CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761345Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 14, 2023

SUBJECT: Assessment Aid Authored Section Correction

APPLICATION/DRUG: Elrexfio (elranatamab-bcmm)

In reference to the Assessment Aid, finalized on August 14, 2023 under BLA 761345, there are the following corrections to the Signature Page:

- Guansheng Liu, PhD, authored Section 19.4.5
- Yuching Yang, PhD, authored and approved Section 19.4.5.
- Youssef Roman, PharmD, PhD, authored Section 19.4.2.
- Jeffrey Kraft, PhD, authored and approved Section 19.4.2.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NATASHA L KORMANIK
08/14/2023 01:10:27 PM

NDA/BLA Multi-disciplinary Review and Evaluation

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

FDA review was conducted in conjunction with other regulatory authorities under Project ORBIS. FDA collaborated with Australia's Therapeutic Goods Administration (TGA), Brazil's Health Regulatory Agency (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 application may still be under review at the other regulatory agencies.

Application Type	Original BLA
Application Number(s)	761345
Priority or Standard	Priority
Submit Date(s)	December 19, 2022
Received Date(s)	December 19, 2022
PDUFA Goal Date	August 19, 2023
Division/Office	Division of Hematologic Malignancies II/ Office of Oncologic Diseases
Review Completion Date	08/09/2023
Established Name	Elranatamab
(Proposed) Trade Name	ELREXFIO
Pharmacologic Class	Bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager
Code name	PF-06863135
Applicant	Pfizer
Formulation(s)	Injection 44 mg/1.1 mL (40 mg/mL) in a single-dose vial 76 mg/1.9 mL (40 mg/mL) in a single-dose vial
Dosing Regimen	The recommended dosage of ELREXFIO is step-up doses of 12 mg on Day 1 and 32 mg on Day 4 followed by 76 mg on Day 8 and then once weekly thereafter through week 24. Responders may switch to biweekly dosing at week 25 onward.
Applicant Proposed Indication(s)/Population(s)	ELREXFIO 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.
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	ELREXFIO 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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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Natasha Kormanik, MSN, FNP-BC, OCN
Pharmacology/Toxicology Reviewer(s)	Daniela Torres, PhD
Pharmacology/Toxicology Team Leader(s)	Brenda Gehrke, PhD
Office of Clinical Pharmacology Reviewer(s)	Yue Xiang, PharmD; Hongshan Li, PhD; Youssef Roman, PharmD, PhD; Guansheng Liu, PhD
Office of Clinical Pharmacology Team Leader(s)	Xiling Jiang, PhD; Jiang Liu, PhD; Jeffrey Kraft, PhD; Yuching Yang, PhD
Clinical Reviewer	Rachel Ershler, MD
Clinical Team Leader	Bindu Kanapuru, MD
Safety Analyst (if applicable)	N/A
Statistical Reviewer	Jing Zhang, PhD
Statistical Team Leader	Qing Xu, PhD
Associate Director for Labeling (ADL)	Elizabeth Everhart, MSN, RN, ACNP
Cross-Disciplinary Team Leader	Bindu Kanapuru, MD
Division Director (DHOT)	Haleh Saber, PhD
Division Director (OCP)	Brian Booth, PhD
Deputy Division Director (OB)	Lisa Rodriguez, PhD
Division Director (OOD)	Nicole Gormley, MD
Office Director (or designated signatory authority)	Marc Theoret, MD

Additional Reviewers of Application

OPQ	Anjali Shukla, PhD (ATL) You Zhuo, PhD
Microbiology	Hamet Toure, PharmD, MPH Maria Guierrez-Hoffman, PhD
OPDP	Jina Kwak, PharmD
OSI	Leigh Marcus, MD
OSE/DEPI	Orestis Panagiotou, MD, PhD
OSE/DMEPA	Nicole Iverson, PharmD, BCPS Christina Topper
OSE/DRM	Robert Pratt, MD
Project Orbis	Dianne Spillman

Project Orbis #90 Partner-Australia's Therapeutic Goods Administration (TGA) Review Team		**ROLE**	**NAME** (b) (6)
		Clinical Team Lead	
		Nonclinical Team Lead	
		Biological Sciences / Quality Team Leads	
		Project Orbis coordination team	
Project Orbis #90 Partner-Brazil's Health Regulatory Agency (ANVISA) Review Team		**ROLE**	**NAME** (b) (6)
		Clinical Assessor	
		Clinical Peer Assessor	
		Non-Clinical Assessor	
		Quality Assessor	
		Quality Assessor Peer	
		ANVISA Project Orbis coordinators	
		ANVISA Project Orbis Biologics Contacts	
Project Orbis #90 Partner-Health Canada (HC) Review Team		**ROLE**	**NAME** (b) (6)
		Clinical Manager (Clinical Evaluation Division – Oncology & Hematology (CEDOH))	
		Senior Clinical Evaluator (Clinical Evaluation Division – Oncology & Radiopharmaceuticals CEDOH)	
		Manager, Biotherapeutics Quality Division 2 (BQD)	
		Senior Biologist/Evaluator BQD1	
		Senior Regulatory Affairs Officer	
		Regulatory Affairs Supervisor	
		Risk Management Reviewer	
Project Orbis #90 Partner-Switzerland's Swissmedic (SMC) Review Team		**ROLE**	**NAME** (b) (6)
		Clinical Assessor	
		Clinical Peer Assessor	
		Clinical Pharmacology Assessor	
		Biostatistician	
		Non-Clinical Assessor	
		Non-Clinical Peer Assessor	

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		Quality Assessor	(b) (6)
		Quality Co-Assessor Virus safety	
		Quality Co-Assessor Microbiology	
		Quality Assessor Peer	
		Risk Management Assessor	
		Regulatory Project Manager	
		SMC Project Orbis coordinators (always cc)	
		Head Clinical Review Unit Oncology	

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

Abbreviation	Definition
AA	accelerated approval
AC	advisory committee
ADA	anti-drug antibody
ADC	antibody-drug conjugate
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AESI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AOM	Application orientation meeting
APRIL	A proliferation-inducing ligand, also known as tumor necrosis factor ligand superfamily member 13 (TNFSF13)
ASC	antibody-secreting cells
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area under curve
BAFF	B-cell activating factor also known as tumor necrosis factor ligand superfamily member 13B (TNFSF13B)
BCMA	B cell maturation antigen
BICR	blinded independent central review
BLA	biologics license application
BLQ	below the limit of quantitation
BM	bone marrow
BMA	bone marrow aspirate
BMB	bone marrow biopsy
BOR	best overall response
BPCA	Best Pharmaceuticals for Children Act
BRA	benefit-risk assessment
BRF	Benefit Risk Framework
bsAb	bispecific antibody
BTD	breakthrough designation
C#	cycle number
C#D#	cycle number day of cycle
C1q	complement component 1q
CAR-T	chimeric antigen receptor T-cell therapy

Abbreviation	Definition
CBER	Center for Biologics Evaluation and Research
CD3	cluster of differentiation 3
CD38	cluster of differentiation 38
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
ClinRO	clinician reported outcome
CL	clearance
CIOMS	Council for International Organizations of Medical Sciences
Cmax	maximum concentration
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
COA	clinical outcome assessment
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
COVID-19	coronavirus disease 2019
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CRO	contract research organization
CRS	cytokine release syndrome
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CTCAE	Common Terminology Criteria for Adverse Events
CTL	cytotoxic T lymphocytes
CV	cardiovascular
dex	dexamethasone
DI	dose intensity
DL	dose level
DLT	dose-limiting toxicity
DMC	data monitoring committee
DOCR	duration of complete response
DOR	duration of response
EC	ethics committee
EC_{50}	half maximal effective concentration
ECG	electrocardiogram

Abbreviation	Definition
ECOG PS	Eastern Cooperative Oncology Group performance status
eCTD	electronic common technical document
EIU	exposure in utero
EMD	extramedullary disease
EORTC	European Organisation for Research and Treatment of Cancer
EORTC EQ-5D	EuroQol Group standardized measure of health-related quality of life
EORTC MY20	European Organization for Research and Treatment of Cancer Multiple Myeloma module
EORTC QLQ-CIPN20	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire- Chemotherapy-induced peripheral neuropathy
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life of Cancer Patients core module
ER	exposure-response
ETASU	elements to assure safe use
F	female
FcγRIIA-131H	Fc gamma receptor IIa with histidine at amino acid 131
FcγRs	Fc gamma receptors
FcRN	Neonatal Fc receptor
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FLC	free light chain
FSFV	first subject first visit
FU	follow-up
GALT	gut-associated lymphoid tissue
GBS	Guillain-Barre syndrome
GCP	good clinical practice
GI	gastrointestinal
GLP	good laboratory practice
GRMP	good review management practice
GVHD	graft versus host disease
HBV	hepatitis B virus
HCV	hepatitis C virus
HD	high dose
HIV	human immunodeficiency virus
HLH	hemophagocytic lymphohistiocytosis
IMiD	immunomodulatory agent
IA	interim analysis
ICANS	immune effector cell-associated neurotoxicity syndrome

Abbreviation	Definition
ICD	informed consent document
ICH	International Conference on Harmonization
IFN	interferon
IG	immunogenicity
IL	interleukin
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IND	Investigational New Drug
iPSP	initial Pediatric Study Plan
IRR	infusion-related reaction
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
IVIG	intravenous immunoglobulin
KarMMa	Efficacy and Safety Study of bb2121 in Subjects With Relapsed and Refractory Multiple Myeloma
K_D	dissociation constant
K-M	Kaplan-Meier
LD	low dose
LLN	lower limit of normal
LOAEL	lowest dose at which there was an observed toxic or adverse effect
LSLV	last subject last visit
M	male
mAb	monoclonal antibody
MAD	mutual acceptance data
MAS	macrophage activation syndrome
MD	mid-dose
mDOR	median duration of response
MedDRA	Medical Dictionary for Regulatory Activities
MGUS	monoclonal gammopathy of undetermined significance
MHC	major histocompatibility complex
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	modified intent to treat
MM	multiple myeloma
mos	months
mOS	median overall survival
MRD	minimal residual disease
MTD	maximum tolerated dose

Abbreviation	Definition
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NE	not evaluable
NK cell	natural killer cell
NME	new molecular entity
No.	number
NOAEL	no-observed-adverse-effect level
oAECI	other adverse events of clinical interest
ObsRO	observer reported outcome
OCE	Oncology Center of Excellence
OCS	Office of Computational Science
OECD	Organisation for Economic Co-operation and Development
OL	open label
OPQ	Office of Pharmaceutical Quality
ORR	overall response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PA #	protocol amendment number
PABAK	prevalence-adjusted bias-adjusted kappa
PBRER	Periodic Benefit-Risk Evaluation Report
PCD	primary completion date
PD	progressive disease
PD	pharmacodynamic(s)
PFS	progression-free survival
PI	proteasome inhibitor
PI	prescribing information
PK	pharmacokinetic(s)
PMC	postmarketing commitment
PMR	postmarketing requirement
PN	peripheral neuropathy
POEMS	polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes
pop.	population
PP	per protocol
PPI	patient package insert
PPK	population pharmacokinetics
PREA	Pediatric Research Equity Act

Abbreviation	Definition
PR	partial response
PR	onset of the P wave to start of QRS complex
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	preferred term
Q#W	every number (#) of weeks
QD	once daily
QOL	quality of life
QRS	combination of Q, R, and S waves; represents ventricular depolarization
QT	time from the beginning of QRS complex to end of T wave
QTcF	corrected QT (Fridericia method)
QW	once weekly
RBC	red blood cell
RD	relative dose
RDI	relative dose intensity
REMS	risk evaluation and mitigation strategy
R-ISS	Revised International Staging System
RMANOVA	repeated measures analysis of variance
RP2D	recommended Phase 2 dose
RRMM	relapse or refractory MM
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
sCR	stringent complete response
SD	standard deviation
SE	standard error
SEM	standard error of the mean
SGE	special government employee
SMM	Smoldering multiple myeloma
SNE	selective inhibitor of nuclear export
SOC	System Organ Class
SPEP	serum protein electrophoresis
SPR	surface plasmon resonance
STORM	Oral Selinexor–Dexamethasone for Triple-Class Refractory Multiple Myeloma
TBD	to be determined
TEAE	treatment emergent adverse event

Abbreviation	Definition
TK	toxicokinetic
TTR	time to response
ULN	upper limit of normal
UPEP	urine protein electrophoresis
US or USA	United States of America
USPI	United States Prescribing Information
VGPR	very good partial response
VHP	voluntary harmonization procedure
wks	weeks
yrs	years

1 Executive Summary

1.1 Product Introduction

Product: Elranatamab (ELREXFIO)

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

Proposed Indication: ELREXFIO 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 four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

Dosing Regimen: The recommended dosage of ELREXFIO is step-up doses of 12 mg on Day 1 and 32 mg on Day 4 followed by 76 mg on Day 8 and then once weekly thereafter through week 24. Responders may switch to biweekly dosing at week 25 onward.

1.2 Conclusions on the Substantial Evidence of Effectiveness

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

"ELREXFIO 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."

Substantial evidence of effectiveness to support the accelerated approval of elranatamab was established with one adequate and well-controlled clinical investigation, MagnetisMM-3 (Study C1071003), with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations. MagnetisMM-3 trial (Study C1071003) (henceforth referred to as Study C1071003 throughout this review), is a Phase 1/2, single-arm, multicenter, multicohort trial evaluating elranatamab monotherapy in patients with relapsed or refractory MM (RRMM) who were refractory to at least one proteasome inhibitor (PI), one immunomodulatory drug (IMiD), and one anti-CD38 monoclonal antibody. The trial included 123 patients naïve to prior B-cell maturation antigen (BCMA)-directed therapy (pivotal Cohort A) and 64 patients with prior BCMA-directed antibody drug conjugate or chimeric antigen receptor T-cell therapy (supportive Cohort B).

The primary efficacy population included 97 patients in Cohort A with RRMM who had received at least 4 prior lines of therapy, including a PI, an IMiD, and an anti-CD38 mAb and who were treated at the proposed dosing regimen. In this efficacy population (n=97), the median age was 69 years (range: 46-89). There were 32 patients (33.0%) <65 years of age, 47 (48.5%) ≥65 to <75 years of age, and 18 (18.6%) ≥75 years of age. There were 58 male patients (59.8%), and most patients were White (59.8%) or had missing or unknown race (21.6%). Only 5.2% of patients in the efficacy population were Black or African American. Patients had received a median of 5 prior lines of therapy (range: 2 to 22) and 96.9% were triple-class refractory, and 94.8% were refractory to their last line of therapy.

The efficacy determination is based on objective response rate (ORR) and duration of response (DOR). The ORR in the efficacy population was 57.7% (95% CI: 47.3%, 67.7%). With a median follow-up of 11.1 months (95% CI: 10.6, 12.0) among responders, the median duration of response was not reached (NR). The DOR rate at 6 months was 90.4% (95% CI: 78.4%, 95.9%) and at 9 months was 82.3% (95% CI: 67.1%, 90.9%). Among the 64 patients enrolled in Cohort B who previously received a PI, IMiD, and an anti-CD38 mAb, the ORR was 33.3% (95% CI: 22.0%, 46.3%). With a median follow-up of 10.2 months (95% CI: 9.9, 11.0) among responders, the median duration of response was not reached (NR). The DOR rate at 9 months was 84.3% (95% CI: 58.7%, 94.7%).

