dataset (***FDA Table 14***)
- ☐ Grade ≥3 thrombocytopenia worse than baseline derived from lab dataset (***FDA Table 14***)
- ☐ Grade ≥3 leukopenia worse than baseline derived from lab dataset (***FDA Table 14***)
- ☐ Grade ≥3 infection derived from AE dataset (Table 30 and Figure 14)
- ☐ TEAE leading to any dose modification (including cycle delay, dose delay, dose skip, drug discontinuation, and dose reduction) (***FDA Table 15***)
- ☐ TEAE leading to cycle delay (***FDA Table 15***)
- ☐ TEAE leading to dose interruption (including dose delay within cycle and dose skip) (***FDA Table 15***)
- ☐ TEAE leading to dose delay within cycle (***FDA Table 15***)
- ☐ TEAE leading to dose skip (***FDA Table 15***)
- ☐ Any Grade ≥3 TEAE
- ☐ Neurologic toxicity TEAE Group 1 (Sensory Neuropathy, Encephalopathy, and Motor Dysfunction grouped preferred terms (PT) combined; see **Section 19.6**) (***FDA Table 16***)
- ☐ Neurologic toxicity TEAE Group 2 (Sensory Neuropathy, Encephalopathy, and Motor Dysfunction grouped PT combined plus the PTs for headache and migraine; see **Section 19.6**) (***FDA Table 16***)

FDA Table 23: Summary of Grade ≥3 Worse-Than-Baseline Cytopenia TEAE Occurrence Rates Derived From Laboratory Dataset Stratified by Exposure Quartile

		Anemia		Neutropenia		Lymphopenia		Thrombocytopenia		Leukopenia	
		N_{event}/ $N_{subject}$	Rate (95% CI)	N_{event}/ $N_{subject}$	Rate (95% CI)	N_{event}/ $N_{subject}$	Rate (95% CI)	N_{event}/ $N_{subject}$	Rate (95% CI)	N_{event}/ $N_{subject}$	Rate (95% CI)
Overall		67/199	33.7 (27.1-40.7)	125/199	62.8 (55.7-69.5)	171/198	86.4 (80.8-90.8)	46/199	23.1 (17.4-29.6)	82/199	41.2 (34.3-48.4)
Stratified by $C_{max,1stdose}$											
Q1	[0.113,4.2]	23/50	46.0 (31.8-60.7)	31/50	62.0 (47.2-75.3)	45/50	90.0 (78.2-96.7)	14/50	28.0 (16.2-42.5)	22/50	44.0 (30.0-58.7)
Q2	(4.2,6.6]	18/50	36.0 (22.9-50.8)	30/50	60.0 (45.2-73.6)	44/49	89.8 (77.8-96.6)	16/50	32.0 (19.5-46.7)	24/50	48.0 (33.7-62.6)
Q3	(6.6,9.21]	13/49	26.5 (14.9-41.1)	30/49	61.2 (46.2-74.8)	40/49	81.6 (68.0-91.2)	8/49	16.3 (7.3-29.7)	15/49	30.6 (18.3-45.4)
Q4	(9.21,43.4]	13/50	26.0 (14.6-40.3)	34/50	68.0 (53.3-80.5)	42/50	84.0 (70.9-92.8)	8/50	16.0 (7.2-29.1)	21/50	42.0 (28.2-56.8)
Stratified by $C_{max,4doses}$											
Q1	[0.265,8.73]	17/44	38.6 (24.4-54.5)	27/44	61.4 (45.5-75.6)	39/44	88.6 (75.4-96.2)	9/44	20.5 (9.8-35.3)	20/44	45.5 (30.4-61.2)
Q2	(8.73,15.2]	16/45	35.6 (21.9-51.2)	32/45	71.1 (55.7-83.6)	41/44	93.2 (81.3-98.6)	11/45	24.4 (12.9-39.5)	19/45	42.2 (27.7-57.8)
Q3	(15.2,22.5]	8/42	19.0 (8.6-34.1)	30/42	71.4 (55.4-84.3)	37/42	88.1 (74.4-96.0)	8/42	19.0 (8.6-34.1)	20/42	47.6 (32.0-63.6)
Q4	(22.5,104]	10/44	22.7 (11.5-37.8)	32/44	72.7 (57.2-85.0)	39/44	88.6 (75.4-96.2)	4/44	9.1 (2.5-21.7)	18/44	40.9 (26.3-56.8)

Individual exposure was predicted using actual dosing information for each patient and the PPK model developed from PK data with cutoff of 14 June 2021. The exposure in each quartile group is in units of ug/mL. Safety data cutoff date was 7 September 2021.

CI=confidence interval; $C_{max,1stdose}$=maximum concentration following the first treatment dose; $C_{max,4doses}$=maximum concentration following the first 4 weekly treatment doses; N_{event}=number of events; $N_{subject}$=number of subjects overall or in the respective exposure quartile groups; PPK = population pharmacokinetic; Q1=lowest exposure quartile group; Q2=second exposure quartile group; Q3=third exposure quartile group; Q4=highest exposure quartile group; TEAE=treatment-emergent adverse event, defined as laboratory-based abnormalities worsening from baseline.

Source: Attachment 8 in Part 2 of Applicant's Response to FDA 24 February 2022 Information Request

FDA Table 24: Summary of TEAE-related Dose Modification Occurrence Rates Stratified by Exposure Quartile

		Dose Modification		Cycle Delay		Dose Interruption		Dose Delay		Dose Skip	
		N_{event}/ $N_{subject}$	Rate (95% CI)	N_{event}/ $N_{subject}$	Rate (95% CI)	N_{event}/ $N_{subject}$	Rate (95% CI)	N_{event}/ $N_{subject}$	Rate (95% CI)	N_{event}/ $N_{subject}$	Rate (95% CI)
Overall		145/199	72.9 (66.1-78.9)	94/199	47.2 (40.1-54.4)	125/199	62.8 (55.7-69.5)	29/199	14.6 (10.0-20.3)	114/199	57.3 (50.1-64.3)
Stratified by $C_{max,1stdose}$											
Q1	[0.113,4.2]	36/50	72.0 (57.5-83.8)	26/50	52.0 (37.4-66.3)	30/50	60.0 (45.2-73.6)	8/50	16.0 (7.2-29.1)	26/50	52.0 (37.4-66.3)
Q2	(4.2,6.6]	35/50	70.0 (55.4-82.1)	22/50	44.0 (30.0-58.7)	33/50	66.0 (51.2-78.8)	6/50	12.0 (4.5-24.3)	32/50	64.0 (49.2-77.1)
Q3	(6.6,9.21]	39/49	79.6 (65.7-89.8)	24/49	49.0 (34.4-63.7)	32/49	65.3 (50.4-78.3)	5/49	10.2 (3.4-22.2)	31/49	63.3 (48.3-76.6)
Q4	(9.21,43.4]	35/50	70.0 (55.4-82.1)	22/50	44.0 (30.0-58.7)	30/50	60.0 (45.2-73.6)	10/50	20.0 (10.0-33.7)	25/50	50.0 (35.5-64.5)
Stratified by $C_{max,4doses}$											
Q1	[0.265,8.73]	35/44	79.5 (64.7-90.2)	25/44	56.8 (41.0-71.7)	29/44	65.9 (50.1-79.5)	6/44	13.6 (5.2-27.4)	27/44	61.4 (45.5-75.6)
Q2	(8.73,15.2]	34/45	75.6 (60.5-87.1)	24/45	53.3 (37.9-68.3)	32/45	71.1 (55.7-83.6)	6/45	13.3 (5.1-26.8)	29/45	64.4 (48.8-78.1)
Q3	(15.2,22.5]	34/42	81.0 (65.9-91.4)	21/42	50.0 (34.2-65.8)	28/42	66.7 (50.5-80.4)	7/42	16.7 (7.0-31.4)	27/42	64.3 (48.0-78.4)
Q4	(22.5,104]	32/44	72.7 (57.2-85.0)	23/44	52.3 (36.7-67.5)	26/44	59.1 (43.2-73.7)	8/44	18.2 (8.2-32.7)	21/44	47.7 (32.5-63.3)