MM is a serious condition, and ORR, supported by DOR data, is an acceptable endpoint for accelerated approval in this disease setting. The FDA considered the prior treatment and lines of therapy of the patient population enrolled on Study 1071003 and efficacy data in the proposed in the context of available therapies. Selinexor + dexamethasone
is the only relevant comparison. Selinexor has regular approval for the treatment of adult patients with RRMM who have received 4 prior therapies and are refractory to 2 PI, 2IMiDs and one CD38 monoclonal antibody, a more refractory patient population. The ORR for selinexor in this refractory patient population was 25.3% (95% CI 16.4, 36.0) and the DOR was 3.8 months (95% CI: 2.3, not estimable). Teclistamab, a bispecific BCMA directed CD3 T-cell engager was approved in 2023 for the same population requested by the Applicant but is not considered available therapy because this remains under accelerated approval. The two CAR T-cell products (idecabtagene vicleucel and ciltacabtagene autoleucel) are not included in the Division's consideration of available therapy due to the requirement for patient-specific manufacturing and the toxicity profile of these products, which preclude many patients with RRMM from being candidates.

The overall response rate of 57.7% with associated durability for elranatamab provides data to support a clinically meaningful treatment effect in the context of available therapy for the indicated patient population, *"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 accelerated approval and favorable benefit-risk determination are supported by the confirmatory trial being well underway. The proposed confirmatory trial is the ongoing randomized controlled study MagnetisMM-5 (C1071005): A Phase 3 Study of elranatamab monotherapy and elranatamab + daratumumab versus daratumumab + pomalidomide + dexamethasone in participants with relapsed/refractory multiple myeloma. The primary endpoint of Study C1071005 is progression-free survival by blinded independent central review (BICR). The study is well underway with 554 of a planned 750 patients as of July 12, 2023.

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). Multiple Myeloma is diagnosed most frequently among people aged 65-74 years 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 drug (IMiD) and an anti-CD38 monoclonal antibody (mAb), have poor outcomes.

Elranatamab is a BCMA-directed CD3 T-cell engaging bispecific monoclonal antibody. The data to support the proposed indication is based on Study C1071003 (MagnetisMM-3), a Phase 1/2, single-arm, multicenter, multicohort trial evaluating elranatamab monotherapy in patients with relapsed or refractory MM (RRMM). The trial included 123 patients naïve to prior B-cell maturation antigen (BCMA)-directed therapy (pivotal Cohort A) and 64 patients with prior BCMA-directed antibody drug conjugate or chimeric antigen receptor T-cell therapy (supportive Cohort B). The primary efficacy population included 97 patients in Cohort A with RRMM with at least 4 prior lines of therapy, including a PI, an IMiD, and an anti-CD38 mAb who were treated at the proposed dosing regimen. The overall response rate (ORR) in the efficacy population was 57.7% (95% CI: 47.3%, 67.7%). With a median follow-up of 11.1 months (95% CI: 10.6, 12.0) among responders, the median duration of response was not reached (NR). The DOR rate at 6 months was 90.4% (95% CI: 78.4%, 95.9%) and at 9 months was 82.3% (95% CI: 67.1%, 90.9%).

The primary safety population included patients from Study C1071003 who received the recommended dosing regimen (N=183) of 12 mg (step-up priming dose one), 32 mg (step-up priming dose two), and 76 mg (full dose). This included patients in Cohort A (no prior BCMA-directed therapy, N=119) and Cohort B (prior BCMA-directed therapy, N=64). The median duration of treatment in the overall safety population was 3.9 months (range: 0.03-19.8 months). The most common adverse reactions (≥ 20%) were CRS, fatigue, injection site reaction, diarrhea, upper respiratory tract infection, musculoskeletal pain, pneumonia, decreased appetite, rash, cough, nausea, and pyrexia. The most common Grade 3 or 4 laboratory abnormalities (≥ 30%) were decreased lymphocytes, decreased neutrophils, decreased hemoglobin, decreased white blood cells, and decreased platelets. Serious adverse events occurred in 68% of patients, and 19% had a dose reduction due to an adverse event. The most common adverse event leading to dose reduction was neutropenia (9.8%).

The key safety concerns for elranatamab are cytokine release syndrome (CRS) and neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS). Cytokine release syndrome and neurologic toxicity were common, occurring in 58% and 59% of patients, respectively. Most patients experienced CRS after the first step-up dose (43%) or the second step-up dose (19%), with 7% of patients having CRS after the first treatment dose. Neurologic toxicity included headache in 18% of patients, encephalopathy in 14%, motor dysfunction in 13%, and sensory neuropathy in 13%. Guillain-Barre Syndrome was reported in 0.5% of patients in the safety population.

Other safety concerns include hepatotoxicity, infections, and neutropenia, which are included in the Warnings and Precautions section of the elranatamab 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 elranatamab 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 a favorable benefit-risk and meet the criteria to support accelerated approval of elranatamab for the treatment of adult patients with RRMM who have received at least four prior lines of therapy including a PI, an IMiD, and an anti-CD38 mAb.

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 elranatamab in patients with RRMM. The proposed confirmatory trial is the ongoing randomized and controlled study MagnetisMM-5 (C1071005): A Phase 3 Study of Elranatamab (PF-06863135) Monotherapy and Elranatamab + Daratumumab Versus Daratumumab + Pomalidomide + Dexamethasone in Participants with Relapsed/Refractory Multiple Myeloma. The primary endpoint of Study C1071005 is progression-free survival by blinded independent central review (BICR). The study is well underway with 554 of a planned 750 patients as of July 12, 2023.

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, relapses are common and 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 drugs (IMiDs), proteasome inhibitors (PIs) and monoclonal antibodies (mAbs). • Patients who have received multiple lines of therapy including a PI, IMiD and an CD38 monoclonal antibody have limited available effective treatment options and have poor outcomes.	• Despite the availability of multiple therapies, RRMM remains an incurable disease.
Benefit	• Assessment of substantial evidence of effectiveness was based on the efficacy results in Study C1071003. • The primary efficacy population included 97 patients treated at the RP2D in Phase 2 Cohort A (BCMA-Naïve), and had received at least 4 prior lines of therapy, including a PI, an IMiD, and an anti-CD38 mAb. • The overall response rate (ORR) in the efficacy population was 57.7% (95% CI: 47.3%, 67.7%). • With a median follow-up of 11.1 months (95% CI: 10.6, 12.0) among responders, the median duration of response was not reached (NR).	• The ORR and durability of response in the single-arm trial provide evidence of effectiveness in this patient population. • A post-marketing requirement (PMR) to verify and describe the clinical benefit of elranatamab in a randomized clinical trial in patients with RRMM will be issued.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	The DOR rate at 6 months was 90.4% (95% CI: 78.4%, 95.9%) and at 9 months was 82.3% (95% CI: 67.1%, 90.9%).	
Risk and Risk Management	• Safety was evaluated in 183 patients in the Phase 1 and Phase 2 cohorts A (BCMA Naïve) and B (BCMA exposed) from Study C1071003 who received the recommended dosing regimen of 12 mg (step-up priming dose one), 32 mg (step-up priming dose two), and 76 mg (full dose). • Fatal adverse reactions occurred in 10% of patients and Serious adverse reactions in 68% of patients. • The most common adverse reactions (≥ 20%) were CRS, fatigue, injection site reaction, diarrhea, upper respiratory tract infection, musculoskeletal pain, pneumonia, decreased appetite, rash, cough, nausea, and pyrexia. • The key safety concerns for elranatamab are cytokine release syndrome (CRS) and neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS). CRS and neurologic toxicity were common, occurring in 58% and 59% of patients, respectively. • Other safety concerns include hepatotoxicity, infections, and neutropenia	• Elranatamab 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 elranatamab. • Patients should be hospitalized for 48 hours after administration of the first step-up dose, and for 24 hours after administration of the second step-up dose. • Elranatamab 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 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)

X	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as			Section 8.1.2 Study Results
			X	Patient reported outcome (PRO)	Section 8.2.6 Exploratory endpoints
			□	Observer reported outcome (ObsRO)	
			□	Clinician reported outcome (ClinRO)	
			□	Performance outcome (PerfO)	
	□	Qualitative studies (eg, individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	□	Patient-focused drug development or other stakeholder meeting summary reports			[eg, Section 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data			
	□	Natural history studies			
	□	Patient preference studies (eg, submitted studies or scientific publications)			
	□	Other: (Please specify)			
□	Patient experience data that was not submitted in the application, but was considered in this review.				

Bindu Kanapuru, MD
Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1 Analysis of Condition

The Applicant's Position:

Multiple myeloma (MM) is a hematological B-cell malignancy characterized by dysregulated proliferation of bone marrow plasma cells. MM diagnostic criteria are set by the International Myeloma Working Group (IMWG) (Rajkumar et al, 2014). MM is defined by the presence of ≥10% of clonal plasma cells in the bone marrow (or plasmacytoma confirmed by biopsy) and by evidence of end-organ damage (hypercalcemia, renal insufficiency, anemia, bone lesions) caused by the plasma cell disorder.

MM is an incurable disease. Despite advances in treatment, including novel agents such as PIs, IMiDs, and most recently, mAbs, a substantial proportion of patients do not respond to treatment (i.e., are refractory) and almost all patients with MM relapse at some point in their disease course. In fact, most patients experience multiple relapses, requiring multiple lines of treatment with different drug combinations (Kumar et al, 2016; Kumar et al, 2017). Relapse or refractory MM (RRMM) is associated with poor prognosis. With each relapse, treatment efficacy decreases leading to reduced duration of response in subsequent lines of therapy as well as increased refractoriness as tumors accumulate mutations and alterations that confer resistance to therapy (Kumar et al, 2016; Kumar et al, 2017; Moreau et al, 2021).

Globally, there are approximately 160,000 new cases and 106,000 deaths per year attributed to MM (Bray et al, 2018). For the US, the American Cancer Society estimates in 2022, approximately 34,470 new MM cases will be diagnosed and approximately 12,640 MM-related deaths will occur (Siegel et al, 2022).

MM is a disease of the older population with an average age of diagnosis of 66 years and only 2% of cases younger than 40 years of age (Kyle et al, 2003; Waxman et al, 2010). MM is slightly more common in males than females (1.2:1 to 1.4:1) and the incidence is higher in Black than White patient populations, and is lower in Asian and Hispanic populations (Kumar et al, 2017).

Overall, patients with MM have poor survival, with a median overall survival (OS) of 5 to 7 years and a 5-year survival rate of ~50%. Patient populations who have poor prognosis in MM include elderly and/or frail patients (age ≥70 years and ECOG PS 3 or 4) and those with high-risk cytogenetic features. Additionally, high tumor burden, renal impairment, and extramedullary disease are also associated with poor treatment outcomes. Furthermore, patients with disease refractory to a PI, IMiD, and an anti-CD38 mAb (triple class refractory RRMM) have a mOS of less than 12 months, highlighting an unmet need for improved treatment options for MM (Gandhi et al, 2019).

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

2.2 Analysis of Current Treatment Options

Currently, there are 4 drugs available for use in the US for the treatment of patients with RRMM who received at least 4 prior lines of therapies and whose disease is refractory to PIs, IMiDs, and anti-CD38 mAbs (Table 1).

Selinexor, a selective inhibitor of nuclear export, was granted accelerated approval in 2019 in combination with dexamethasone for the treatment of adult patients with RRMM who received at least 4 prior therapies and whose disease is refractory to at least 2 PIs, at least 2 IMiDs, and an anti-CD38 mAb. In a single arm, open-label study (STORM Part 2), selinexor in combination with dexamethasone demonstrated an ORR of 25.3% with a mDOR of 3.8 months (Selinexor USPI).

Available therapies which share a mechanism of action directed to BCMA include idecabtagene vicleucel, ciltacabtagene autoleucel, and teclistamab.

Idecabtagene vicleucel and ciltacabtagene autoleucel, autologous CAR-T cell immunotherapies, were granted approval in March 2021 and February 2022, respectively, for adult patients with RRMM after 4 or more prior lines of therapy, including a PI, an IMiD, and an anti-CD38 mAb. Higher responses rates have been observed with these therapies in comparison to selinexor in combination with dexamethasone. In an open-label, single-arm, multicenter study (KarMMa) in adult patients with relapsed and refractory multiple myeloma who had received at least 3 prior lines of antimyeloma therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody, idecabtagene vicleucel demonstrated an ORR of 72% (treated population) and median DOR of 11 months after a median follow-up for duration of response of 10.7 months (Idecabtagene vicleucel USPI). In an open-label, single-arm, multicenter trial (CARTITUDE-1) in adult patients with relapsed or refractory multiple myeloma, who previously received at least 3 prior lines of therapy including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody, ciltacabtagene autoleucel demonstrated an ORR of 97.9% (treated population) with a median DOR of 21.8 months (Berdeja et al, 2021).

Autologous CAR-T treatments are limited to patients whose cells are successfully manipulated ex vivo to allow for re-infusion. Additional limitations of patient access to CAR-T therapies include:

- limited authorized centers currently available for commercial CAR-T-cell treatments,
- difficulty in reaching the target dose and/or risk of manufacturing failure,
- delay in manufacturing times for these treatments, and
- performance status, comorbidities, and disease burden as potential challenges for consideration concerning patient eligibility.

Teclistamab, a BCMA-directed bispecific antibody, was recently granted accelerated approval in October 2022 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. Results from a Phase 2, open-label, single-arm trial (MajesTEC-1) in BCMA-naive patients demonstrated an ORR of 61.8% and median DOR of Not reached after a median follow-up of 7.4 months among responders (Teclistamab USPI).

Table 1: Applicant – Summary of Treatment Armamentarium Relevant to Proposed Indication

Product(s) Name	Relevant Indication	Year & Type of Approval*	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments [Combine by Pharmacologic Class, if relevant]						
Small molecules						
Selinexor (selective inhibitor of nuclear export [SNE]) (+ dexamethasone [glucocorticoid])	RRMM adults with ≥4 prior therapies and disease refractory to ≥2 PIs, ≥2 IMiDs, and an anti-CD38 mAb	2019/ Accelerated approval; 2020/ Full approval	Selinexor 80 mg + dex 20 mg on days 1 and 3 of every week	• ORR: 25.3% (n/N=21/83; 95% CI: 16.4, 36) • mDOR (mos): 3.8 (95% CI: 2.3, not estimable)	AEs in ≥20% of patients: thrombocytopenia, fatigue, nausea, anemia, decreased appetite, decreased weight, diarrhea, vomiting, hyponatremia, neutropenia, leukopenia, constipation, dyspnea, upper respiratory tract infection.	Clinically relevant adverse reactions including life-threatening thrombocytopenia, neutropenia, neurological toxicity; serious and fatal infections; severe gastrointestinal toxicity (including nausea, vomiting, diarrhea, anorexia, weight loss); severe or life-threatening neutropenia; new onset or exacerbation of cataracts

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Table 1: Applicant – Summary of Treatment Armamentarium Relevant to Proposed Indication

Product(s) Name	Relevant Indication	Year & Type of Approval*	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
BCMA-directed Chimeric Antigen Receptor T cell therapy						
Idecabtagene vicleucel (autologous T-cell immunotherapy)	RRMM with ≥4 prior lines of therapy including a PI, an IMiD and, an anti-CD38 mAb	2021/ Full approval	IV infusion single dose infusion bag(s) containing a cell suspension of 300 to 460 x 10^6 chimeric antigen receptor (CAR)-positive T cells in ≥1 infusion bags	• ORR: 72% (72/100) evaluable pop. • mDOR (mos): 11.0	AEs in ≥20% of patients: CRS, infections–pathogen unspecified, fatigue, musculoskeletal pain, hypogammaglobulinemia, diarrhea, upper respiratory tract infection, nausea, viral infections, encephalopathy, edema, pyrexia, cough, headache, decreased appetite.	Box warning for Cytokine Release Syndrome, neurologic toxicities, HLH/MAS, prolonged cytopenia Requires patients to undergo leukapheresis and be administered a lymphodepleting regimen of cyclophosphamide and fludarabine before infusion; may require bridging therapy while awaiting T-cell manufacturing. Challenges associated with manufacturing time and limited number of centers available for CAR-T cell treatments. Available only through a restricted program (REMS)

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Table 1: Applicant – Summary of Treatment Armamentarium Relevant to Proposed Indication

Product(s) Name	Relevant Indication	Year & Type of Approval*	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Ciltacabtagene autoleucel (autologous T-cell immunotherapy)	RRMM with ≥4 prior lines of therapy including a PI, an IMiD and an anti-CD38 mAb	2022/ Full approval	IV infusion single dose infusion bag containing a cell suspension of 0.5-1.0×10^6 CAR-positive viable T cells per kg body weight up to a maximum of 1×10^8 CAR-positive viable T cells per single-dose infusion	• ORR: 97.9% (95/97) evaluable pop. • mDOR (mos): 21.8	AEs in ≥20% of patients: pyrexia, cytokine release syndrome, hypogammaglobulinemia, hypotension, musculoskeletal pain, fatigue, infections-pathogen unspecified, cough, chills, diarrhea, nausea, encephalopathy, decreased appetite, upper respiratory tract infection, headache, tachycardia, dizziness, dyspnea, edema, viral infections, coagulopathy, constipation, and vomiting. Lab AEs in ≥50% of patients: thrombocytopenia, neutropenia, anemia, aminotransferase elevation, hypoalbuminemia.	Box warning for CRS, neurologic toxicities, HLH/MAS, prolonged and recurrent cytopenia. Requires patients to undergo leukapheresis and be administered a lymphodepleting regimen of cyclophosphamide and fludarabine before infusion; may require bridging therapy while awaiting T-cell manufacturing. Challenges associated with manufacturing time and limited number of centers available for CAR-T cell treatments. Available only through a restricted program (REMS)

Table 1: Applicant – Summary of Treatment Armamentarium Relevant to Proposed Indication

Product(s) Name	Relevant Indication	Year & Type of Approval*	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
BCMA-directed Bispecific Antibodies						
Teclistamab (B-cell maturation antigen (BCMA)-directed CD3 T-cell engager)	RRMM with ≥4 prior lines of therapy including a PI, an IMiD and an anti-CD38 mAb	2022/ Accelerated approval	SC, Step-up dosing schedule (0.06 mg/kg on D1, 0.3 mg/kg on D4, 1.5 mg/kg on Day 7), then 1.5 mg/kg one week after first treatment dose and weekly thereafter.	• ORR: 61.8% (95% CI: 52.1, 70.9) • mDOR: NE (9.0, NE)	CRS, Neurologic toxicity (including ICANS), infections AEs in ≥20% of patients: pyrexia, CRS, musculoskeletal pain, injection site reaction, fatigue, respiratory tract infection, nausea, headache, pneumonia, and diarrhea. Most common Grade 3 to 4 laboratory abnormalities (≥20%): decreased lymphocytes, decreased neutrophils, decreased white blood cells, decreased hemoglobin, and decreased platelets.	Box warning for CRS, neurotoxicity, including ICANS; available only through a restricted program (REMS)

*Accelerated approval or full approval

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The Applicant's Position:

Despite improvements in outcomes observed with available therapies described in Table 1, there continues to be a critical unmet need for new treatment options for patients with RRMM who have received at least a PI, an IMiD, and an anti-CD38 monoclonal antibody.

Based on the totality of the data from pivotal and supporting studies, elranatamab treatment was efficacious and provided clinically meaningful deep and durable responses in participants with RRMM in the proposed indication.

The FDA's Assessment:

In general, the FDA agrees with the Applicant's assessment of the current treatment options for patients who are triple class exposed (i.e., who have received a PI, an IMiD, and an anti-CD38 monoclonal antibody). While idecabtagene vicleucel and ciltacabtagene autoleucel are not "off the shelf" options and have limitations, as described above, they do provide high response rates for this patient population. Idecabtagene vicleucel has an ORR of 72% (300-460 x 10^6 CAR-positive T-cells) with a median duration of response for PR or better of 11.0 months (300-460 x 10^6 CAR-positive T-cells. Ciltacabtagene autoleucel has an ORR of 97.9% with a median duration of response of 21.8 months. In addition to the treatments specifically indicated for patients who are triple class exposed, patients may respond to another agent in the same class as agents they have previously received. Teclistamab, a bispecific BCMA directed CD3 T-cell engager was approved in 2023 for the same population requested by the Applicant but is not considered available therapy because this remains under accelerated approval. Treatment options for patients with RRMM are included in Table 2.

Table 2: FDA – Treatment Options for Patients with RRMM

Drug/Combination	Approval	Indication
Bortezomib	AA (2003)	RRMM/>2L
Bortezomib	Regular (2005)	RRMM/ 1-3L
Liposomal doxorubicin HCl	Regular (2007)	RRMM/ ≥1L
Lenalidomide with dex	Regular (2005)	RRMM/≥1L
Carfilzomib	AA (2012)	RRMM/≥1L
Carfilzomib with Rd	Regular (2015)	RRMM/≥1-3 prior lines
Carfilzomib with dex	Regular (2016)	MM, 1-3 prior lines
Pomalidomide with dex	AA (2013)	RRMM/≥2L, including lenalidomide and PI
Pomalidomide with dex	Regular (2015)	RRMM/≥2L, including lenalidomide and PI
Panobinostat with Vd ^	AA (2015)	RRMM/≥2L, including bortezomib and IMiD
Ixazomib with Rd	Regular (2015)	RRMM/≥1L
Daratumumab-IV	AA (2015)	RRMM/≥3L including PI and IMiD
Daratumumab-IV with Rd	Regular (2016)	RRMM/≥1L
Daratumumab-IV with Vd	Regular (2016)	RRMM/≥1L
Daratumumab-IV with Pd	Regular (2017)	RRMM/≥2L, including lenalidomide and PI

Elotuzumab with Rd	Regular (2015)	RRMM/1-3L
Elotuzumab with Pd	Regular (2018)	RRMM/≥2L, including lenalidomide and PI
Selinexor with dex+	AA (2019)*	RRMM/≥4L, including 2 PIs, 2 IMiDs, anti-CD38 mAb
Selinexor with Vd	Regular (2020)	RRMM/≥1L
Daratumumab-IV with Kd	Regular (2020)	RRMM/1-3L
Daratumumab-SC	Regular (2020)	RRMM/≥3L, including PI and IMiD or PI/IMiD double-refractory
Daratumumab-SC with Rd	Regular (2020)	RRMM/≥1L
Isatuximab with Pd	Regular (2020)	RRMM/≥2L, including lenalidomide and PI
Isatuximab with Kd	Regular (2021)	RRMM/1-3L
Daratumumab-SC with Pd	Regular (2021)	RRMM/≥1L, including lenalidomide and PI
Daratumumab-SC with Kd	Regular (2021)	RRMM/1-3L
Idecabtagene vicleucel (BCMA-CART)+	Regular (2021)	RRMM/≥4L, including PI, IMiD, anti-CD38 mAb
Ciltacabtagene autoleucel (BCMA CAR-T)+	Regular (2022)	RRMM/≥4L, including PI, IMiD, anti-CD38 mAb
Teclistamab-cqyv+	AA (2022)	RRMM/≥4L, including PI, IMiD, anti-CD38 mAb

* Accelerated approval converted to regular following verification of clinical benefit;
^ Accelerated approval of Panobinostat was withdrawn in 2021 due to lack of due diligence in verifying clinical benefit; Red text indicates approved regimens for patients with 4 or more prior lines of therapy including an IMiD, PI, and anti-CD38
+ Approved for the proposed patient population
Abbreviations: AA= accelerated approval, anti-CD38 mAb=anti CD38 monoclonal antibodies, dex= dexamethasone, IMiD=immunomodulatory drug, IV=intravenous, Kd=carfilzomib and dexamethasone, L=lines of therapy, Pd=pomalidomide and dexamethasone, PI=proteasome inhibitor, Rd=lenalidomide and dexamethasone, RRMM=relapsed refractory multiple myeloma, SC=subcutaneous, Vd=bortezomib and dexamethasone; not shown is melphalan flufenamide-accelerated approval granted February 26, 2021 but currently withdrawn from the US market. Also not shown is belantamab mafodotin which received accelerated approval in 2020 but was withdrawn from the US market.
Source: FDA Analysis

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

The Applicant's Position:

The product is not marketed in the United States. An IND was opened to initiate the first in human phase 1 Study C1071001. The pivotal Phase 2 Study C1071003 was also conducted under this IND.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment of the U.S. Regulatory Actions and Marketing History. The initial IND for elranatamab (IND 133940) was received in August 2017.

3.2 Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Table 3: Applicant – Submission Regulatory Activity with FDA

Interaction Date	Interaction Type	Primary Outcome
29 Jan 2021	Fast Track Designation	Granted Fast Track designation.
12 Oct 2021	Orphan-Drug Designation	Orphan Drug Status Granted.
15 Nov 2021	Pediatric Study Plan	Full waiver for all pediatric age groups iPSP Agreement received
14 Jan 2022	Type C Meeting (BLA format and content)	General agreement reached on most elements of the registration plan.
09 Mar 2022	CMC Format and Content Meeting	General agreement reached on most elements of the CMC registration plan.
21 Oct 2022	Follow up Format and Content Meeting	Additional alignment on format and scope of proposed BLA, including need for formal request of rolling submission.
27 Oct 2022	Rolling Review Request	Request for Submission of Portions of an Application
27 Oct 2022	BTD Granted	BTD granted
2 Nov 2022	Rolling Review Granted	FDA Letter granting permission to submit under Rolling Review
3 Nov 2022	Initial BLA submission	Submission of complete CMC and nonclinical sections of BLA 761345 under rolling review
17 Nov 2022	Request for Project Orbis participation	Submission of Request for participation in the Orbis program

The FDA's Assessment:

The FDA generally agrees with the Applicant's outline of the Presubmission/Submission regulatory activity included in Table 3. Additional submission related activities/interactions and details are noted below:

- IND 133940 was initially submitted to the Agency on August 28, 2017 to support the investigation of elranatamab for the treatment of patients with RRMM. The IND was considered safe to proceed on September 27, 2017.
- September 14, 2020: Type C Meeting
    - Discussion of the proposed development plan to support registration of elranatamab monotherapy for the treatment of RRMM.
    - The FDA conveyed preliminary comments regarding the design of the phase 2 study C1071003.
    - The FDA also conveyed concerns with the Sponsor's proposal to seek accelerated approval based on a single-arm trial, including the need to ensure that the primary efficacy population includes patients with a minimum of 6 months of follow-up from the time of response to allow for an adequate assessment of durability of response.
- January 14, 2022: Type C Meeting (BLA format and content)
    - The FDA reiterated concerns regarding the Sponsor's proposal to seek accelerated approval based on the results of Study C1071003, given the challenges with interpretation of the data from a single-arm trial. The FDA recommended a randomized trial with a primary endpoint of PFS as the initial registration approach for elranatamab in multiple myeloma.

  - The FDA expressed concerns with the limited duration of follow-up and stated that in order to allow for an adequate assessment of durability of response and safety, the results should be based on at least 9-12 months of follow-up from the time of response. The FDA stated that this information should be provided at the time of initial BLA submission.
  - The FDA reiterated that if the Sponsor decides to submit a BLA for accelerated approval, the confirmatory trial should be well underway at the time of submission.
  - Agreement was made regarding a future CMC meeting to discuss the analytical comparability plan.
- April 5, 2022: Type C Meeting for dose optimization
  - Sufficient feedback was obtained in the preliminary comments and the meeting was cancelled.
- July 22, 2022: Type B EOP1 Meeting
  - Purpose: to discuss the clinical data including PK, PD, safety, and efficacy data from the Phase 1 Study C1071001, the Phase 2 Study C1071003 interim-analysis, and the safety lead-in from the Phase 3 Study C1071005. This meeting was also to discuss the totality of the clinical data to support the dose for the planned Part 2 of Study C1071005 (Phase 3 randomized portion) to serve as the confirmatory study.
  - Agreement was reached on the elranatamab monotherapy dosing regimen with the proposed 2-step 12/32 mg priming doses followed by a target dose of 76 mg QW.
  - The Agency expressed concerns that the data was not sufficient to support the proposed dosing for the elranatamab+daratumumab combination arm. The Agency requested that the Sponsor submit the updated safety data from the first 30 patients treated in Study C1071005 Part 1 to support their dosing for the combination regimen.
  - The FDA reiterated concerns regarding the Sponsor's proposal to seek accelerated approval based on the results of Study C1071003.
- October 21, 2022: Type C Meeting - Follow up Format and Content Meeting
- October 27, 2022: Breakthrough Therapy Designation (BTD) granted for the treatment of adult patients with RRMM who have received at least four prior lines of therapy, including a PI, IMiD, and an anti-CD38 monoclonal Ab.
- November 3, 2022: Initial BLA components submitted (CMC and non-clinical)
- December 16, 2022: Type B pre-BLA Meeting
- December 19, 2022: BLA submission; REMS proposal submitted
  - The FDA recommended that all patients have a minimum of 9-12 months of follow-up from the onset of the first response to allow for an adequate assessment of durability of response and safety.
  - The FDA reiterated concerns regarding the limitations of use of a single-arm trial to support accelerated approval. The FDA also reiterated that the confirmatory trial should be well-underway at the time of BLA submission and noted that agreement

had not yet been reached regarding the proposed dose of elranatamab in combination with daratumumab in the proposed phase 3 confirmatory trial.

- January 20, 2023: Application Orientation Meeting (AOM) for BLA 761345.
- April 12, 2023: Mid-cycle Communication Teleconference: FDA conveyed concerns regarding the risks of CRS, neurologic toxicity, and hepatic toxicity. The FDA also stated that additional items still under review included the adequacy of the hospitalization/monitoring requirements after elranatamab dosing, the adequacy of the data from Cohort B (prior BCMA-directed therapy) to assess the benefit-risk of elranatamab in this patient population, the adequacy of the MRD data included, the applicability to the U.S. patient population (including racial and ethnic minorities), and the duration of response.
- July 13, 2023: Late-cycle Teleconference: FDA reiterated the concerns regarding the risks of CRS and neurologic toxicity. The adequacy of the proposed safety mitigation measures, including hospitalization, is under review. The FDA also reiterated that there was limited representation of racial and ethnic minority patients in Study C1071003, which presents a challenge regarding the generalizability of the data to a U.S. patient population.

The FDA also notes additional interactions related to the ongoing phase 3 confirmatory trial, Study C1071005 (March 15, 2021 Type C Meeting, July 22, 2022 Type B EOP1 Meeting, and December 16, 2022 pre-BLA meeting). Study C1071005 is an ongoing, open-label, phase 3 randomized study evaluating the safety and efficacy of elranatamab monotherapy and elranatamab in combination with daratumumab vs. daratumumab/pomalidomide/dexamethasone (DPd) in patients with RRMM who have received 1-3 prior lines of therapy including lenalidomide and a PI. The primary endpoint is PFS by BICR. The expectation that the confirmatory trial be ongoing at the time of submission of the BLA was conveyed to the Sponsor at the Type C meeting on January 14, 2022.

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 two clinical sites (Site 1003 and Site 1102) as well as of the Applicant, Pfizer, Inc. in support of BLA 761345. Site 1003 in New York, NY (Investigator: Alexander Lesokhin, M.D.) enrolled 14 patients, and Site 1102 in Paris, France (Investigator: Bertrand Arnulf, M.D.) enrolled 15 patients. The sites were selected for inspection based on their high enrollment and calculated risk scores from the OSI Clinical Investigator Site Selection Tool. Overall, no significant regulatory violations were identified. The Applicant's oversight and monitoring of Study C1071003 were adequate. 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

Elranatamab (also referred to as PF-06863135) is a bispecific antibody directed against B-cell maturation antigen (BCMA) and cluster of differentiation 3 (CD3). BCMA is expressed on the surface of multiple myeloma (MM) and plasma cells, and CD3 is expressed on the surface of T-cells. Elranatamab directs T-cell mediated lysis of MM cells and the proposed indication is relapsed or refractory MM.