Dose modification includes cycle delay, dose delay, dose skip, drug discontinuation and dose reduction. Dose interruption includes dose delay and dose skip. Individual exposure was predicted using actual dosing information for each patient and the PPK model developed from PK data with cutoff of 14 June 2021. The exposure in each quartile group is in units of ug/mL. Safety data cutoff date was 7 September 2021.

CI=confidence interval; $C_{max,1stdose}$=maximum concentration following the first treatment dose; $C_{max,4doses}$=maximum concentration following the first 4 weekly treatment doses; N_{event}=number of events; $N_{subject}$=number of subjects overall or in the respective exposure quartile groups; PPK=population pharmacokinetic; Q1 = lowest exposure quartile group; Q2 = second exposure quartile group; Q3 = third exposure quartile group; Q4 = highest exposure quartile group; TEAE = treatment-emergent adverse event, defined as laboratory-based abnormalities worsening from baseline.

Source: Attachment 11 in Part 2 of Applicant's Response to FDA 24 February 2022 Information Request

FDA Table 25: Summary of Neurologic Toxicity Event Occurrence Rates Stratified by Exposure Quartile

		Group 1 Event		Group 2 Event	
		N_{event}/ $N_{subject}$	Rate (95% CI)	N_{event}/ $N_{subject}$	Rate (95% CI)
Overall		75/199	37.7 (30.9-44.8)	98/199	49.2 (42.1-56.4)
Stratified by $C_{max,1stdose}$					
Q1	[0.113,4.2]	18/50	36.0 (22.9-50.8)	25/50	50.0 (35.5-64.5)
Q2	(4.2,6.6]	21/50	42.0 (28.2-56.8)	27/50	54.0 (39.3-68.2)
Q3	(6.6,9.21]	14/49	28.6 (16.6-43.3)	17/49	34.7 (21.7-49.6)
Q4	(9.21,43.4]	22/50	44.0 (30.0-58.7)	29/50	58.0 (43.2-71.8)
Stratified by $C_{max,4doses}$					
Q1	[0.265,8.73]	17/44	38.6 (24.4-54.5)	23/44	52.3 (36.7-67.5)
Q2	(8.73,15.2]	18/45	40.0 (25.7-55.7)	22/45	48.9 (33.7-64.2)
Q3	(15.2,22.5]	13/42	31.0 (17.6-47.1)	18/42	42.9 (27.7-59.0)
Q4	(22.5,104]	20/44	45.5 (30.4-61.2)	27/44	61.4 (45.5-75.6)

Note: The symptoms of CRS or ICANS are excluded. Individual exposure was predicted using actual dosing information for each patient and the PPK model developed from PK data with cutoff of 14 June 2021. The exposure in each quartile group is in units of ug/mL. Safety data cutoff date was 04 January 2022.
CI=confidence interval; $C_{max,1stdose}$=maximum concentration following the first treatment dose; $C_{max,4doses}$=maximum concentration following the first 4 weekly treatment doses; Group 1=Sensory Neuropathy, Encephalopathy, or Motor Dysfunction; Group 2=Sensory Neuropathy, Encephalopathy, Motor Dysfunction, or Headache (including Migraine); N_{event}=number of events; $N_{subject}$=number of subjects overall or in the respective exposure quartile groups; PPK=population pharmacokinetic; Q1=lowest exposure quartile group; Q2=second exposure quartile group; Q3=third exposure quartile group; Q4=highest exposure quartile group.
Source: Table 1 in Applicant's Response to FDA 01 July 2022 Information Request

Table 30, Figure 14, Figure 15, and Figure 16 display the rates of Grade ≥3 cytopenias derived from the AE dataset ("adae.xpt") across exposure quartiles. However, cytopenias are laboratory-based adverse reactions and so the cytopenia rates in the AE dataset may differ from those in the laboratory analysis dataset ("adlb.xpt"). E-R analyses should utilize rates and grades of cytopenia events from the laboratory analysis dataset, which are shown in **FDA Table 14**.

The rate of Grade ≥3 anemia appeared to decrease with higher exposure which is likely due to confounding between ISS stage and exposure. Worse ISS stage tended to have higher rates of Grade ≥3 anemia and Grade ≥3 thrombocytopenia (Figure 15A). However, worse ISS stage was associated with lower exposure in the PPK analysis (**Section 19.4.2.2**). Exposure differences are unlikely to cause the difference in cytopenia rates across ISS stage.

Overall, the E-R safety analyses did not identify any safety concern with the proposed treatment dose of 1.5 mg/kg SC once weekly. The key safety concern with step-up dosing is cytokine release syndrome (CRS), and the E-R safety analysis for step-up dosing and CRS is detailed in **Section 19.4.3.5**.

19.4.3.5 Reviewer's Independent E-R Safety Analysis

CRS mitigation and management is a crucial part of the teclistamab benefit/risk assessment (see **Section 8.2.5.1**). The Reviewer conducted exploratory multivariate E-R safety analyses of CRS to assess whether the proposed step-up dosing regimen resulted in any peaks in exposure associated with unnecessarily high CRS incidence. The exploratory E-R analysis supported the need for a step-up dosing regimen prior to the weekly treatment dosing in order to mitigate the risk of CRS. The exploratory E-R analysis did not identify any safety concerns regarding CRS for the proposed 0.06/0.3/1.5 mg/kg SC step-up dosing regimen. Additionally, multivariate analyses suggest that tocilizumab administration to treat CRS with step-up dose 1 may impact the CRS rate with step-up dose 2.

Data

Exposure and CRS incidence for step-up dose 1 and step-up dose 2 were investigated because more than half of CRS events occurred with these two dose events (143/225 CRS events [63.6%]).

The incidence of CRS with each dose event is summarized in **FDA Table 17**.