In vitro studies showed binding to human and monkey CD3ε and BCMA, and much lower affinity to rodent BCMA. The binding affinity to the human neonatal Fc receptor for IgG (FcRn) was 2-fold less than for the monkey FcRn. There was no detectable binding to human Fc-γ receptors (FcγRs) or to C1q, thus effector function is not anticipated. The in vitro cytokine release assay (CRA) showed elranatamab treatment induced cytokine release (TNFα, IL6 and IFNγ), consistent with the expected pharmacology of elranatamab.

The panel of myeloma cell lines evaluated showed a broad range of BCMA expression. In this panel of cell lines, elranatamab induced concentration-dependent cytotoxic T lymphocyte (CTL) activity that correlated with BCMA expression. Additionally, elranatamab induced concentration-dependent cytotoxicity of myeloma cells ex vivo in bone marrow samples from patients with myeloma. A single administration of elranatamab resulted in dose-dependent anti-tumor activity that was greatest in MM xenograft models with moderate or high levels of BCMA (MM.1S and OPM2). In the model with the lowest level of BCMA (MOLP8), a single administration of elranatamab resulted in non-dose-dependent anti-tumor activity, but repeated administration (2 doses) prolonged anti-tumor activity compared to a single administration. Safety pharmacology parameters were evaluated in the toxicology studies in cynomolgus monkeys; there were no clear elranatamab-induced effects on the central nervous, respiratory, or cardiovascular systems.

General toxicology studies were conducted in cynomolgus monkeys, a pharmacologically relevant species to assess the toxicity of elranatamab. Recovery was not assessed in any of the general toxicology studies. In the 1-month intravenous (IV) repeat-dose study, elranatamab doses of 0.01, 0.05, and 0.3 mg/kg/week (total of 5 doses) showed minimal clinical signs or adverse findings. Decreased cellularity in lymphoid tissues (spleen, lymph nodes, and gut-associated lymphoid tissue) correlated with decreased B-cells and clinical chemistry changes (decreased globulin and total protein). Skin discoloration correlated with epidermal hyperplasia and inflammation. Increased cytokine levels were considered transient since they were mainly observed after the first dose but not after subsequent doses. The decrease in B-cells and increase in activated and proliferating T-cells are consistent with the mechanism of action of elranatamab. Plasma cell analysis did not detect changes in antibody secreting cells (ASCs). Exposure increased in an approximately dose proportional manner and antibody drug antibody (ADA) incidence was greatest at the low dose (67%) and not detected (0%) at the high dose.

An elranatamab dose of 0.3 mg/kg was evaluated in the 1-month repeat-dose subcutaneous (SC) toxicity study (total of 5 doses). Increased cytokine levels were primarily detected after the first dose and generally returned to baseline 24 hours post-dose. Inflammation observed at the injection site did not correlate with other findings. ADA incidence was 17% at 0.3 mg/kg elranatamab on day 22. There were no other notable findings.

In the 3-month repeat-dose SC toxicity study, elranatamab doses of 0.3, 3, and 6 mg/kg/week (total of 14 doses) showed adverse clinical signs that correlated with decreased body weight and food consumption and contributed to mortality. In general, findings were similar in moribund and terminal animals. Decreased red blood cell mass parameters were associated with erythrocyte lysis, likely due to secondary infections. Increased white blood cells (WBC) were associated with microscopic findings (inflammation/infiltration and presence of bacterial colonies) that were suggestive of an inflammatory state due to secondary infection. Decreased lymphocytes in lymphoid organs, immunoglobulins, ASCs and B-cells were observed and were related to the pharmacology of the product. Immunophenotyping changes (decreased B-cells and increased activating and proliferating T-cells) were consistent with the expression of BCMA on B-cells and activation of T-cells. The increase in cytokine levels observed mainly after the first dose was consistent with the mechanism of action of elranatamab. A non-dose-dependent near complete depletion of ASCs was observed in animals treated with elranatamab. The exception was in 2 animals (0.3 mg/kg) in which ASCs were depleted on day 43 but returned to baseline by day 93; this finding correlated with ADA development in these animals. There was a greater than dose proportional increase in exposure on day 85, and an approximately dose proportional increase on day 43.

Embryofetal developmental toxicity was evaluated using a weight of evidence (WOE) risk assessment and took into consideration the pharmacology of the product, the effects seen in

the repeat-dose toxicity studies and the effects seen in humans. T-cell activation, cytokine release, and associated inflammatory response may adversely impact a pregnant woman or a developing fetus. In addition, based on findings of B-cell depletion in repeat-dose toxicity studies, B-cell depletion may occur in a newborn from in-utero exposure to the product. Due to the potential for elranatamab to elicit embryofetal toxicities, the use of effective contraception is recommended for female patients of reproductive potential during treatment and for 4 months after the last elranatamab dose. The recommendation for the duration of contraception is based on 5 x $T_{1/2}$ from the FDA guidance "Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations", where $T_{1/2}$ = 22 days for elranatamab. While infiltration/inflammation was observed in male and female reproductive organs in toxicology studies, a conclusion cannot be made on the effects on fertility since the findings were of low incidence, minimal severity and/or the studies were confounded by ADA formation and bacterial infections.

The nonclinical pharmacology, pharmacokinetics (PK), and toxicology data submitted to BLA 761345 are adequate to support the approval of elranatamab for the proposed indication.

5.2 Referenced NDAs, BLAs, DMFs

The Applicant's Position: None

5.3 Pharmacology

Primary pharmacology

The Applicant's Position:

Elranatamab is a heterodimeric humanized bispecific antibody that binds BCMA on plasma cells, plasmablasts, and multiple myeloma cells and CD3ε on T cells leading to selective cytolysis of these BCMA expressing cells. The anticancer activity of elranatamab involves selective therapeutic targeting and activation of T cells redirected against BCMA-expressing malignant plasma cells. Thus, elranatamab circumvents the need for T cells to recognize specific antigenic peptides in the context of MHC class I on myeloma cells and greatly expands the available pool of T cells that can be engaged to eliminate BCMA-expressing myeloma cells.

In vitro studies with elranatamab established binding affinity and specificity for both BCMA and CD3ε (Table 4). Elranatamab bound human and cynomolgus monkey BCMA and CD3δε with high affinity and blocked human BCMA interaction with human APRIL and BAFF ligands. Elranatamab also bound human and cynomolgus monkey FcRn (Table 4) but did not bind human FcγRs, except for weak binding to FcγRIIA-131H. In addition, elranatamab didn't bind C1q. Tumor cell killing mediated by elranatamab was established with a panel of cancer cell lines expressing various levels of BCMA (Table 4). Elranatamab effectively mediated myeloma cell lysis of primary tumor cells from 4 myeloma patients, redirecting patient T cells to lyse tumor cells in a dose-dependent manner.

In vivo efficacy was shown following single dose administration of elranatamab in 3 established xenograft models which correlated with BCMA expression; additionally, prolonged tumor regression was seen in a cell line expressing low levels of BCMA following repeated dosing with elranatamab (Figure 1).

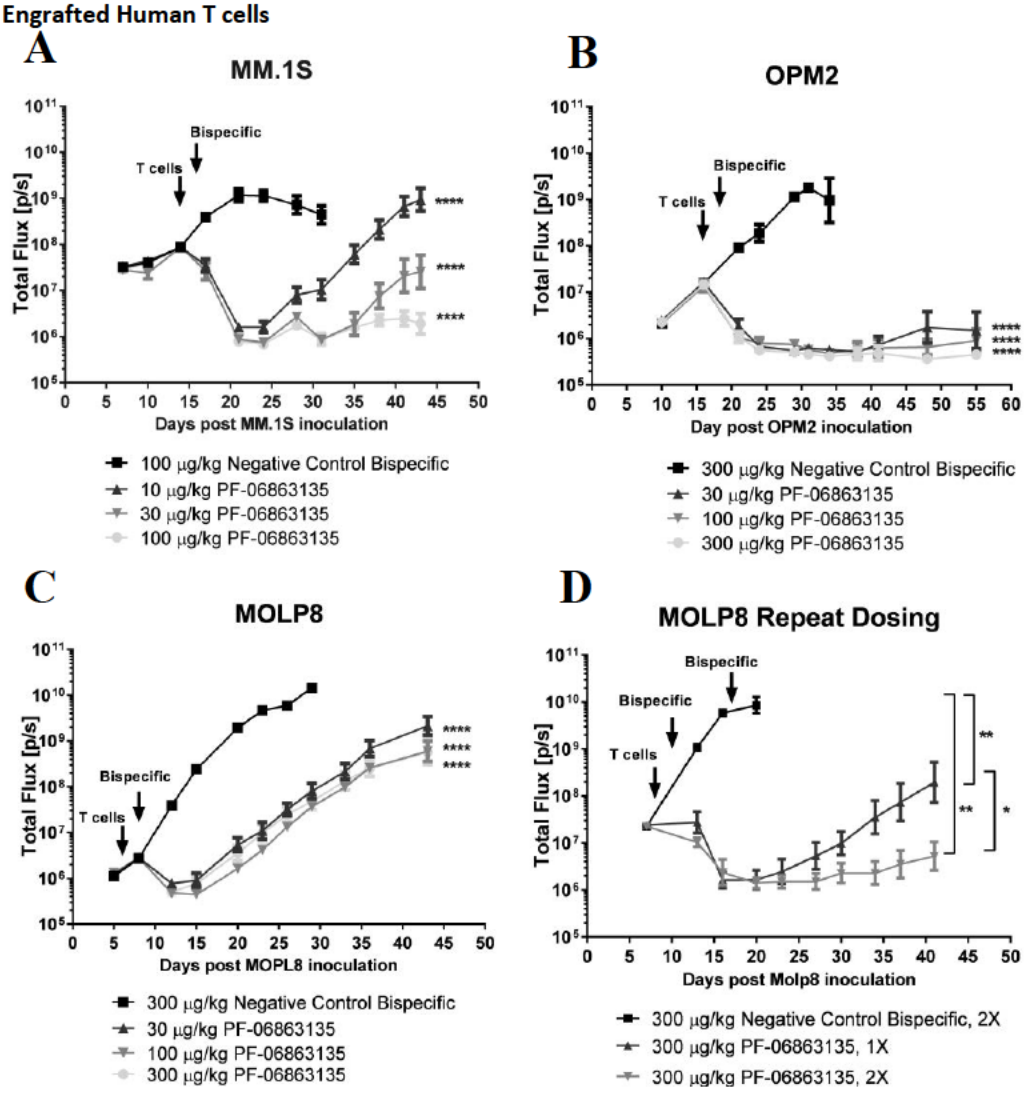
Table 4: Applicant – Summary of Elranatamab In Vitro Pharmacology

Kinetics and Affinities of PF-06863135 Against BCMA and CD3δε by SPR at 37°C[a]		
Antigen	**K_D ± SD (nM)**	
Mouse BCMA-Fc	1.5 ± 0.11	
Rat BCMA-Fc	5.4 ± 0.23	
Monkey BCMA-Fc	0.057 ± 0.0099	
Human BCMA-Fc	0.038 ± 0.0075	
Human CD3δε	17 ± 0.21	
Monkey CD3δε	14 ± 1.6	
Kinetics and Affinities of PF-06863135 Against Human and Monkey FcRn by SPR at 37°C[a]		
Antigen	**Sample**	**K_D ± SD (nM)**
Human FcRn	PF-06863135	800 ± 25
	Ab19_hIgG2ΔA-D265A	800 ± 38
Monkey FcRn	PF-06863135	400 ± 62
	Ab19_hIgG2ΔA-D265A	700 ± 47

CTL Activity and T-cell Activation Following Incubation of PF-06863135 with a Panel of Cell Lines Expressing a Range of Endogenous Cell Surface BCMA[b]				
		EC_{50} ± SD (pM)		
Cell line	**SABC, BCMA mAB**	**CTL Activity**	**CD69 on CD8+ T cells**	**CD25 on CD8+ T cells**
JJN3 Luc2 GFP	16,291	2.1 ± 0.7	2.8 ± 0.8	9.4 ± 3.5
MM1S Luc2 GFP	12,963	56.8 ± 38.4	10.0 ± 2.53	16.6 ± 1.14
OPM2 Luc2 GFP	9,428	92.0 ± 28.4	23.1 ± 11.6	22.4 ± 2.8
L363 Luc2 GFP	6,088	193.0 ± 47.1	43.2 ± 17.0	115.3 ± 15.5
KMS-12-BM Luc2 GFP	5,569	13.7 ± 8.6	6.4 ± 4.4	10.7 ± 4.5
MOLP8 Luc2 GFP	1,960	748.2 ± 560.0	33.6 ± 1.2	50.4 ± 4.0

a Human and monkey BCMA (N=4). Mouse and rat BCMA, monkey and human CD3de and monkey and human FcRn (N=3).
b. N = 3 human donors.

Figure 1: Applicant – Elranatamab Single-Agent Activity in Established Orthotopic Myeloma Models With Engrafted Human T cells



In vivo efficacy of elranatamab (PF-06863135) in 3 established orthotopic myeloma xenograft tumor models. Plot depicts mean logarithmic luminescence or Total Flux (±SEM). N=10 animals/group for MM.1S and MOLP8 models. N=7 animals/group for the OPM2 model. Statistics represent RMANOVA with Dunnett's post-hoc test, all groups were compared to negative control (****P<0.001, **P<0.01), and Wilcoxon signed-rank test, single dose compared to double dose (*P=0.0117).

The FDA's Assessment:

The binding of elranatamab to BCMA and CD3ε was determined by surface plasmon resonance (SPR). Binding affinities were similar for human and monkey BCMA and for human and monkey CD3ε; elranatamab showed less potent binding to rodent BCMA (40-fold lower in mice and 142-fold lower in rats; Table 3 from the Applicant). Elranatamab did not show binding to mouse or rat CD3ε at 1 µM.

Human A proliferation-inducing ligand (APRIL) and human B-cell activating factors (BAFF) are endogenous BCMA ligands; binding to BCMA leads to the activation of signaling that results in B-cell activation, differentiation and maturation into plasma cells, and long-term plasma cell survival. The interaction between APRIL or BAFF with human BCMA in the presence of elranatamab was assessed by biolayer interferometry (BLI). Results showed that APRIL and BAFF bind to BCMA and that this interaction is blocked in the presence of elranatamab (data included in the Applicant's submission). Elranatamab showed binding to human FcRn with a K_d=800 nM and binding to monkey FcRn with a K_d=400 nM (Table 3 from the Applicant). Binding of elranatamab to human FcγRs or C1q was not detectable as determined by SPR or enzyme-linked immunosorbent assay (ELISA), respectively.

A panel of myeloma cell lines was evaluated for endogenous expression of BCMA using an anti-BCMA monoclonal antibody (mAb) to quantify receptor density. Cell surface expression of BCMA was determined from specific antigen binding capacity (SABC), which showed a range of 1,960 to 16,291 receptors per cell (Table 3 from the Applicant). Myeloma cell killing was assessed via the CTL assay where human CD3+ T-cells were incubated with luciferase expressing myeloma cells and exposed to a range of elranatamab concentrations to determine myeloma cell viability. The CTL assay showed EC_{50} values ranging from 2.1 to 748.2 pM (Table 3 from the Applicant). T-cell activation was evaluated via flow cytometry with the T-cell activation markers CD69 and CD25. In CD8 T-cells expressing either CD69 or CD25, elranatamab had EC_{50} values ranging from 2.8 to 43.2 pM and 9.4 to 115.3 pM, respectively (Table 3 from the Applicant). Four bone marrow samples from patients with myeloma (containing a mixture of T-cells and myeloma cells) were exposed to a range of elranatamab concentrations and myeloma cell viability was assessed via flow cytometry. Elranatamab showed cytotoxic activity in primary patient samples with EC_{50} values ranging from 20.8 to 276.3 pM.

The anti-tumor activity of elranatamab was evaluated in MM xenograft models (with MM.1S, OPM2, and MOLP8 cell lines) that had varying levels of BCMA expression. A single administration of elranatamab showed dose-dependent tumor growth inhibition and tumor regression in MM.1S and OPM2 xenograft models. In the MOLP8 xenograft model, tumor growth inhibition or tumor regression was not dose-dependent. Tumor relapse/outgrowth was observed in all dose groups and in all models with the greatest outgrowth observed in the low dose groups (Figure 1 from the Applicant).

Secondary Pharmacology

The Applicant's Position:

No secondary pharmacology studies were conducted. Off-target toxicity is a rare event for antibody-based therapies. The observed nonclinical toxicology of elranatamab is associated with its primary pharmacology.

The FDA's Assessment:

The FDA concurs.

Safety Pharmacology

The Applicant's Position:

No safety pharmacology studies were conducted. Safety pharmacology was evaluated as part of the general toxicology studies performed with elranatamab.

No effect was observed on ECG, heart rate, respiratory or CNS safety pharmacology parameters evaluated as part of the general toxicology studies performed in cynomolgus monkeys with elranatamab.

The FDA's Assessment:

We agree that the safety pharmacology assessment in the toxicology studies in cynomolgus monkeys did not show elranatamab induced effects on cardiovascular endpoints (ECG or heart rate). Respiratory and CNS safety pharmacology parameters were monitored by clinical observations only in the toxicology studies; no clear elranatamab-induced effects were noted.

5.4 ADME/PK

The Applicant's Position:

Single-dose PK and repeat-dose TK were evaluated in monkeys following SC and IV dosing of elranatamab. After single IV dosing, the mean t½ values ranged from approximately 4 to 6 days. In the repeat-dose GLP toxicity studies in monkeys, there were no consistent sex-related differences in systemic exposure (as assessed by C_{max} and AUC), and systemic exposure increased with increasing dose in an approximately dose-proportional manner. Marked accumulation was observed after 3 months of repeat SC dosing. The presence of ADA was observed after repeat SC and IV dosing.

Tissue distribution studies with elranatamab were not conducted in nonclinical species. Metabolism and excretion studies were not conducted as these are not considered necessary or relevant for biologics such as elranatamab (ICH S6). In vitro or in vivo pharmacokinetic drug interaction studies have not been conducted.

Absorption: Report Number: Not applicable
Distribution: Report Number: Not applicable
Protein binding and tissue distribution studies were not conducted for elranatamab in nonclinical species. The Vss of elranatamab in monkeys was approximately 0.1 L/kg after single IV dosing, consistent with the limited distribution expected for an IgG (Lin et al, 1999; Mascelli et al, 2007).
Metabolism: Report Number: Not applicable
Metabolism studies were not conducted with elranatamab as these are not considered necessary or relevant for biologics such as elranatamab (ICH S6). Similar to other therapeutic proteins with molecular weights above the glomerular filtration cut-off, elranatamab is expected to be metabolized primarily by catabolic degradation (Lobo et al, 2004; Mascelli et al, 2007; Vugmeyster et al, 2012).
Excretion: Report Number: Not applicable
Standard elimination studies routinely conducted for small molecule drugs are not considered necessary or relevant to biotechnology-derived pharmaceuticals such as elranatamab (ICH S6); therefore, an excretion study was not conducted in nonclinical species for elranatamab.
Summary PK parameters from pharmacokinetic studies: Single Dose PK Study with PF-06863135 in Monkeys **(**Report Number: PF-06863135_24Mar17_022648)

Species	Cynomolgus Monkey					
Sex/Number of Animals	Male/1 and Female/1					
Feeding Condition (Fed/Fasted)	Fed					
Vehicle/Formulation	Phosphate Buffered Saline					
Method of Administration	Intravenous Bolus					
Matrix	Serum					
Sampling Time Points	Predose, 0.25, 6, 24, 48, 72, 96, 120, 168, 222, 288 and 336 hours postdose					
Analyte	PF-06863135					
Analytical Method	LBA[a]					
	0.001 mg/kg			**0.01 mg/kg**		
	Animal 001M	**Animal 003F**	**Mean**	**Animal 002M**	**Animal 004F**	**Mean**
AUC_{inf} (µg•h/mL)	1.09	1.69	1.39	15.0	12.3	13.7
AUC_{last} (µg•h/mL)	0.717	0.978	0.848	13.4	11.6	12.5
CL (mL/min/kg)	0.0153	0.00986	0.0126	0.0111	0.0136	0.0124
V_{ss} (L/kg)	0.144	0.123	0.134	0.0991	0.0972	0.0982
$t_{½}$ (h)	118	165	142	100	79.7	89.9
Notes: Immunophenotyping and plasma cell analysis were also conducted as part of this study and are described in the study report; standard deviation not calculated (n<3). a. Non-validated method described in the study report.						

Integrative summary table of C_{max} and AUC parameters across toxicology studies (general, reproductive, and carcinogenicity, if conducted):

Mean Toxicokinetic Parameters After Once-Weekly Repeat IV Dosing (1-Month Study)

Study No.	**Dose (mg/kg/dose)a**	**Study Day**	**C_{max} (µg/mL)**	**AUC_{168} (µg•h/mL)**	**Incidence of ADA Induction**
16GR380	0.01	1	0.236	10.4	67%
		22	0.219	18.0	
	0.05	1	1.27	58.0	17%
		22	1.42	118	
	0.3	1	9.34	453	0%
		22	10.4	715	

a. Animals were dosed at N = 3/sex/dose group.

Mean Toxicokinetic Parameters After Once-Weekly Repeat SC Dosing (1-Month Study)

Study No.	Dose (mg/kg/dose)	Study Day	C_{max} (µg/mL)	T_{max} (h)	AUC_{168} (µg•h/mL)	Incidence of ADA Induction
17GR290	0.3	1	2.09	56	275	17%
		22	2.84	25	378	

a. Animals were dosed at N = 3/sex/dose group.

Mean Toxicokinetic Parameters After Once-Weekly Repeat SC Dosing (3-Month Study, 20GR302)

Dose (mg/kg/dose)	**Study (Day)**	**C_{max} (µg/mL)**	**T_{max} (h)**	**AUC_{168} (µg•h/mL)**	**Incidence of ADA Induction**
0.3	1	1.52	100	208	33%
	43	6.31	33	826	
	85	4.97	32	647	
3.0	1	15.9	64	2100	0%

	43	83.4	72	12200	
	85	101	72	15300	
6.0b	1	40.9	80	5630	0%
	43	185	60	26900	

Note: SC Bioavailability (~50%) was calculated using Day 1 AUC168 values from the 0.3 mg/kg dose groups ([208 µg•h/mL, SC 20GR302/ 453 µg•h/mL, IV 16GR380] •100).
a. Animals were dosed at N = 3 /sex/dose group.
b. Due to early animal deaths, TK analysis wasn't performed on Day 85.

Tabulation of any exposure margins used in proposed labeling:

Concentrations of Elranatamab Associated with Key Responses

Key Response(s)	Dose (mg/kg/week)	C_{max}[a] (ng/mL)	AUC_{last}[a] (ng•h/mL)	Exposure Margin[b]	
				C_{max}	AUC_{last}
1-Month Subcutaneous Toxicity Study in Cynomolgus Monkeys (3/sex/dose) 17GR290					
Clinical pathology/pharmacology: cytokines Histopathology: Injection site inflammation	0.3 NOAEL	2840	378000	0.1x	2.7x
3-Month Subcutaneous Toxicity Study in Cynomolgus Monkeys (3/sex/dose) 20GR302					
Moribundity (1/6 animals) Clinical observations: ¯ activity, emesis, soft feces; ¯ body weight and/or food consumption Clinical pathology/pharmacology: ¯ immunoglobulins, ¯total B cells, - cytokines; ¯ RBC mass, total protein, globulin Histopathology: Secondary infection - ¯ cellularity of spleen, lymph node, GALT Inflammation and/or infiltration of kidney and gastrointestinal system	0.3 LOAEL	4970	647000	0.2x	4.7x
Same as above, plus: Incidence of moribundity (4/6 animals);	3	101000	15300000	3.9x	111x
Same as above, plus: Incidence of moribundity (6/6 animals)	6	185000[c]	26900000[c]	7.2x	194x

a. AUC_{168} and C_{max} values indicate mean serum concentrations. Reported values were obtained near termination, or as specified.
b. Exposure margins (i.e., safety margins) are calculated from human population PK modeling exposure estimates for elranatamab (Section 2.7.2). Steady-state total exposure estimates for a typical patient receiving 6 cycles of 76 mg QW after a priming dose are Cmax = 25,784 ng/mL and AUCtau = 138,309 ng•h/mL (3,319,405 ng•day/mL).
c. Day 43 values due to early moribundity.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment. In the single dose PK study in monkeys, a single dose of 1 or 10 µg/kg was administered IV (1 animal per sex/group). There were no sex-related differences in exposure and the mean $T_{1/2}$ values ranged from 90-142 hours (approximately 4-6 days). Immunophenotyping analysis showed an increase in the ratio of individual animals from baseline (percentage) of activated (up to 14 times [x]) and proliferating

(2.8-11.33x) CD4 and CD8 T-cells on day 4, and a decrease in the absolute number of B-cells from 1 animal (0.41x) on day 4 from the 10 µg/kg group; no notable immunophenotyping changes were detected following the 1 µg/kg dose. Plasma cell analysis showed a trend towards increasing ASCs in both dose groups on days 4 and 8 compared to pre-dose levels. Quantitation of soluble BCMA (sBCMA) was also conducted, but did not show any changes following the 1 µg/kg dose; following the 10 µg/kg dose, there was a 3.7-fold increase over baseline. sBCMA concentrations peaked by 6 hours post-dose and returned to baseline by 120 hours post-dose.

In the 1-month repeat-dose IV study, exposure (as assessed by C_{max} and AUC) increased in an approximately dose proportional manner. ADA incidence was greatest at the low dose (67%) and decreased to 0% at the high dose. In the 1-month repeat-dose SC study, 0.3 mg/kg elranatamab resulted in 17% ADA incidence. In the 3-month repeat-dose SC study, ADA incidence was 33% in the low dose group (0.3 mg/kg).

5.5 Toxicology

5.5.1 General Toxicology

The Applicant's Position:

Elranatamab is a bispecific antibody intended for the treatment of advanced cancers. Therefore, the toxicology program was designed in accordance with ICH S9 guidance, as well as all other relevant guidance. All pivotal toxicity studies were conducted in accordance with US FDA GLP regulations in an OECD MAD member state.

Intravenous administration was originally assessed before subcutaneous administration was chosen as the clinical route. Monkeys were dosed for longer durations and at higher doses using SC administration, making the IV data less significant to the overall toxicology package. Effects were generally consistent between routes.

Cynomolgus monkey was identified as the only relevant nonclinical toxicology species based on elranatamab binding affinities for BCMA and CD3. The toxicities observed in monkeys were consistent with the primary pharmacology of elranatamab, i.e., T cell engagement with BCMA-expressing cells. The key effects identified in repeat-dose toxicity studies up to 3 months in duration were: transiently increased cytokines, decreased BCMA-expressing cells (B cells and plasma cells), fluctuations in T cell and NK cell numbers, immunosuppression, and secondary infection. Recovery was not formally assessed in any study, but effects are expected to recover.

Study title/study number/eCTD location: 1-Month Intravenous Toxicity Study of PF-06863135 In Cynomolgus Monkeys / 16GR380 / Module 2.6.7.7A and 4.2.3.2 **Key Drug-related Adverse Findings** • All animals survived; NOAEL is highest dose tested 0.3 mg/kg/week • Limited clinical signs were transient emesis and skin discoloration • Cytokines increased 6 hours after the first dose and returned to baseline by 24 hours • B cell and plasma cells decreased; peripheral T cell and NK cell numbers fluctuated • Lymphocyte cellularity in lymphoid organs increased and/or decreased **GLP compliance:** Yes	
Methods	
Dose and frequency of dosing:	0, 0.01, 0.05, and 0.3 mg/kg/week (5 doses)
Route of administration:	Intravenous
Formulation/Vehicle:	Solution / (b) (4) histidine, 85 mg/mL sucrose, (b) (4) (b) (4) 0.2 mg/mL polysorbate 80, pH 5.8
Species/Strain:	Monkey/Cynomolgus
Number/Sex/Group:	3/sex/group
Age:	3-4 years

Study title/study number/eCTD location: 1-Month Subcutaneous Toxicity Study of PF 06863135 in Cynomolgus Monkeys / 17GR290 / Module 2.6.7.7B and 4.2.3.2 **Key Drug-related Adverse Findings** • All animals survived; NOAEL is highest dose tested 0.3 mg/kg/week • No significant clinical signs or changes in body weight or food consumption • Cytokines increased 6 hours after the first dose and returned to baseline by 24 hours • BCMA-expressing cells decreased; peripheral T cell and NK cell numbers fluctuated **GLP compliance:** Yes	
Methods	
Dose and frequency of dosing:	0 and 0.3 mg/kg/week (5 doses)
Route of administration:	Subcutaneous
Formulation/Vehicle:	Solution / (b) (4) histidine, 85 mg/mL sucrose, (b) (4) (b) (4) 0.2 mg/mL polysorbate 80, pH 5.8
Species/Strain:	Monkey/Cynomolgus
Number/Sex/Group:	3/sex/group
Age:	3-4 years

Dose (mg/kg/dose)	**0 (Control)**		**0.3**	
Sex	**M**	**F**	**M**	**F**
Immunophenotyping				
IL-2 (pg/mL)				
D1_H0	<3.20-14.66	<3.20-18.98	<3.20	4.88-134.60
D1_H6	<3.20-13.86	<3.20-15.57	11.9x	6.94x
D1_H24	<3.20-14.79	<3.20-13.86	-	-
IL-6 (pg/mL)				
D1_H0	<3.20-5.50	<3.20-15.40	<3.20	<3.20-57.44
D1_H6	<3.20-6.88	<3.20-5.35	69.15x-445.48x	21.56x, 293.90x
D1_H24	5.00-60.33	<3.20-6.09	-	-

IL-10 (pg/mL)				
D1_H0	<12.20-73.81	<12.20-61.91	<12.20-18.89	37.64-1406.62
D1_H6	<12.20-45.68	<12.20-106.10	26.04x, 95.75x, 824.61x	13.14x, 99.00x
D1_H24	<12.20-52.30	<12.20-46.42	7.09x	-
IFN-g (pg/mL)				
D1_H0	<3.20-6.84	<3.20-16.70	<3.20	6.32-92.34
D1_H6	<3.20-4.83	<3.20-15.92	7.40x, 31.53x, 86.18x	7.16x, 10.40x
D1_H24	<3.20-5.70	<3.20-12.87	-	-
Histopathology				
Number Examined	2	3	3	3
Injection Site				
Inflammation	0	0	2	3
Minimal	-	-	1	3
Moderate	-	-	1	-

Study title/study number/eCTD location: 3-Month Subcutaneous Toxicity Study of PF-06863135 in Cynomolgus Monkeys / 20GR302 / Module 2.6.7.7C and 4.2.3.2

Key Drug-related Adverse Findings

- Immunosuppression led to secondary infections and moribund euthanasia at all doses; no NOAEL was identified; dose-dependence was evident by incidence and timing
- Clinical signs included decreased activity, lateral recumbency, altered feces, hunched posture, emesis, and/or decreased skin turgor; body weight and/or food consumption were decreased
- Findings consistent with immunosuppression were noted in the spleen, lymph nodes, and GALT; adverse decreases in circulating immunoglobulins; and near complete depletion of circulating ASCs and B cells
- Other microscopic findings attributed to secondary infection included inflammation/infiltration of the GI system and kidneys and intralesional bacterial colonies and/or viral inclusion bodies in multiple organs
- Red cell mass decreases were adverse at 6 mg/kg/week and attributed to an erythrocyte destructive process likely due to sepsis/infections
- Changes in circulating cytokines and immune cell populations were as reported in previous studies