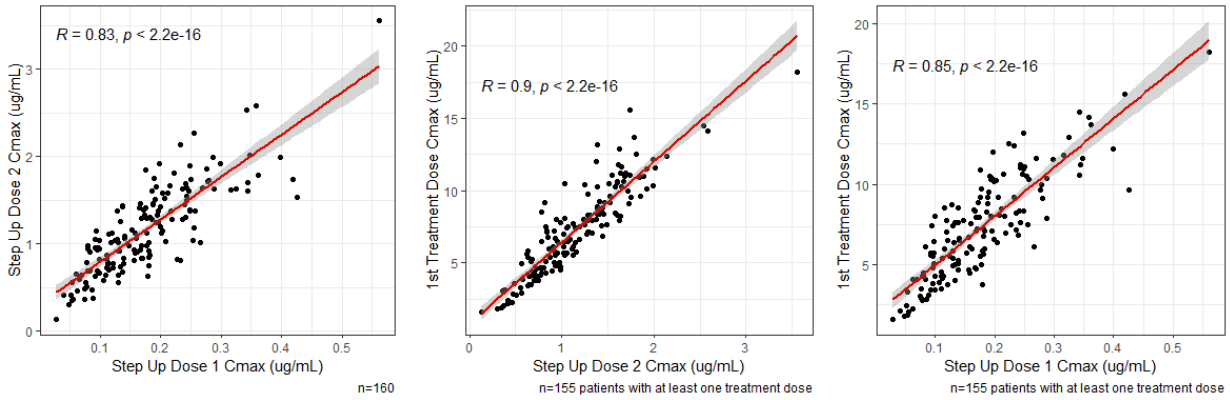
FDA Table 26: Number of Patients Experiencing CRS and Number of CRS Events Per Dose Event

	E-R Safety Dataset (n=199 patients)				Phase 2 Cohort A Patients with E-R Safety Data (n=120 patients)			
	Any Grade CRS		Grade ≥2 CRS		Any Grade CRS		Grade ≥2 CRS	
Dose Event	**Patients with CRS**	**CRS events**	**Patients with CRS**	**CRS events**	**Patients with CRS**	**CRS events**	**Patients with CRS**	**CRS events**
Step-up Dose 1	77	78	26	26	50	50	19	19
Step-up Dose 2*	65	65	10	10	43	43	8	8
Step-up Dose 2* Repeat 1	1	1	0	0	1	1	0	0
Step-up Dose 3**	0	0	0	0	N/A	N/A	N/A	N/A
Cycle 1 Day 1	49	50	10	10	32	32	7	7
Cycle 1 Day 8	9	9	1	1	6	6	1	1
Cycle 1 Day 15	6	6	0	0	2	2	0	0
Cycle 1 Day 22	2	2	0	0	2	2	0	0
Cycle 2 Day 1	7	7	0	0	2	2	0	0
Cycle 2 Step-up Dose 2 Repeat 1	1	1	1	1	1	1	1	1
Cycle 2 Day 8	1	1	0	0	1	1	0	0
Cycle 2 Day 15	1	1	0	0	0	0	0	0
Cycle 3 Day 8	1	1	1	1	1	1	1	1
Cycle 18 Step Up Adhoc Dose Repeat 1	1	1	0	0	0	0	0	0
Missing Visit Number	2	2	2	2	2	2	2	2
Total number of CRS events	**-**	**225**	**-**	**51**	**-**	**143**	**-**	**39**
Total number of patients with at least one CRS event at any time during study	**136**	**-**	**37**	**-**	**88**	**-**	**26**	**-**

*193/199 patients in the E-R safety dataset received two or more planned step-up doses.
**11/199 patients in the E-R safety dataset received exactly three planned step-up doses.
Dose event names copied from AE dataset. Safety data cutoff date was 7 September 2021.
CRS = cytokine release syndrome; E-R = exposure-response.
Source: Reviewer analysis of Applicant's adverse event dataset (adae.xpt)

For the reviewer's exploratory E-R safety analysis of CRS, individual Cmax was predicted using the PPK model developed from PK data with cutoff of 14 June 2021 (**Section 19.4.2.2**) and actual dosing information for each patient. Patients with high C_{max} following one dose event were more likely to have high C_{max} following other dose events, as shown in **FDA Figure 9**.

FDA Figure 9: Statistical Associations between Individual Predicted Peak Concentrations Following Step up Dose 1, Step up Dose 2, and 1st Treatment Dose in Patients who Received SC RP2D



In the E-R safety dataset, 160 patients in Phase 1 and Phase 2 Cohort A were scheduled to receive SC RP2D (0.06 mg/kg SC, followed 2 to 4 days later by 0.3 mg/kg SC, followed 2 to 4 days later by 1.5 mg/kg SC and then 1.5 mg/kg SC QW thereafter). All 160 patients received step-up dose 1 (0.06 mg/kg) and step-up dose 2 (0.3 mg/kg). 155/160 patients received one or more treatment doses (1.5 mg/kg QW).
Solid red line = linear regression. R = pearson correlation coefficient.
E-R = exposure-response; QW = once weekly; RP2D = recommended Phase 2 Dose; SC = subcutaneous.
Source: Reviewer analysis of Applicant's E-R Safety Dataset

AUC and C_{ave} were not used in the E-R safety analysis of CRS because AUC, C_{ave}, and time between step-up doses may be confounded by CRS rates. Because the amount administered increases substantially with each subsequent step-up dose, previous exposure and the time between step-up doses are not expected to impact C_{max}. The median T_{max} for step-up dose 1 was 2.8 days (range 0.8 to 2.8 days), but step-up dose 2 could be administered 2 to 7 days after step-up dose 1. CRS onset occurred a median of 2.0 days (range 1 to 6 days) after last dose. Patients with shorter time between step-up dose 1 and step-up dose 2 may not have had enough time to develop CRS with step-up dose 1, while patients who experienced CRS with step-up dose 1 may have had a longer time between doses while they recovered from CRS. These confounding factors would complicate interpretation of the exposure effect on CRS rate.

Any Grade CRS with Step-up Dose 1

The E-R analysis of CRS incidence with step-up dose 1 included 186 patients with E-R and baseline sBCMA data who were scheduled to receive a treatment regimen with two step-up doses before the first weekly treatment dose and who received exactly one administration of step-up dose 1 before step-up dose 2.

The following covariates were investigated for associations with CRS incidence with step-up dose 1 using multivariate logistic regression: step-up dose 1 individual predicted C_{max}, body weight, CrCl, eGFR, renal function group based on eGFR, BMPC group (below median or above median), baseline sBCMA, sBCMA group (below median or above median), age, albumin, AST, ALT, ALP, total bilirubin, total protein, type of myeloma (IgG or non-IgG), cytogenetic risk (high, standard, or not reported), ISS stage, extramedullary plasmacytoma at baseline (yes or no), sex, race (White, Asian, Black or African American, Other), ethnicity (Hispanic or non-Hispanic), liver function category, triple-class refractory status (yes or no), number of prior lines (3 or fewer, 4, 5, or 6 or more), ECOG (0 vs. 1 or greater), LDH, and MajesTEC-1 Phase (Phase 1 or Phase 2).

Step-up dose 1 C_{max} was retained in the model while all other covariates underwent forwards selection then backwards elimination. The final model is described in **FDA Table 18**.

FDA Table 27: Final Multivariate Model of Incidence of CRS with Step up Dose 1 in the E-R Safety Dataset

	Estimate	Standard Error	p value
Intercept	1.737	1.161	0.135
Step-up dose 1 C_{max} (ug/mL)	3.664	1.919	0.056
Baseline sBCMA (ng/mL)	-0.0026	0.0012	0.026
Age (years)	-0.039	0.017	0.021

E-R = exposure-response; sBCMA = soluble B cell maturation antigen; Step-up dose 1 C_{max} = maximum concentration following step-up dose 1 before administration of step-up dose 2.
Source: Reviewer analysis of Applicant's E-R dataset (ir5dataset-csv.xpt) provided in part 2 of Applicant's Response to FDA 24 February 2022 information request

The final model predicted that patients with higher step-up dose 1 Cmax were more likely to experience CRS with step-up dose 1 compared to patients with lower exposure following step-up dose 1 (**FDA Figure 10**). The final model also indicated that patients with higher baseline sBCMA and higher baseline age were less likely to experience CRS with step-up dose 1. The magnitude of sBCMA and age effects on step-up dose 1 CRS are visualized in **FDA Figure 11** and **FDA Figure 12**, respectively. The association between higher baseline sBCMA and lower step-up dose 1 CRS rate appears to be congruent with the model of ORR (see **Section 19.4.3.2**) which identified that higher baseline sBCMA was associated with lower ORR. Patients who do not respond to teclistamab would likely have less T cell engager-mediated cell killing and thus less release of cytokines.

FDA Figure 10: Exploratory E-R Safety Model-Predicted Effect of Step up Dose 1 C_{max} on Step up Dose 1 CRS Rate

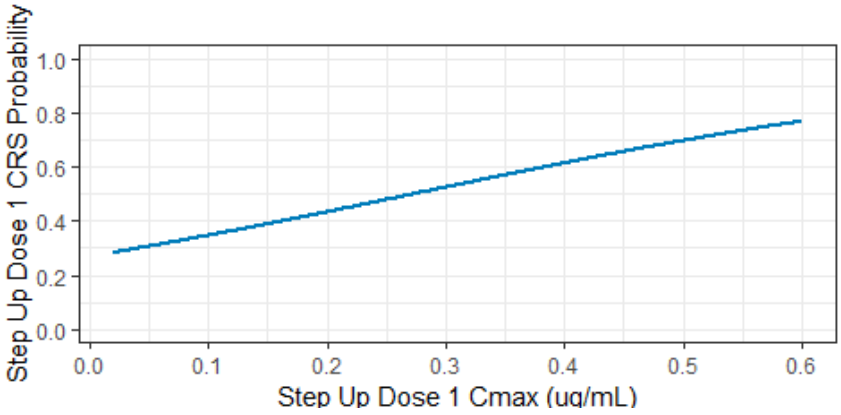
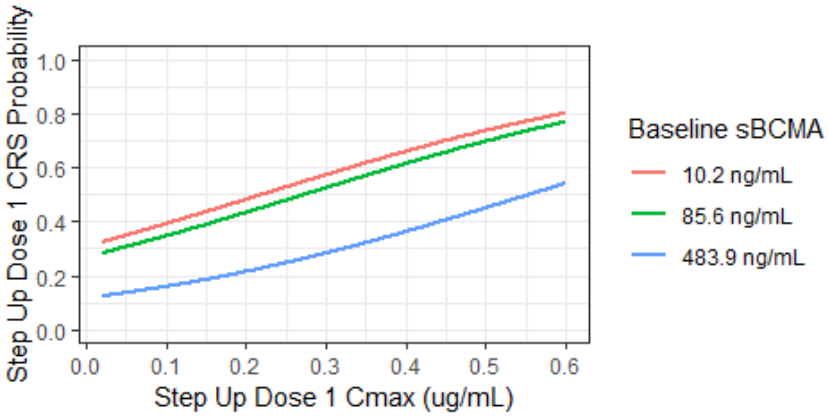


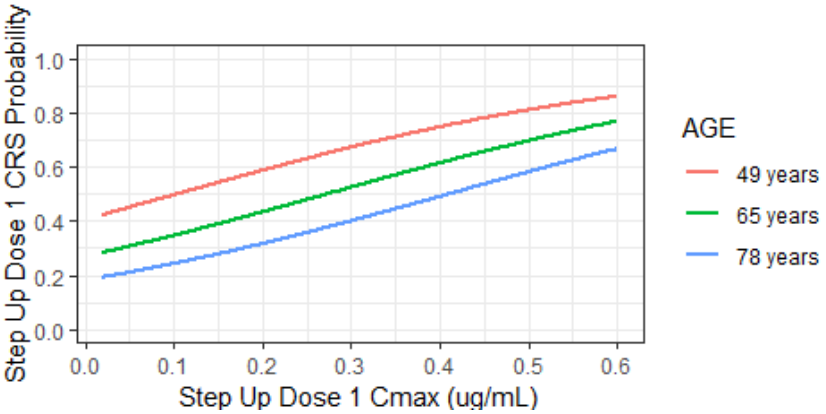
Figure shows predicted CRS rate for median age of 65 years and median baseline sBCMA of 85.61 ng/mL.
CRS = cytokine release syndrome; E-R = exposure-response; sBCMA = soluble B cell maturation antigen; Step-up dose 1 C_{max} = maximum concentration following step-up dose 1 before administration of step-up dose 2.
Source: Reviewer analysis of Applicant's E-R dataset (ir5dataset-csv.xpt) provided in part 2 of Applicant's Response to FDA 24 February 2022 information request

FDA Figure 11: Exploratory E-R Safety Model-Predicted Effect of sBCMA on Step up Dose 1 CRS Risk versus Step up Dose 1 C_{max}



30.0, 85.6, and 483.91 ng/mL are the 5th percentile, median, and 95th percentile of sBCMA in the E-R dataset, respectively.
Figure shows predicted CRS risk for median age of 65 years.
CRS = cytokine release syndrome; E-R = exposure-response; sBCMA = soluble B cell maturation antigen; Step-up dose 1 C_{max} = maximum concentration following step-up dose 1 before administration of step-up dose 2.
Source: Reviewer analysis of Applicant's E-R dataset (ir5dataset-csv.xpt) provided in part 2 of Applicant's Response to FDA 24 February 2022 information request

FDA Figure 12: Exploratory E-R Safety Model-Predicted Effect of Age on CRS Risk versus Step up Dose 1 C_{max}



49, 65, and 78 years are the 5th percentile, median, and 95th percentile of age in the E-R dataset, respectively.
Figure shows predicted CRS risk for median sBCMA value of 85.61 ng/mL.
CRS = cytokine release syndrome; E-R = exposure-response; sBCMA = soluble B cell maturation antigen; Step-up dose 1 C_{max} = maximum concentration following step-up dose 1 before administration of step-up dose 2.
Source: Reviewer analysis of Applicant's E-R dataset (ir5dataset-csv.xpt) provided in part 2 of Applicant's Response to FDA 24 February 2022 information request

Any Grade CRS with Step-up Dose 2

The E-R analysis of CRS incidence with step-up dose 2 included 185 patients with E-R and baseline sBCMA data who were scheduled to receive a treatment regimen with two step-up doses before the first weekly treatment dose and who received exactly one administration of step-up dose 1 and one administration of step-up dose 2 before the first treatment dose.