GLP compliance: Yes

Methods:

Dose and frequency of dosing	0, 0.3, 3, and 6 mg/kg/week (14 doses)
Route of administration	Subcutaneous
Formulation/Vehicle	Solution / (b) (4) histidine, 85 mg/mL sucrose, (b) (4) (b) (4) 0.2 mg/mL polysorbate 80, pH 5.8
Species/Strain	Monkey/Cynomolgus
Number/Sex/Group	3/sex/group
Age	5-8 years
Satellite groups	None
GLP compliance	Yes

Dose (mg/kg/week)	0 (Control)		0.3		3		6	
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Died or Euthanized Moribund	0		1		4		6	

Immunophenotyping-Blood	**Combined Sexes**		**Combined Sexes**		**Combined Sexes**		**Combined Sexes**	
B cells	0.72x-1.23x		0.00x-0.01x		0.00x		0.00x	
T cells	0.82x-1.38x		0.33x-0.61x		0.20x-0.62x		0.18x-0.70x	
CD4+T cells	0.80x-1.33x		0.33x-0.68x		0.23x-0.53x		0.23x-0.72x	
CD8+T cells	0.64x-1.57x		0.30x-0.51x		0.10x-0.59x		0.10x-0.56x)	
NK cells	0.58x-1.62x		2.01x-2.95x		1.95x-2.24x		1.89x-4.13x	
CD69+CD4+T cells (%)	1.14x-4.34x		5.44x-13.11x		4.84x-7.23x		5.51x-11.03x	
CD69+CD8+T cells (%)	0.95x-3.63x		6.96x-14.02x		4.25x-5.03x		4.57x	
Ki-67+CD4+T cells (%)	0.63x-4.24x		5.38x-11.35x		4.47x-9.13x		4.70x-7.36x	
Ki-67+CD8+T cells (%)	0.86x-13.17x		14.38x-32.80x		18.36x-29.42x		14.41x-29.44x	
Cytokines	**Combined Sexes**		**Combined Sexes**		**Combined Sexes**		**Combined Sexes**	
IL2								
Day 57 (0 HPD)	0.69x-1.29x		-		-		5.95x	
Day 57 (7 HPD)	0.69x-1.00x		-		-		4.95x	
Unscheduled euthanasia	NA		-		-		5.63x	
Day 92 (0 HPD)	0.69x-1.39x		26.75x		-		NA	
IL2RA								
Day 57 (24 HPD)	0.88x-1.65x		2.17x-5.52x		2.87x-5.23x		4.02x-11.62x	
Unscheduled euthanasia	NA		13.94x		2.83x-8.13x		3.79x-15.05x	
Day 93 (0 HPD)	1.02x-2.21x		3.96x-8.47x		3.04x-6.90x		NA	
IL6								
Day 1 (7 HPD)	1.00x-2.28x		116.64x-377.03x		287.13x-1179.36x		223.57x-1349.14x	
Day 57 (0 HPD)	1.00x		-		16.39x		605.74x	
Day 57 (7 HPD)	1.00x		-		7.74x		2.39x-768.31x	
Unscheduled euthanasia	NA		10.94x		2.42x-216.82x		2.04x-3.32x	
Day 92 (0 HPD)	1.00x		3.75x-6.91x		3.69x		NA	
Day 92 (7 HPD)	1.00x		4.75x		5.18x		NA	
IL10 (pg/mL)								
Day 1 (7 HPD)	1.00x-1.69x		32.36x-112.54x		22.72x-1166.71x		285.49x-805.00x)	
Day 57 (0 HPD)	1.00x		2.21x		3.07x		17.41x-39.65x	
Day 57 (7 HPD)	1.00x		-		-		18.48x-39.86x	
Unscheduled euthanasia	NA		21.07x		2.56x-12.22x		2.01x-2.42x	
Day 92 (0 HPD)	1.00x		2.22x		-		NA	
IFNγ (pg/mL)								
Day 1 (7 HPD)	1.00x		12.65x -80.13x		78.37x-296.01x		59.11x-235.50x	
Day 57 (0 HPD)	1.00x		-		-		3.91x	
Day 92 (7 HPD)	1.00x		3.89x		-		NA	
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Histopathology – Unscheduled deaths								
Number Examined	0	0	1	0	2	2	3	3
Spleen								

Decreased cellularity, lymphoid follicle								
Minimal	NA	NA	0	0	0	0	0	1
Mild	NA	NA	0	0	0	2	0	0
Marked	NA	NA	1	0	2	0	3	1
Deposition pigment, red pulp								
Minimal	NA	NA	0	0	1	0	0	0
Mild	NA	NA	0	0	0	0	1	0
Lymph node, mesenteric								
Necrosis								
Mild	NA	NA	0	0	0	1	0	0
Marked	NA	NA	0	0	0	1	0	0
Decreased cellularity, lymphocyte								
Minimal	NA	NA	1	0	1	0	0	0
Mild	NA	NA	0	0	0	1	3	1
Moderate	NA	NA	0	0	0	0	0	1
Lymph node, axillary								
Decreased cellularity, lymphocyte								
Minimal	NA	NA	0	0	1	0	0	0
Moderate	NA	NA	0	0	0	0	0	1
Lymph node, draining								
Decreased cellularity, lymphocyte								
Minimal	NA	NA	0	0	1	0	1	1
Mild	NA	NA	0	0	1	1	2	0
Moderate	NA	NA	0	0	0	0	0	1
Gut-associated lymphoid tissue								
Decreased cellularity, lymphocyte								
Minimal	NA	NA	1	0	0	0	2	1
Mild	NA	NA	0	0	2	1	0	1
Marked	NA	NA	0	0	0	0	1	0
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Histopathology – Day 93								
Number Examined	3	3	2	3	1	1	0	0
Spleen								
Decreased cellularity, lymphoid follicle								
Mild	0	0	0	1	0	1	NA	NA
Moderate	0	0	0	1	0	0	NA	NA
Marked	0	0	2	0	1	0	NA	NA
Deposition pigment, red pulp								
Mild	0	0	1	0	0	0	NA	NA
Lymph node, mesenteric								
Necrosis								
Moderate	0	0	0	0	1	0	NA	NA
Decreased cellularity, lymphocyte								
Minimal	0	2	1	0	0	1	NA	NA
Mild	0	0	1	0	0	0	NA	NA

Lymph node, axillary								
Decreased cellularity, lymphocyte								
Mild	0	0	1	0	1	0	NA	NA
Lymph node, draining								
Decreased cellularity, lymphocyte								
Minimal	0	0	2	1	1	1	NA	NA
Gut-associated lymphoid tissue								
Decreased cellularity, lymphocyte								
Minimal	0	0	1	0	1	1	NA	NA
Mild	0	0	1	0	0	0	NA	NA
Small intestine, jejunum								
Atrophy, mucosa								
Mild	0	0	1	0	0	0	NA	NA
Infiltration, mononuclear cell								
Minimal	0	0	1	0	0	0	NA	NA
Mild	0	0	1	0	0	0	NA	NA
Small intestine, ileum								
Atrophy, mucosa								
Mild	0	0	1	0	0	0	NA	NA
Infiltration, mononuclear cell								
Minimal	0	0	1	0	0	0	NA	NA
Mild	0	0	1	0	0	0	NA	NA
Large intestine, cecum								
Atrophy, mucosa								
Minimal	0	0	1	0	0	0	NA	NA
Large intestine, colon								
Atrophy, mucosa								
Minimal	0	0	0	2	0	0	NA	NA
Mild	0	0	1	0	0	0	NA	NA
Infiltration, mononuclear cell								
Minimal	0	0	0	2	0	0	NA	NA
Mild	0	0	1	0	0	0	NA	NA
Necrosis, crypt								
Minimal	0	0	0	1	0	0	NA	NA
Mild	0	0	1	0	0	0	NA	NA
Stomach								
Atrophy, mucosa								
Minimal	0	0	1	0	0	0	NA	NA
Infiltration, mononuclear cell								
Minimal	0	0	0	1	0	0	NA	NA
Mild	0	0	1	0	0	0	NA	NA
Kidney								
Infiltration, mononuclear cell								
Minimal	0	1	0	3	1	1	NA	NA
Mild	0	0	2	0	0	0	NA	NA
Degeneration/regeneration, tubular epithelium								

Minimal	0	0	2	1	0	0	NA	NA
Liver								
Inflammation, neutrophilic								
Minimal	0	0	0	0	1	0	NA	NA
Vacuolation, hepatocyte								
Mild	0	0	1	0	0	0	NA	NA
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Lung								
Inflammation, granulomatous								
Minimal	0	0	0	0	1	0	NA	NA
Mild	0	0	0	1	0	0	NA	NA
Lymph node, mesenteric								
Necrosis								
Moderate	0	0	0	0	1	0	NA	NA
Epididymis								
Infiltration, mononuclear cell								
Minimal	0	NA	0	NA	1	NA	NA	NA
Mild	0	NA	2	NA	0	NA	NA	NA

The FDA's Assessment:

The FDA agrees with the Applicant's assessment for the general toxicology studies overall; however, the review below provides additional information and some clarifications regarding the methods and data presented by the Applicant.

A 1-month repeat-dose study evaluated weekly IV administration (total of 5 doses) of elranatamab at doses of 0.01, 0.05, and 0.3 mg/kg. Monkeys were euthanized on day 30, one day after the last dose was administered. Clinical signs included emesis at all doses and dark/red skin discoloration observed in 3 animals from the mid and high dose groups. Skin discoloration was observed on the eyelid, abdomen, inguinal or forelimb areas. Decreased lymphocytes, leukocytes, large unstained cells, and basophils were observed (Table 5). Microscopic findings included skin inflammation and epidermal hyperplasia, and increased/decreased cellularity in GALT, spleen, and mesenteric lymph nodes. Decreased globulin and total protein, and increased albumin/globulin ratio changes were observed at all doses (Table 6). Cytokine levels were evaluated 6 hours post-dose on days 1, 8, and 29, but were not evaluated at 24 hours post-dose in this study as suggested by the Applicant in the assessment above. An information request (IR) was sent to the Applicant and their response described that the assessment of cytokines 24 hours post-dose comes from the 1-month and 3-month SC studies. Increases in IL6, IL10, and IFNy were observed at all doses, primarily after the first dose. Immunophenotyping showed a dose-dependent decrease in B-cells, overall decrease in T-cells (CD4+ and CD8+) and NK cells, and increased activated and proliferating T-cells (CD25 or CD69+ T-cells and ki67+ T-cells). Plasma cell analysis was conducted to determine changes in ASCs in blood and bone marrow samples; based on the FDA's review, no significant changes

were noted in plasma cells. The Applicant's response to the IR suggested that the results from the plasma cell analysis may have been attributed to a technical issue with the assay.

Table 5: FDA – Summary of hematology changes (% change from baseline) from the 1-month IV toxicology study in monkeys

Test	Male				Female			
	Control	LD	MD	HD	Control	LD	MD	HD
Basophils	-17.8%	-66.7%	-66.7%	-50.0%	0.0%	-33.3%	-23.3%	-38.9%
Large Unstained Cells	-18.7%	-30.0%	-70.8%	-71.5%	-16.7%	6.7%	-6.1%	-71.1%
Leukocytes	7.1%	-28.0%	-35.4%	-31.1%	10.7%	5.7%	-16.7%	-19.6%
Lymphocytes	-12.0%	-50.8%	-73.3%	-66.1%	-3.9%	-15.9%	-43.6%	-56.6%

LD=low dose, MD= mid dose, HD=high dose
Source: FDA Analysis

Table 6: FDA – Summary of clinical chemistry changes (% change from baseline) from the 1-month IV toxicology study in monkeys

Test	Male				Female			
	Control	LD	MD	HD	Control	LD	MD	HD
Albumin/Globulin	0.0%	14.4%	53.7%	51.3%	-4.8%	12.3%	43.4%	72.8%
Globulin	-1.6%	-11.5%	-35.0%	-34.0%	1.3%	-12.4%	-30.1%	-40.7%
Total Protein	-2.3%	-4.3%	-15.1%	-14.4%	-2.0%	-7.0%	-15.8%	-18.4%

LD=low dose, MD= mid dose, HD=high dose
Source: FDA Analysis

The purpose of the 1-month repeat-dose SC toxicity study was to assess the local tolerance and toxicokinetics of elranatamab at 0.3 mg/kg administered once weekly for a total of 5 doses. All animals were euthanized on day 30, one day after the last dose was administered. The dose of 0.3 mg/kg elranatamab did not induce mortality, clinical signs, or changes in body weight or food consumption. Increases in IL2, IL6, IL10 and IFNγ (up to 11.9x, 445x, 825x, and 86.18x from baseline, respectively) were detected 6 hours post-first dose and almost all returned to baseline levels 24 hours post-dose (except for IL10 in 1 male, returned to 7.1x baseline). Minimal or moderate inflammation at the injection site occurred in 2 of 3 males and 3 of 3 females. Immunophenotyping for BCMA, T-cells or NK cells was not conducted during this study.

The 3-month repeat-dose toxicity study evaluated elranatamab doses of 0.3, 3 or 6 mg/kg administered SC once weekly for a total of 14 doses. Study endpoints were obtained from all animals including moribund and terminal animals. Moribund euthanasia was dose-dependent, occurred at all doses, and followed clinical signs including decreased body weight, decreased activity, hunched posture, liquid feces, emesis, decreased skin turgor, and lateral recumbency.

Decreased body weight ranged from 0.8x-0.9x (relative to baseline). Decreased red blood cell mass parameters (down to 0.3x, 0.3x, and 0.2x from baseline for RBC, HCT, and HGB, respectively) and increase in reticulocytes (up to 14x from baseline) were observed in the elranatamab treated groups. Decreased lymphocytes and eosinophils (down to 0.1x and 0x, respectively) and increases in WBCs (up to 2x) were observed in moribund animals. Decreased total protein (0.5x-0.9x) included decreases in globulin, albumin, and immunoglobulins including IgA, IgM, and IgG. Notable findings included decreased lymphocyte cellularity in lymphoid tissues (spleen, lymph nodes, and GALT), infiltration in organs of the GI system (stomach, small and large intestines), kidney, and inflammation of the liver and lung. Additional findings (not shown in the Applicant's summary) included infiltration/inflammation/thrombus/necrosis, and bacterial colonies in multiple organs. Findings in the reproductive organs consisted of the following: minimal to mild mononuclear infiltrates in the epididymis at all elranatamab doses and seminiferous tubule dilation or infiltrates in the testis at the low and mid doses, respectively. Minimal mononuclear cell infiltrates were present in the cervix at all doses (also in 1 control animal) and in the uterus at the mid and high doses (also in 1 control animal). Minimal neutrophilic inflammation of the uterine serosa was present in one female from the high dose group. Immunophenotyping showed a near complete depletion of B-cells, increased activated (CD69+) and proliferating (Ki67+) T-cells, and increased NK cells. The highest levels of IL6, IL10, and IFNγ were observed at all doses on day 1 at 7 hours post-dose; lower levels were seen throughout the study and at the terminal timepoint (day 92).

ASCs were evaluated prior to dosing, on day 43, and on day 93 from peripheral blood mononuclear cells (PBMCs) via the enzyme linked immunospot assay (ELISPOT). On days 43 and 93, the number of ASCs in the control group ranged from 247-1156 per million PBMCs. On day 43, ASCs across all elranatamab treated groups ranged from 0-15 ASCs per million PBMCs. On day 93, in 5 of 7 remaining animals ASCs ranged from 0-3 per million PBMCs. The other 2 animals had 229 or 2008 ASCs per million PBMC; these 2 animals also had ADAs.

5.5.2 Genetic Toxicology

The Applicant's Position:

No genetic toxicity studies have been conducted with elranatamab.