The following covariates were investigated for associations with CRS incidence with step-up dose 1 using multivariate logistic regression: step-up dose 1 C_{max}, step-up dose 2 C_{max}, CRS event with step-up dose 1 (yes or no), tocilizumab administration for treatment of CRS with step-up dose 1 (yes or no), body weight, CrCl, eGFR, renal function group based on eGFR, BMPC group (below median or above median), baseline sBCMA, sBCMA group (below median or above median), age, albumin, AST, ALT, ALP, total bilirubin, total protein, type of myeloma (IgG or non-IgG), cytogenetic risk (high, standard, or not reported), ISS stage, extramedullary plasmacytoma at baseline (yes or no), sex, race (White, Asian, Black or African American, Other), ethnicity (Hispanic or non-Hispanic), liver function category, triple-class refractory status (yes or no), number of prior lines (3 or fewer, 4, 5, or 6 or more), ECOG (0 vs. 1 or greater), LDH, and MajesTEC-1 Phase (Phase 1 or Phase 2). An interaction term between step-up dose 1 Cmax and step-up dose 2 Cmax was also investigated.

Step-up dose 1 C_{max} and step-up dose 2 C_{max} were retained in the model while other covariates underwent forwards selection then backwards elimination. The final model is shown in **FDA Table 19**.

FDA Table 28: Final Multivariate Model of Incidence of CRS with Step up Dose 2 in the E-R Safety Dataset

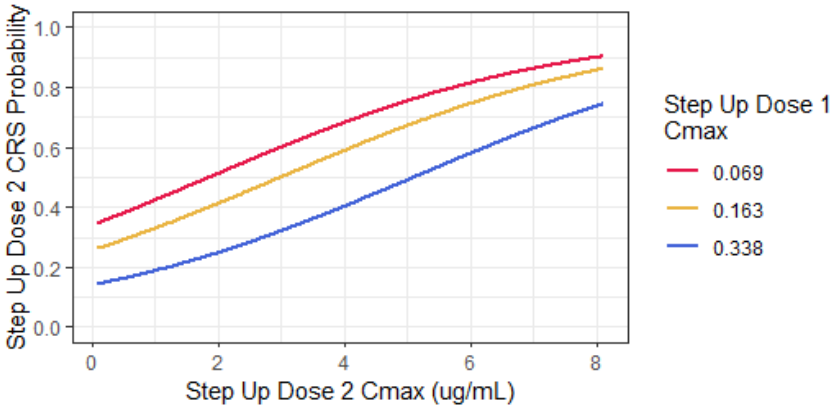
	Estimate	Standard Error	p value
Intercept	-1.964	0.565	0.001
Step-up dose 1 C_{max} (ug/mL)	-4.299	2.375	0.070
Step-up dose 2 C_{max} (ug/mL)	0.357	0.178	0.045
CRS event with step-up dose 1	-2.385	0.712	0.001
Tocilizumab administration for treatment of CRS with step-up dose 1	1.085	0.385	0.005
Baseline ALP (U/L)	0.013	0.005	0.017
Male sex (versus female)	0.744	0.362	0.040

ALP = alkaline phosphatase; CRS = cytokine release syndrome; E-R = exposure-response; Step-up dose 1 C_{max} = maximum concentration following step-up dose 1 before administration of step-up dose 2; Step-up dose 2 C_{max} = maximum concentration following step-up dose 2 before administration of first treatment dose.
Source: Reviewer analysis of Applicant's E-R dataset (ir5dataset-csv.xpt) provided in part 2 of Applicant's Response to FDA 24 February 2022 information request

The final model indicated that the rate of CRS decreased with higher step-up dose 1 C_{max} and increased with higher step-up dose 2 C_{max} (**FDA Figure 13**). Patients who experienced CRS with step-up dose 1 had a higher risk of CRS with step-up dose 2 compared to patients who had not experienced CRS before step-up dose 2. However, tocilizumab administration with step-up dose 1 lowered the risk of CRS with step-up dose 2. In the E-R analysis of CRS with step-up dose 2, 73/185 (39.5%) patients experienced CRS with step-up dose 1 and 26/185 (14.1%) patients received tocilizumab to treat CRS occurring with step-up dose 1. MajesTEC-1 patients who received tocilizumab after step-up dose 1 may still have therapeutically relevant tocilizumab concentrations, inhibition of IL-6 signaling, or both during step-up dose 2 (which was administered 2 to 7 days after step-up dose 1).

The MajesTEC-1 study permitted tocilizumab administration to treat any grade CRS at the Investigator's discretion. If protocol or administration rates of tocilizumab differ from MajesTEC-1, the rate of CRS may also differ from the MajesTEC-1 CRS rate due to the potential effect of recent tocilizumab administration on CRS probability with subsequent doses.

FDA Figure 13: Effect of Step up Dose 2 C_{max} and Step up Dose 1 C_{max} on Step up Dose 2 CRS Risk



0.0691 ug/mL, 0.1631 ug/mL, and 0.3381 ug/mL are the 5th percentile, median, and 95th percentile of step-up dose 1 Cmax in the E-R dataset, respectively.
Figure shows predicted CRS risk for median ALP of 66 U/L, male sex, and no CRS or tocilizumab administration with step-up dose 1. Predicted CRS risk based on exploratory Reviewer E-R safety model.
ALP = alkaline phosphatase; CRS = cytokine release syndrome; E-R = exposure-response; Step-up dose 1 C_{max} = maximum concentration following step-up dose 1 before administration of step-up dose 2; Step-up dose 2 C_{max} = maximum concentration following step-up dose 2 before administration of first treatment dose.
Source: Reviewer analysis of Applicant's E-R dataset (ir5dataset-csv.xpt) provided in part 2 of Applicant's Response to FDA 24 February 2022 information request

Conclusions
The reviewer's exploratory E-R analysis of CRS with step-up dosing supported the need for a step-up dosing regimen prior to the weekly treatment dose of teclistamab to mitigate the risk of CRS in patients with relapsed or refractory multiple myeloma. The E-R safety analysis did not identify any safety concerns with the proposed step-up dosing of teclistamab.

Additionally, tocilizumab administration for any grade CRS at the investigator's discretion may have impacted the rate of CRS for a given dose or overall in MajesTEC-1. If tocilizumab protocol or tocilizumab administration rates differed from those of MajesTEC-1, the rates of any grade CRS and severe (i.e., Grade ≥2) CRS may differ as well.

19.4.3.6 Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position:

A positive E-R relationship was observed for ORR assessed by investigator based on IMWG 2011 criteria in Phase 1 across the teclistamab exposure range associated with SC doses from 0.08 to 3 mg/kg weekly, and the response at the concentration range of RP2D is approaching the ORR plateau (ie, maximum response). At RP2D, responders and non responders had comparable and overlapping exposure range. Additionally, no apparent positive E-R trend was observed in the incidence of Grade ≥3 TEAEs of anemia, neutropenia, lymphopenia, thrombocytopenia, and

infections across the predicted exposure quartiles in subjects who received teclistamab SC. Therefore, the recommended teclistamab RP2D of 1.5 mg/kg SC administered weekly, with the first treatment dose preceded by step-up doses of 0.06 and 0.3 mg/kg is considered effective and appropriate in patients with relapsed or refractory multiple myeloma, with no need for dose adjustments based on efficacy, safety, and clinical pharmacology findings.

The FDA's Assessment:
FDA generally agrees with the Applicant's E-R conclusions supporting the proposed step-up doses of 0.06 mg/kg then 0.3 mg/kg followed by 1.5 mg/kg once weekly in adults with relapsed or refractory multiple myeloma.

19.5 MajesTEC-1 Eligibility Criteria

The full eligibility criteria from Amendment 11 of Protocol 64007957MMY1001 (MajesTEC-1) are as follows: (Source: Protocol 64007957MMY1001 Amendment 11, pp. 78-84, copied with minor modifications to formatting and removal cross references to attachments and other sections of the protocol)

Inclusion Criteria

1. ≥18 years of age.
2. Documented diagnosis of multiple myeloma according to IMWG diagnostic criteria.
3. **Part 1 and Part 2:** Measurable multiple myeloma that is relapsed or refractory to established therapies with known clinical benefit in relapsed/refractory multiple myeloma or be intolerant of those established multiple myeloma therapies, and a candidate for teclistamab treatment in the opinion of the treating physician. Prior lines of therapy must include a PI, an IMiD, and an anti-CD38 monoclonal antibody in any order during the course of treatment. Subjects who could not tolerate a PI, IMiD, or an anti-CD38 monoclonal antibody are allowed. See Section 8.1 regarding prior treatment with anti-CD38 therapies. In Part 2 (dose expansion), in addition to above criteria, multiple myeloma must be measurable per current IMWG published guidelines by central laboratory assessment. If central laboratory assessment is not available, relevant local laboratory measurement must exceed the minimum required level by at least 25%.
   Part 3:
   Measurable disease
   Cohort A, Cohort B, and Cohort C: Multiple myeloma must be measurable by central laboratory assessment:
   - Serum monoclonal paraprotein (M-protein) level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or
   - Light chain multiple myeloma without measurable disease in the serum or the urine: Serum immunoglobulin free light chain (FLC) ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda FLC ratio.

   If central laboratory assessments are not available, relevant local laboratory measurements must exceed the minimum required level by at least 25%.
   Prior treatment

- Cohort A: Subjects must have 1) received ≥3 prior lines of therapy and 2) previously received a PI, an IMiD, and an anti-CD38 monoclonal antibody.
- Cohort B: received ≥4 prior lines of therapy and whose disease is penta-drug refractory to an anti-CD38 monoclonal antibody, ≥2 PIs, ≥2 IMiDs (refractory multiple myeloma as defined by IMWG consensus criteria).
- Cohort C: received ≥3 prior lines of therapy that included a PI, an IMiD, an anti-CD38 monoclonal antibody, and an anti-BCMA treatment (with CAR-T cells or an ADC).
  Note for all 3 cohorts:
  - Induction with or without hematopoietic stem cell transplant and with or without maintenance therapy is considered a single line of therapy.
  - Undergone ≥1 complete cycle of treatment for each line of therapy, unless progressive disease was the best response to the line of therapy.
  - Subject must have documented evidence of progressive disease based on investigator's determination of response by the IMWG 2016 criteria on or within 12 months of their last line of therapy. Also, subjects with documented evidence of progressive disease (as above) within the previous 6 months and who are refractory or non-responsive to their most recent line of therapy afterwards are eligible.

4. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1.
5. Pretreatment clinical laboratory values meeting the following criteria during the Screening Phase:
   - Hemoglobin ≥8 g/dL (≥5 mmol/L) (without prior red blood cell [RBC] transfusion within 7 days before the laboratory test; recombinant human erythropoietin use is permitted)
   - Platelets ≥75×109/L for subjects in whom <50% of bone marrow nucleated cells are plasma cells; otherwise platelet count ≥50×109/L (without transfusion support in the 7 days prior to the laboratory test)
   - Absolute neutrophil count ≥1.0×109/L (prior growth factor support is permitted but must be without support in the 7 days prior to the laboratory test)
   - AST and ALT ≤3.0×upper limit of normal (ULN)
   - Serum creatinine ≤1.5 mg/dL or creatinine clearance: ≥40 mL/min/1.73 m^2 or estimated glomerular filtration rate ≥40 mL/min/1.73 m^2 based upon calculation (Modified Diet in Renal Disease formula calculation). A 24-hour urine collection can be utilized to calculate creatinine clearance.
   - Total bilirubin ≤2.0×ULN; except in subjects with congenital bilirubinemia, such as Gilbert syndrome (in which case direct bilirubin ≤1.5×ULN is required).
   - Corrected serum calcium ≤14 mg/dL (≤3.5 mmol/L) or free ionized calcium <6.5 mg/dL (<1.6 mmol/L)
6. Women of childbearing potential must have a negative pregnancy test at screening and prior to the first dose of study drug using a highly sensitive pregnancy test either serum (β human chorionic gonadotropin [β-hCG]) or urine.
7. Women of childbearing potential and fertile men who are sexually active must agree to use a highly effective method of contraception (<1%/year failure rate) from the time of signing the ICF during the study and for 90 days after the last dose of study drug. Contraception must be consistent with local regulations regarding the use of birth control methods for subjects

participating in clinical trials. When a woman is of childbearing potential the following are required:

- Subject must agree to practice a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly). Examples of highly effective contraceptives include:
  - user-independent methods: 1) implantable progestogen-only hormone contraception associated with inhibition of ovulation; 2) intrauterine device; intrauterine hormone-releasing system; 3) vasectomized partner;
  - user-dependent methods: 1) combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral or intravaginal or transdermal; 2) progestogen-only hormone contraception associated with inhibition of ovulation (oral or injectable)
  - A woman using hormonal contraceptives must use an additional barrier method.

In addition to the highly effective method of contraception, a man:

- Who is sexually active with a woman of childbearing potential must agree to use a barrier method of contraception (eg, condom with spermicidal foam/gel/film/cream/suppository)
- Who is sexually active with a woman who is pregnant must use a condom

Women and men must agree not to donate eggs (ova, oocytes) or sperm, respectively, during the study and for 90 days after the last dose of study drug.

Note: If the childbearing potential changes after start of the study or the risk of pregnancy changes, a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria. If reproductive status is questionable, additional evaluation should be considered. It should be noted that interaction between hormonal contraception and teclistamab have not been studied. Therefore, it is unknown whether teclistamab may reduce the efficacy of the contraceptive method.

8. Subject must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and is willing to participate in the study. Consent is to be obtained prior to the initiation of any study-related tests or procedures that are not part of standard of care for the subject's disease.
9. Willing and able to adhere to the prohibitions and restrictions specified in this protocol.

<u>Exclusion Criteria</u>

1. Prior treatment with any BCMA-targeted therapy, with the exception of Cohort C in Part 3.
2. Prior antitumor therapy as follows, before the first dose of study drug:
   - Targeted therapy, epigenetic therapy, or treatment with an investigational drug or used an invasive investigational medical device within 21 days or at least 5 half-lives, whichever is less.
   - Monoclonal antibody treatment for multiple myeloma within 21 days.
   - Cytotoxic therapy within 21 days.
   - Proteasome inhibitor therapy within 14 days.
   - Immunomodulatory agent therapy within 7 days.
   - Gene modified adoptive cell therapy (eg, chimeric antigen receptor modified T cells,

natural killer [NK] cells) within 3 months
- Radiotherapy within 14 days or focal radiation within 7 days.