The FDA's Assessment:

The FDA concurs.

5.5.3 Carcinogenicity

The Applicant's Position:

No carcinogenicity studies have been conducted with elranatamab.

The FDA's Assessment:

The FDA concurs.

5.5.4 Reproductive and Developmental Toxicology

The Applicant's Position:

No reproductive and/or developmental toxicity studies have been conducted with elranatamab. Effects on reproductive organs were assessed in pivotal studies using sexually mature male and female cynomolgus monkeys. Additionally, an integrated weight of evidence assessment was conducted to evaluate the potential for elranatamab to elicit developmental effects.

Based on pivotal studies, elranatamab is not expected to negatively impact reproductive function. However, the weight of evidence assessment identified a risk of fetal harm. With this risk identified and reported in the label, no additional studies are warranted.

- Assessment based on an integrated review of published literature about the roles of BCMA, CD3, and cytokines in reproduction and development; nonclinical toxicity data; and clinical adverse event data.
- Reduction of B cells alters immune function in pregnancy and negatively impacts offspring; elranatamab reduces BCMA-expressing plasma cells and subsets of B cells resulting in complete near complete or partial depletion in both cynomolgus monkeys and humans.
- Alterations in the timing and balance of inflammatory and anti-inflammatory cytokines can contribute to adverse outcomes of pregnancy; elranatamab induces cytokine release in monkeys and humans.

Study title/study number/eCTD location: 3-Month Subcutaneous Toxicity Study of PF-06863135 in Cynomolgus Monkeys / 20GR302 / Module 2.6.7.7C and 4.2.3.2
Study type (eg, fertility and early embryonic development, embryo-fetal development, or pre- and postnatal development): Repeat-dose toxicity
Key Drug-related Adverse Findings

- Nonadverse epididymal finding of minimal to mild mononuclear infiltrates at all doses
- No findings in female reproductive organs

GLP compliance: Yes

Methods	
Dose and frequency of dosing:	0, 0.3, 3, and 6 mg/kg/week (14 doses)
Route of administration:	Subcutaneous
Formulation/Vehicle:	Solution / (b) (4) histidine, 85 mg/mL sucrose, (b) (4) (b) (4) 0.2 mg/mL polysorbate 80, pH 5.8
Species/Strain:	Monkey/Cynomolgus
Number/Sex/Group:	3/sex/group
Age:	5-8 years
Satellite groups:	None
Study design:	PF-06863135 was evaluated for toxicity and toxicokinetics in sexually mature cynomolgus male and female monkeys (3/sex/group), animals were administered doses of 0.3, 3, or 6 mg/kg/week by subcutaneous injection once weekly for 3 months (14 total doses).

The FDA's Assessment:
A WOE risk assessment was conducted to evaluate the potential of elranatamab to elicit embryofetal developmental effects. The pharmacology of the product and effects seen in animals and humans were considered for the WOE risk assessment. Elranatamab induced a partial to near complete depletion of B-cells in repeat-dose toxicity studies and increased cytokine levels in in vitro and in vivo studies that could result in cytokine release syndrome (CRS) in humans. The WOE risk assessment referenced published literature supporting that CRS can cause adverse pregnancy outcomes, specifically by disrupting the regulation of inflammatory signals during the establishment of pregnancy, pregnancy maintenance, and parturition. The WOE risk assessment also referred to published literature that showed a reduction of B-cells does not appear to affect a normal pregnancy but can result in reduced B-cells in offspring. The assessment of BLA 761345 does not rely on product-specific published literature.

5.5.5 Other Toxicology Studies

The Applicant's Position:

Local Tolerance

Elranatamab caused only nonadverse minimal to moderate injection site inflammation when evaluated in the pivotal toxicity studies.

Antigenicity

Elranatamab caused only minimal ADA induction in the 3-month toxicity study with 33% induction at the LD, and 0% at the MD and HD.

Immunotoxicity

The primary pharmacology of elranatamab is through activation of the immune system by dual engagement of CD3 and BCMA. Therefore, elranatamab induces T cell-mediated cytotoxicity and cytokine release, which has been observed in both monkeys and humans.

Impurities

Based on an in vitro assay, the potency and overall safety of elranatamab is not impacted by low levels of (b) (4) impurities.

Tissue Expression and Cross-Reactivity

In general, there was concordance between monkey and human data to support monkey as a relevant toxicology species. BCMA+ cells were rare (<0.4% of WBCs), most abundant in bone marrow, and displayed a more mature/terminally differentiated phenotype to B cells. In the pivotal tissue cross-reactivity study, the staining of mononuclear cells and bone marrow cells was consistent with the known expression of BCMA by B cells and CD3 by T cells.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment for other toxicology studies. Additional information is provided below.

Commonly found impurities include [redacted]. These impurities were spiked (levels of [redacted]%) into elranatamab and cytokine release was evaluated in an in vitro CRS assay using PBMCs. Elranatamab induced a concentration-dependent increase in TNFα, IL2 and IFNγ levels. Spiked impurities did not induce significant increases in the cytokine levels compared to elranatamab alone.

In addition to the toxicology studies mentioned above, the Applicant also conducted an in vitro CRA using whole blood from 8 healthy human donors. Elranatamab concentrations of 0.005, 0.5, and 50 µg/mL were incubated with whole blood samples for 24 hours and the release of TNFα, IL6 and IFNγ was evaluated. Elranatamab induced cytokine release primarily from samples treated with concentrations of 0.5 and 50 µg/mL. IFNγ release was detected in all samples with 0.5 and 50 µg/mL elranatamab (402-2313 pg/mL and 719-3009 pg/mL, respectively); 5 of the 8 donors had IFNγ levels similar to or greater than levels elicited by the lipopolysaccharide positive control. TNFα (ranged from below the lower limit of quantitation up to 124 pg/mL) and IL6 levels (ranged from below the lower limit of quantifation up to 204 pg/mL) were detected from a subset of samples; TNFα and IL6 levels were lower than those from the positive control.

X X

Primary Reviewer Supervisor

6 Clinical Pharmacology

6.1 Executive Summary

The FDA's Assessment:

Elranatamab is a T-cell engaging bispecific antibody that binds CD3 expressed on the surface of T cells and B-cell maturation antigen (BCMA) on the multiple myeloma (MM) cell, which directs T cells to myeloma target cells leading to cytolysis of the BCMA expressing cells. The Applicant is seeking approval of elranatamab for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least four prior lines of therapy, including a proteasome inhibitor (PI), an immunomodulatory drug (IMiD), and an anti-CD38 antibody. The proposed subcutaneous (SC) dosing regimen is shown in Table 7 below (hereafter referred to as 12/32/64 mg). The proposed dosage is administered until disease progression or unacceptable toxicity.

Table 7: FDA – Recommended Dose and Schedule

Dosing Schedule	Day	ELREXFIO Dose	
Step-up Dosing Schedule	Day 1[a]	Step-up dose 1	12 mg
	Day 4[a,b]	Step-up dose 2	32 mg
	Day 8[a,c]	First treatment dose	76 mg
Weekly Dosing Schedule (b) (4)	One week after first treatment dose and weekly thereafter[d] through week 24	Subsequent treatment doses	76 mg
Biweekly (Every 2 Weeks (b) (4)) Dosing Schedule ***Responders only week 25 onward**	Week 25 and every 2 weeks thereafter[d]	Subsequent treatment doses	76 mg

a. Administer pre-treatment medications prior to each dose in the ELREXFIO step-up dosing schedule, which includes step-up dose 1, step-up dose 2, and the first treatment dose *[see Dosage and Administration (2.3)]*.
b. A minimum of 2 days should be maintained between step-up dose 1 (12 mg) and step-up dose 2 (32 mg).
c. A minimum of 3 days should be maintained between step-up dose 2 (32 mg) and the first treatment (76 mg) dose.
d. A minimum of 6 days should be maintained between treatment doses.

Source: Table 1 elranatamab USPI.

The efficacy evidence to support the proposed indication is primarily provided from the pivotal phase 2 study C1071003(1003) Cohort A, which included patients with RRMM who had not received prior BCMA-directly therapy (BCMA naïve). The study demonstrated an objective

response rate (ORR) of 57.7% (95% CI: 47.3, 67.7) and a complete response rate (CR) of 26% as well as an overall acceptable safety profile.

The key review issues are focused on the evaluation of dose selection, recommendations for restarting therapy after dose delay, drug-drug interaction (DDI) due to cytokine release, and immunogenicity.

Recommendations

The Office of Clinical Pharmacology has reviewed the information submitted in BLA 761345. This BLA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below in Table 8.

Table 8: FDA – Key Clinical Pharmacology Review Issues and Recommendations

Review Issue	Recommendations and Comments
Pivotal and supportive evidence of effectiveness	The primary evidence of effectiveness comes from the pivotal study 1003 cohort A. The proposed dosage regimen (12/32/76 mg) is supported by an ORR 57.7% (95% CI: 47.3, 67.7)
General dosing instructions	The proposed dosage regimen (12/32/76 mg) is selected with the following rationale: • The step-up dosing schedule helps to mitigate cytokine release syndrome (CRS) risk in the subsequent full therapeutic doses at 12/32 mg. • CRS grade and incidence for each dose event did not differ significantly across body weight quartiles. • The proposed dosing regimens demonstrated clinically meaningful ORR and an acceptable safety profile in patients enrolled in study 1003. • Exposure-response (E-R) efficacy analyses identified a trend between free average elranatamab exposure on day 28 ($C_{ave, Day 28}$), and ORR; ORR appeared to be plateaued at the selected recommended phase 2 dose (RP2D) of 76 mg QW. • E-R safety analysis did not identify any safety concerns with exposure following the proposed dosage of (12/32/76mg). The treatment duration is supported by observed efficacy data and a quantitative systems pharmacology (QSP) model: • Majority (85%) of patients with RRMM were able to maintain or improve response during Q2W dosing compared to the proceeding dose window in study 1003. • Median time to response was 1.22 (ranges from 0.89 to 7.36) months • According to the analyses of quantitative systems pharmacology (QSP) modeling, a comparable CD3-elranatamab-membrane

Review Issue	Recommendations and Comments
	BCMA trimer to tumor ratio was predicted in virtual responders after switching from QW to Q2W
Dosage recommendations for restarting therapy after dose delay	The proposed dosage recommendation for restarting therapy after dose delay aims to mitigate CRS risk and is supported by: • No increase in the risk of CRS following dose delays shorter than the proposed cut-offs for re-priming when compared to the overall RP2D expansion cohort. However, there is limited safety data for longer duration of dose delay without repriming (i.e., >14 days of dose delay for step-up doses and >28 days of dose delay for full treatment). • Based on the totality of data including population pharmacokinetic (PK) simulation and clinical data, the FDA revised the restart therapy recommendation to allow continuation with next planned dose if dose delay is ≤ 42 days following any full treatment dose. See section **Error! Reference source not found.** for additional discussion
Dosing in patient subgroups (intrinsic and extrinsic factors)	• No dosage adjustment is needed according to body weight, age, sex, race, mild to moderate renal impairment, or mild hepatic impairment.
Drug-drug interactions	• Elranatamab administration resulted in the transient release of cytokines, which may suppress cytochromes P450 (CYP450) enzymes and cause drug-drug interactions. Increased exposure of CYP450 substrates is more likely to occur up to 14 days after the second 32mg dose on week 1 day 4 and during and after CRS. • Monitor for toxicity of drugs that are CYP450 substrates where minimal concentration changes may lead to serious adverse reactions. Adjust the dose of the concomitant drug as needed.
Immunogenicity	• Anti-elranatamab antibodies (ADA) developed in 8.9% of patients during treatment with the RP2D dosage in study 1003. Among the 15 patients who tested positive for ADAs, 60% (9/15) tested positive for neutralizing antibodies against elranatamab. • The effect of these antibodies on the PK, pharmacodynamic (PD), safety, and/or effectiveness of elranatamab is unknown.
Labeling	• Overall, the proposed labeling recommendations are acceptable upon the Applicant's agreement with the FDA -recommended revisions to the labeling.

6.2 Summary of Clinical Pharmacology Assessment

6.2.1 Pharmacology and Clinical Pharmacokinetics

Data:

Elranatamab clinical pharmacokinetics (PK) (both free, i.e., sBCMA-unbound and total) and pharmacodynamics (PD) were characterized based on results from 321 participants with relapsed/refractory MM enrolled in 4 clinical studies. Non-compartmental analysis (Studies C1071001 and C1071002), pooled population PK, population PK/PD, and Quantitative Systems Pharmacology (QSP) analyses were conducted (Section 19.4). These analyses support the following conclusions:

Pharmacokinetics: On average, elranatamab exhibited approximately dose-proportional PK over the dose range evaluated via SC route (fixed doses of 6 to 76 mg).

Model-predicted absolute bioavailability from SC route is ~56.2%. Median Tmax after the first dose across dose levels for the SC route ranged from 3 to 7 days. Apparent clearance of total elranatamab (CL/F) was 0.44 L/day (69%) calculated as dose/simulated AUC_{tau} after multiple weekly doses on week 24. Population mean for unbound elranatamab clearance and volume of distribution were 0.324 L/day and 4.777 L, respectively, which is generally consistent with large molecules (mAbs) with linear PK. The major elimination pathway of elranatamab in humans is expected to be via non-specific catabolic degradation.

Exposure-response analyses: Exposure-efficacy analysis showed that higher elranatamab exposure was associated with higher probability of ORR. Baseline sBCMA had a significant, inverse association with ORR. Free elranatamab exposure was lower in patients with high baseline sBCMA. No significant association between elranatamab exposure and/or Q2W switch and DOR was identified.

Higher early elranatamab exposure metrics ($C_{max, 24}$ [both free and total]) was associated with higher probability of any Grade CRS and Grade ≥2 CRS. Exposure-safety analyses for Grade ≥3 neutropenia (most common AE leading to dose modifications), Grade ≥3 infections, and Grade ≥2 peripheral neuropathy indicate no clinically meaningful relationship with elranatamab exposure. The relatively flat exposure-safety relationship indicates a similar probability of experiencing these events with 76 mg QW regimen versus lower doses.

Immunogenicity: The overall immunogenicity risk for elranatamab is low. ADA incidence was low, with low titer, a relatively early onset, and transient.

The Applicant's Position:
The clinical pharmacology findings including PK, PD, exposure-response for efficacy and safety endpoints, and immunogenicity analyses support the recommended dosing regimen.

The FDA's Assessment:
The elranatamab clinical pharmacology program included data from the dose escalation study C1071001, dose finding study C1071002, C1071009 and pivotal study 1003. The results of these studies generally provided adequate characterization of elranatamab pharmacokinetic properties. Refer to section 6.2.2 for additional details.

Absorption: The mean bioavailability of elranatamab was 56.2% when administered subcutaneously. The median (min, max) Tmax after elranatamab SC administration was 7 (3 to 7) days.

Distribution: The steady state volume of distribution of elranatamab was 7.76 L (33%).

Elimination: The half-life of elranatamab is 22 (64%) days at the 76 mg dosage, with clearance of 0.324 L/day (100%) following 24 weeks dosing.

Pharmacokinetic and Pharmacodynamic: Free elranatamab exposure increased with dose in an approximately dose-proportional manner over the dose range evaluated via SC route (6 to 76 mg). The patient with higher sBCMA baseline BCMA appeared to have lower free elranatamab concentration. Declines in free sBCMA concentrations were observed in responders on cycle 2 day 1.

Refer to sections 6.3.1, 19.4.1 and 19.4.2 for details of PK and PD of elranatamab.

6.2.2 General Dosing and Therapeutic Individualization

6.2.2.1 General Dosing

Data:

The totality of PK, PD, and safety data supports the 2 step-up priming dose regimen of 12 mg / 32 mg with premedications as the recommended elranatamab priming dosing regimen given a) the observed incidence of all Grades CRS and Grade ≥2 CRS, b) sufficient stimulation of cytokines with the first dose of 12 mg, and c) the predictable timing and manageable profile of CRS with this regimen.