3. Toxicities from previous anticancer therapies that have not resolved to baseline levels or to Grade 1 or less except for alopecia or peripheral neuropathy.
4. Received a cumulative dose of corticosteroids equivalent to ≥140 mg of prednisone within the 14-day period before the first dose of study drug (does not include pretreatment medication)
5. Stem cell transplantation:
   - An allogeneic stem cell transplant within 6 months. Subjects who received an allogeneic transplant must be off all immunosuppressive medications for 6 weeks without signs of graft-versus-host disease.
   - Received an autologous stem cell transplant ≤12 weeks before the first dose of study drug.
6. Known active CNS involvement or exhibits clinical signs of meningeal involvement of multiple myeloma.
7. Plasma cell leukemia (>2.0×109/L plasma cells by standard differential), Waldenström's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), or primary amyloid light-chain amyloidosis.
8. Known to be seropositive for human immunodeficiency virus or acquired immune deficiency syndrome.
9. Hepatitis B infection or at risk for hepatitis B virus (HBV) reactivation as defined according to the American Society of Clinical Oncology guidelines. In the event the infection status is unclear, quantitative levels are necessary to determine the infection status. Active Hepatitis C infection as measured by positive hepatitis C virus (HCV)-RNA testing. Subjects with a history of HCV antibody positivity must undergo HCV-RNA testing.
10. Pulmonary compromise requiring supplemental oxygen use to maintain adequate oxygenation.
11. Known allergies, hypersensitivity, or intolerance to the study drug (teclistamab) or its excipients (refer to Investigator's Brochure).
12. Any serious underlying medical condition, such as:
13. Pregnant or breast-feeding, or planning to become pregnant while enrolled in this study or within 90 days after receiving the last dose of study drug.
14. Plans to father a child while enrolled in this study or within 90 days after receiving the last dose of study drug.
15. Major surgery within 2 weeks of the first dose, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study or within 2 weeks after the last dose of study drug administration (note: subjects with planned surgical procedures to be conducted under local anesthesia may participate).

Any potential subject who meets any of the following criteria will be excluded from participating in Part 3:

16. The following cardiac conditions:
    - New York Heart Association stage III or IV congestive heart failure
    - Myocardial infarction or coronary artery bypass graft (CABG) ≤6 months prior to enrollment

- History of clinically significant ventricular arrhythmia or unexplained syncope, not believed to be vasovagal in nature or due to dehydration
- History of severe non-ischemic cardiomyopathy

17. Myelodysplastic syndrome or active malignancies (ie, progressing or requiring treatment change in the last 24 months) other than relapsed/refractory multiple myeloma. The only allowed exceptions are:
    - Non-muscle invasive bladder cancer treated within the last 24 months that is considered completely cured.
    - Skin cancer (non-melanoma or melanoma) treated within the last 24 months that is considered completely cured.
    - Noninvasive cervical cancer treated within the last 24 months that is considered completely cured.
    - Localized prostate cancer (N0M0):
        - With a Gleason score of 6, treated within the last 24 months or untreated and under surveillance.
        - With a Gleason score of 3+4 that has been treated more than 6 months prior to full study screening and considered to have a very low risk of recurrence,
        - Or history of localized prostate cancer and receiving androgen deprivation therapy and considered to have a very low risk of recurrence.
    - Breast cancer:
        - Adequately treated lobular carcinoma in situ or ductal carcinoma in situ,
        - Or history of localized breast cancer and receiving antihormonal agents and considered to have a very low risk of recurrence.
    - Malignancy that is considered cured with minimal risk of recurrence.
18. Live, attenuated vaccine within 4 weeks prior to the first dose of teclistamab.

19.6 FDA Grouped Terms

FDA Table # lists the grouped preferred terms utilized in the FDA safety analyses.

FDA Grouped Term (GT)	Preferred Terms
Abdominal pain (GT)	Abdominal discomfort Abdominal pain Abdominal pain upper
Acute kidney injury (GT)	Acute kidney injury Renal impairment
Anemia (GT)	Anemia Iron deficiency anemia Microcytic anemia
Cardiac arrhythmia (GT)	Atrial flutter Cardiac arrest

	Sinus bradycardia Sinus tachycardia Supraventricular tachycardia Tachycardia Ventricular tachycardia
Cardiac failure (GT)	Cardiac failure Left ventricular failure
Congestion (GT)	Nasal congestion Sinus congestion
Contusion (GT)	Contusion Muscle contusion
Cough (GT)	Allergic cough Cough Productive cough Upper-airway cough syndrome
COVID-19 (GT)*	Asymptomatic COVID-19 COVID-19
Dyspnea (GT)	Dyspnea Dyspnea exertional
Edema (GT)	Face edema Fluid overload Fluid retention Edema peripheral Peripheral swelling
Encephalopathy (GT)	Agitation Apathy Aphasia Confusional state Delirium Depressed level of consciousness Disorientation Dyscalculia Hallucination Lethargy Memory impairment Mental status changes Somnolence
Fatigue (GT)	Asthenia Fatigue
Hemorrhage (GT)	Conjunctival hemorrhage Epistaxis Hematoma Hematuria Hemoperitoneum Hemorrhoidal hemorrhage Lower gastrointestinal hemorrhage

	Melaena Mouth hemorrhage Subdural hematoma
Herpesvirus infection (GT)	Herpes zoster Oral herpes
Hypertension (GT)	Essential hypertension Hypertension
Injection site reaction (GT)	Application site erythema Injection site bruising Injection site cellulitis Injection site discomfort Injection site erythema Injection site hematoma Injection site induration Injection site inflammation Injection site oedema Injection site pruritus Injection site rash Injection site reaction Injection site swelling
Motor dysfunction (GT)	Cogwheel rigidity Dysgraphia Dysphonia Gait disturbance Hypokinesia Muscle rigidity Muscle spasms Muscular weakness Peroneal nerve palsy Psychomotor hyperactivity Tremor VIth nerve paralysis
Musculoskeletal pain (GT)	Arthralgia Back pain Muscle discomfort Musculoskeletal chest pain Musculoskeletal pain Myalgia Neck pain Non-cardiac chest pain Pain in extremity
Pain (GT)	Ear pain Flank pain Groin pain Oropharyngeal pain Pain Pain in jaw

	Toothache Tumor pain
Pneumonia (GT)*	COVID-19 Enterobacter pneumonia Lower respiratory tract infection Metapneumovirus pneumonia Pneumocystis jirovecii pneumonia Pneumonia Pneumonia adenoviral Pneumonia klebsiella Pneumonia moraxella Pneumonia pneumococcal Pneumonia pseudomonal Pneumonia respiratory syncytial viral Pneumonia staphylococcal Pneumonia viral
Rash (GT)	Rash Rash maculopapular Rash pruritic
Sensory neuropathy (GT)	Dysaesthesia Hypoaesthesia Hypoaesthesia oral Neuralgia Paraesthesia Paraesthesia oral Peripheral sensory neuropathy Sciatica Vestibular neuronitis
Sepsis (GT)	Bacteremia Meningococcal sepsis Pseudomonal bacteremia Pseudomonal sepsis Sepsis Staphylococcal bacteremia
Thrombophlebitis (GT)	Thrombophlebitis Thrombophlebitis superficial
Thrombosis (GT)	Deep vein thrombosis Peripheral embolism Pulmonary embolism Thrombosis in device Venous thrombosis limb
Transaminase elevation (GT)	Alanine aminotransferase increased Aspartate aminotransferase increased
Upper respiratory tract infection (GT)	Bronchitis Influenza-like illness Nasopharyngitis

	Pharyngitis Respiratory tract infection Respiratory tract infection bacterial Rhinitis Rhinovirus infection Sinusitis Tracheitis Upper respiratory tract infection Viral upper respiratory tract infection
Urinary tract infection (GT)	Cystitis Cystitis escherichia Cystitis klebsiella Escherichia urinary tract infection Urinary tract infection Urinary tract infection bacterial

*Some events of COVID-19 were recoded as COVID-19 pneumonia based on review of verbatim terms.

19.7 Additional FDA Safety Analyses

The FDA's Assessment:

In the 26 Apr 2022 Clinical Information Request, FDA requested that the Applicant provide additional analyses regarding outcomes in patients with CRS who received tocilizumab and patients with CRS who did not receive tocilizumab. Select analyses from the Applicant's 05 May 2022 response are copied below. The median duration of CRS was 2 days regardless of whether tocilizumab was administered (Table 8 from the Applicant's response). The median time to next teclistamab dose was 4 days regardless of whether tocilizumab was administered (Table 6 from the Applicant's response). A slightly higher percentage of patients with CRS who received tocilizumab experienced a dose interruption of teclistamab compared to patients with CRS who did not receive tocilizumab, but the overall incidence of dose interruptions due to CRS was low (Table 10 from the Applicant's response). Based on the absence of any substantial differences in these key outcomes, FDA concluded that, overall, there were no clinically meaningful difference in outcomes between patients with Grade 1 or 2 CRS who received tocilizumab and patients with Grade 1 or 2 CRS who did not receive tocilizumab. Therefore, this additional data that was provided did not provide support for the inclusion of tocilizumab use to manage teclistamab-induced CRS in the USPI.

Table 8: Duration of Treatment-emergent Cytokine Release Syndrome (CRS); All Treated Analysis Set (Study 64007957MMY1001)

	RP2D	Total
Analysis set: All Treated	165	340
Number of CRS events	192	399
Tocilizumab administered		
Number of CRS events treated with tocilizumab[a]	68 (35.4%)	116 (29.1%)
Duration of CRS, days		
N	68	116
Mean (SD)	2.4 (1.68)	2.2 (1.55)
Median	2.0	2.0
Range	(1; 9)	(1; 9)
No Tocilizumab		
Number of CRS events that were not treated with tocilizumab[b]	124 (64.6%)	283 (70.9%)
Duration of CRS, days		
N	124	283
Mean (SD)	1.9 (1.04)	1.8 (0.94)
Median	2.0	2.0
Range	(1; 7)	(1; 7)

Key: CRS=cytokine release syndrome; RP2D = recommended Phase 2 dose
[a] Treatment for CRS and CRS symptoms are considered.
[b] Includes CRS events where tocilizumab was not administered for the CRS event or symptoms.
Note: Percentages calculated with the number of CRS events in the all treated analysis set as denominator.
Note: Adverse events are reported until 100 days (Phase 1) or 30 days (Phase 2) after the last dose of teclistamab or until the start of subsequent anticancer therapy, if earlier.
Note: Duration is defined as end date of CRS – start date of CRS +1.
Note: CRS was graded by Lee criteria (Lee et al 2014) in Phase 1 non-RP2D and by ASTCT consensus grading system (Lee et al 2019) in Phase 1 RP2D, Phase 2, and Cohort C.

Table 6: Time to Next Teclistamab Dose in Subjects with Treatment-emergent Cytokine Release Syndrome (CRS); All Treated Analysis Set (Study 64007957MMY1001)

	RP2D	Total
Analysis set: All Treated	165	340
Number of CRS events	192	399
Tocilizumab administered		
Number of CRS events treated with tocilizumab[a]	68 (35.4%)	116 (29.1%)
Time from CRS to next dose of teclistamab, days		
N	65	111
Mean (SD)	5.5 (5.50)	5.6 (4.54)
Median	4.0	5.0
Range	(2; 44)	(2; 44)
No Tocilizumab		
Number of CRS events that were not treated with tocilizumab[b]	124 (64.6%)	283 (70.9%)
Time from CRS to next dose of teclistamab, days		
N	124	282
Mean (SD)	4.6 (2.45)	5.4 (2.85)
Median	4.0	5.0
Range	(2; 22)	(2; 23)

Key: CRS=cytokine release syndrome; RP2D = recommended Phase 2 dose
[a] Treatment for CRS and CRS symptoms are considered.
[b] Includes CRS events where tocilizumab was not administered for the CRS event or symptoms.
Note: Percentages calculated with the number of CRS events in the all treated analysis set as denominator.
Note: Time from CRS to next dose of teclistamab is defined as start date of the next teclistamab dose after the CRS event – start date of CRS +1
Note: Adverse events are reported until 100 days (Phase 1) or 30 days (Phase 2) after the last dose of teclistamab or until the start of subsequent anticancer therapy, if earlier.

Table 10: Subjects with Treatment-emergent Cytokine Release Syndrome (CRS) Leading to Dose Interruption; All Treated Analysis Set (Study 64007957MMY1001)

TSFAE24F11A_FDA: Subjects with Treatment-emergent Cytokine Release Syndrome (CRS) Leading to Dose Interruption; All Treated Analysis Set (Study 64007957MMY1001)

	RP2D	Total
Analysis set: All Treated	165	340
Number of CRS events	192	399
Dose interruption due to CRS	13 (6.8%)	27 (6.8%)
Treated with tocilizumab[a]	9 (4.7%)	14 (3.5%)
Not treated with tocilizumab[b]	4 (2.1%)	13 (3.3%)

Key: CRS=cytokine release syndrome; RP2D = recommended Phase 2 dose
[a] Treatment for CRS and CRS symptoms are considered.
[b] Includes CRS events where tocilizumab was not administered for the CRS event or symptoms.
Note: Dose interruption includes delays within cycle and dose skipped.
Note: Percentages calculated with the number of CRS events in the all treated analysis set as denominator.
Note: Adverse events are reported until 100 days (Phase 1) or 30 days (Phase 2) after the last dose of teclistamab or until the start of subsequent anticancer therapy, if earlier.

Multi-Disciplinary Review Signature Page

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Lauren Price, PharmD	OCP/DCPI	Sections: 6, 19.4	**Select one:** ☑ Authored ☐ Approved
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Clinical Pharmacology Team Leader	Nan Zheng, PhD	OCP/DCPI	Sections: 6, 19.3	**Select one:** ☐ Authored ☑ Approved
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