Higher elranatamab exposure was associated with higher probability of ORR. The 76 mg QW regimen achieves the highest free elranatamab exposure at a given baseline sBCMA level in the dose range evaluated, and results in higher probability of achieving an objective response vs lower doses, with no expected impact on safety. The relatively flat exposure-safety relationship for Grade ≥3 neutropenia, Grade ≥3 infections, Grade ≥2 peripheral neuropathy, and QTcF prolongation support a full dose of 76 mg QW and do not suggest that selection of a lower dose would mitigate the risk for AEs.

Maintained and deepening clinical benefit was observed in Study C1071003 with the switch from QW to Q2W dosing after 24 weeks for responding participants. Rapid and deep declines in free sBCMA concentrations was observed in responding participants suggesting reduced disease burden and/or saturation of sBCMA. Therefore, lower dosing intensity (i.e., Q2W) are adequate to maintain the responses achieved during initial treatment phases (after 24 weeks of initial QW dosing). Neither elranatamab exposure nor the Q2W switch had a significant impact on DOR. QSP simulations indicate similar maintenance of responses with Q2W switch compared to 76 mg QW continuously.

The Applicant's Position:
The clinical pharmacology findings including PK, PD, and exposure-response for efficacy and safety analyses support the recommended dosing regimen; 76 mg QW administered as a SC injection with a 2-dose step-up priming regimen (12 mg on Day 1 and 32 mg on Day 4) administered during the first week of treatment. The dosing interval should transition to 76 mg Q2W after at least 24 weeks for patients who have achieved a response.

The FDA's Assessment:
FDA agrees that proposed dosing regimen of elranatamab 76 mg QW administered as a SC injection with a 2-dose step-up priming regimen (12 mg on Day 1 and 32 mg on Day 4) for the indicated patient population is acceptable.

- *Step-up dosing regimen*

The proposed 12/32 step-up dosing regimen is acceptable based on the following assessments:

1) The proposed RP2D regimen of 12/32/76 mg resulted in a lower incidence of all Grade and Grade ≥2 CRS compared to the single step-up dosing regimen 44/76 mg. The single step-up dose regimen resulted in rates of overall CRS and Grade ≥ 2 CRS of 83% and 47% respectively in patients with RRMM, compared to 57.9% and 13.7% in the RP2D regimen (Table 9).

2) Following administration of the RP2D in the primary safety population, CRS mainly occurred following the initial 3 doses of elranatamab in cycle 1, with the highest rate observed following the step-up dose 1 at 12 mg on cycle 1 day 1. The risk of CRS in subsequent cycles was mitigated by the initial 12/32/76 mg step-up doses (Table 10,
3) APPEARS THIS WAY ON ORIGINAL

5) Figure 2). Nineteen patients (18%) who did not experience CRS following the first 12mg dose step-up dose could still experience CRS following the second step-up dose of 32mg. Seven patients (8.3%) had CRS during the third dose or the first treatment dose (76 mg) among the patients who did not experience CRS for step-up 1 and 2 dose.

6) An alternative two step-up regimen of 4/20/76 mg also resulted in low overall grade CRS and grade 2 CRS compared to a single step-up dosing regimen 44/76 mg. However, a comparison by dose indicated that the CRS mitigation effect of the 4/20 mg step-up dose may not be as good as the 12/32 mg step-up dose, given the higher incidences of CRS including Grade 2 CRS at the 76 mg dose following the 4/20 mg step-up dose. See Table 10.

7) The efficacy data indicated that dose levels of 16 mg and above are active dose with highest efficacy observed at dose level 76 mg in study C1071001 (Table 9).

Table 9: FDA – Summary of Response Rates (ORR and CRR) and CRS Rate by ASTCT Grade Following the Different Elranatamab Fixed Dose and Step-up Regimens (Studies C1071001, C1071002, C1071003 and C1071009)

Dose Levels	N	ORR	CR +sCR		Any grade CRS	Grade 2 CRS	Grade 3 CRS
Fix Dose (ug/kg)							
0.1 IV	2	0	0		0	0	0
0.3 IV	3	0	0		0	0	0
1 IV	2	0	0		0	0	0
3 IV	3	0	0		0	0	0
10 IV	2	0	0		1 (50)	0	0
30 IV	5	0	0		4 (80)	0	0
50 IV	6	0	0		6 (100)	5 (83)	0
80 SC	6	0	0		2 (33)	1 (17)	0
130 SC	6	0	0		2 (50)	0	0
215 SC	4	2 (50)	2 (50)		3 (75)	1(25)	0
360 SC	4	3 (75)	1 (25)		3 (75)	1 (25)	0
600 SC	6	4 (67)	3 (50)		6(100)	1 (17)	0
1000 SC	6	5(83)	3(50)		6 (100)	2 (33)	0
Step-up dose (mg)							
44/76 mg [a]	26/30	15 (58)	8(31)		25(83)	14 (47)	1 (3%)
4/20/76 mg [b]	33/45	17(52)	3 (9.1)		29 (64)	6 (13)	0
12/32/76 mg [c]	97/183	56 (58)	25(26)		106(58)	25 (14)	1 (0.5%)

ORR: objective response rate; CR or Better: include all patient achieved complete Response and stringent complete response; VGPR: very good partial response; PR: partial response; SD: stable disease. IV: intravenous administration; SC: subcutaneous administration.

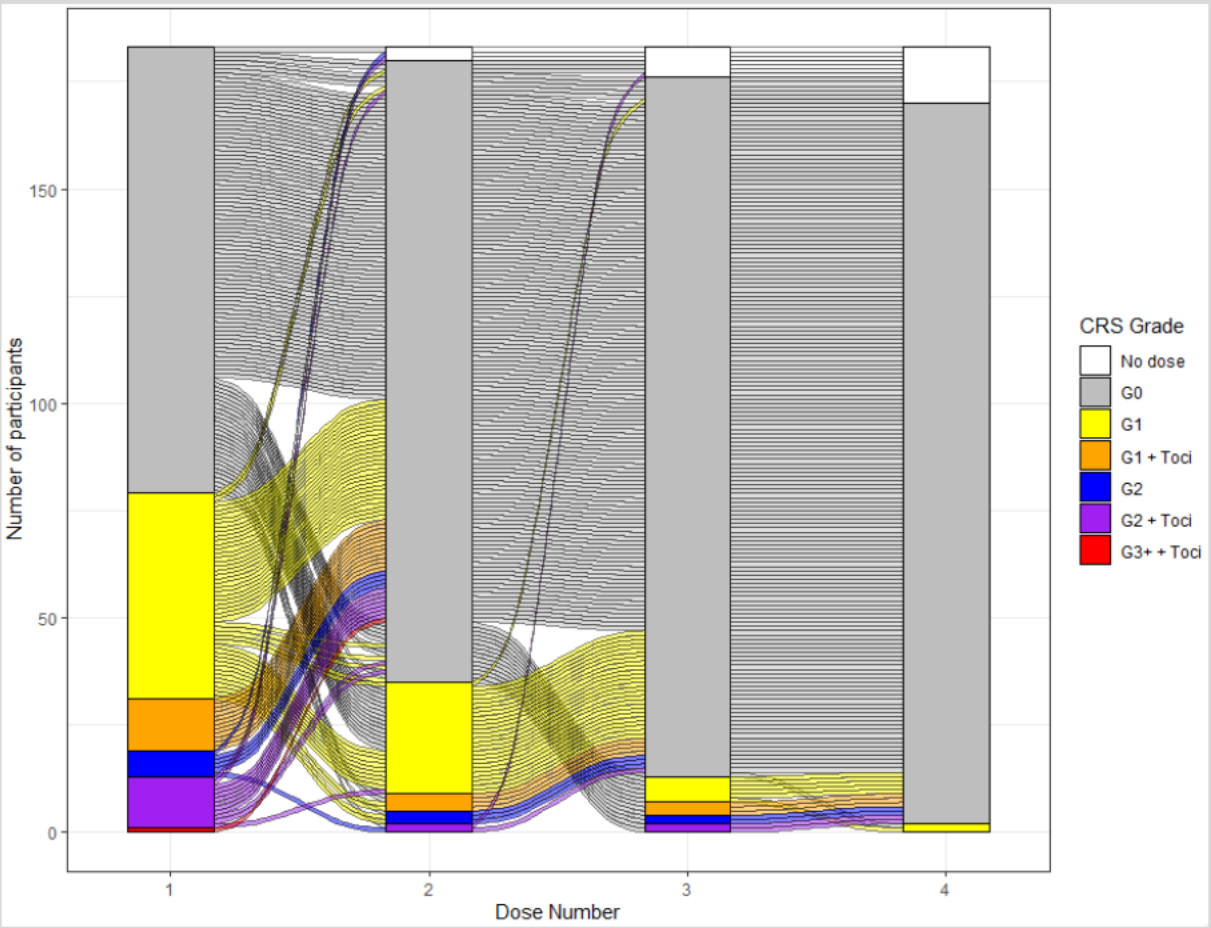
a. Efficacy result based on all participants in pooled studies result C1071001 (n=22) and C1071002 (n=4). Safety result is based on based on participants in pooled studies result C1071001 (n=22), C1071002 (n=4) and C1071003 (n=4)
b. Efficacy and safety data based on participant in study C1071009.
c. Efficacy based on cohort A in study C1071003, and safety data based on all participant but the first four participant received 44 mg step-up dose in study C1071003.
Source: Reviewer's analysis created from CRS C1071001, C1071002, C1071009, C1071003 Table 14.2.1.5.1 and Applicant's response to information request on 3/10/2023

Table 10: FDA – Summary of CRS Events by Dosing Period in Patients with RRMM Stratified by Priming Dose Regimens

12/32/76 mg regimen (N=183)[a]					
N (%)	**Step-up Dose 1**	**Step-up Dose 2**	**First Full Dose**	**Second Full Dose and after**	**Any time**
Patients with ≥1 CRS event	79 (43%)	35 (19%)	13 (7%)	3 (1.6%)	106 (58%)
Grade 1	60 (32.8%)	30 (16%)	9 (5%)	3 (1.6%)	80 (44%)
Grade 2	18 (9.8%)	5 (3%)	4(2%)	0	25 (14 %)
Grade 3	1 (0.5%)	0	0	0	1 (0.5%)
4/20/76 regimen (N=45)[b]					
Patients with ≥1 CRS event	14 (31%)	12 (27%)	8 (18 %)	7 (16%)	29 (64%)
Grade 1	12 (27%)	11 (24%)	6 (13%)	6 (13%)	23 (51%)
Grade 2	2 (4 %)	1(2%)	2 (4%)	1 (2%)	6 (13%)
Grade 3	0	0	0	0	0
44/76 regimen (N=30)[c]					
Patients with ≥1 CRS event	25 (83%)	N/A	1 (3%)	0	25 (83%)
Grade 1	10 (33%)	N/A	1 (3%)	0	10 (33%)
Grade 2	14 (47%)	N/A	0	0	14 (47%)
Grade 3	1 (3%)	N/A	0	0	1 (3%)

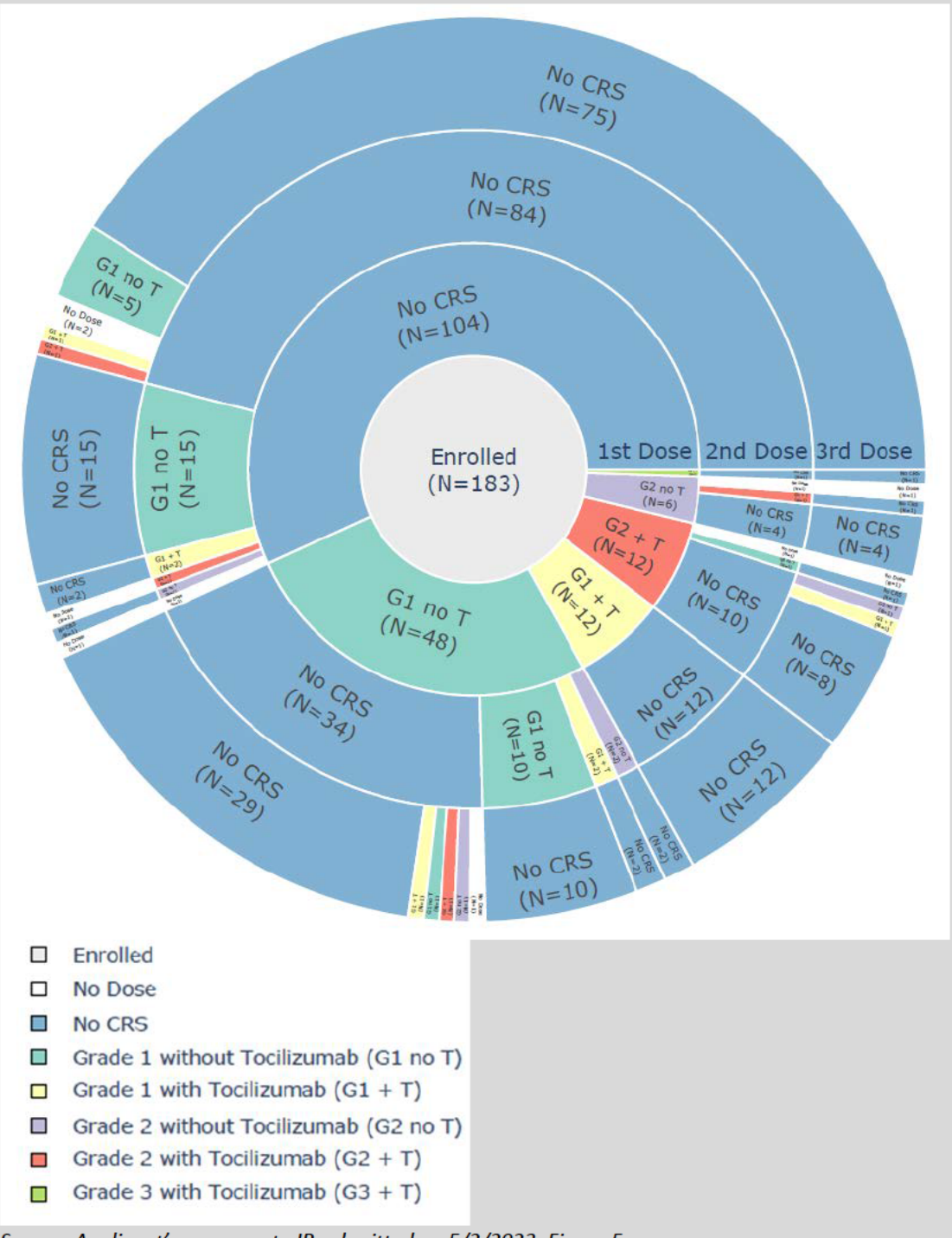
a. Safety data based on all participant but the first four participant received 44 mg step-up dose in study C1071003
b. Safety data based on participant in study C1071009
c. Safety data base on from all participants received a single step-up dose in Studies C1071001 (n=22), C1071002 (n=4) and C1071003 (n=4)
Source: summary of clinical pharmacology, table 30 and Applicant's response to information request on 3/10/2023

Figure 2: FDA – Sankey Plot for CRS Grade and Tocilizumab use in Participants who Received Elranatamab Priming Doses of 12 mg and 32 mg Followed by Full Treatment Dose of 76 mg (Study C1071003)



The individual patient CRS profiles after the first dose (12 mg, Dose Number 1), second dose (32 mg, Dose Number 2), third or fourth or more doses (76 mg, Doses Number 3 and ≥ 4) in patients who received 2 step-up priming dose regimen of 12/32 with or without tocilizumab use are presented.
+Toci: CRS occurrence with tocilizumab use.
Source: Applicant's response to IR on March 10, 2023, Figure 1

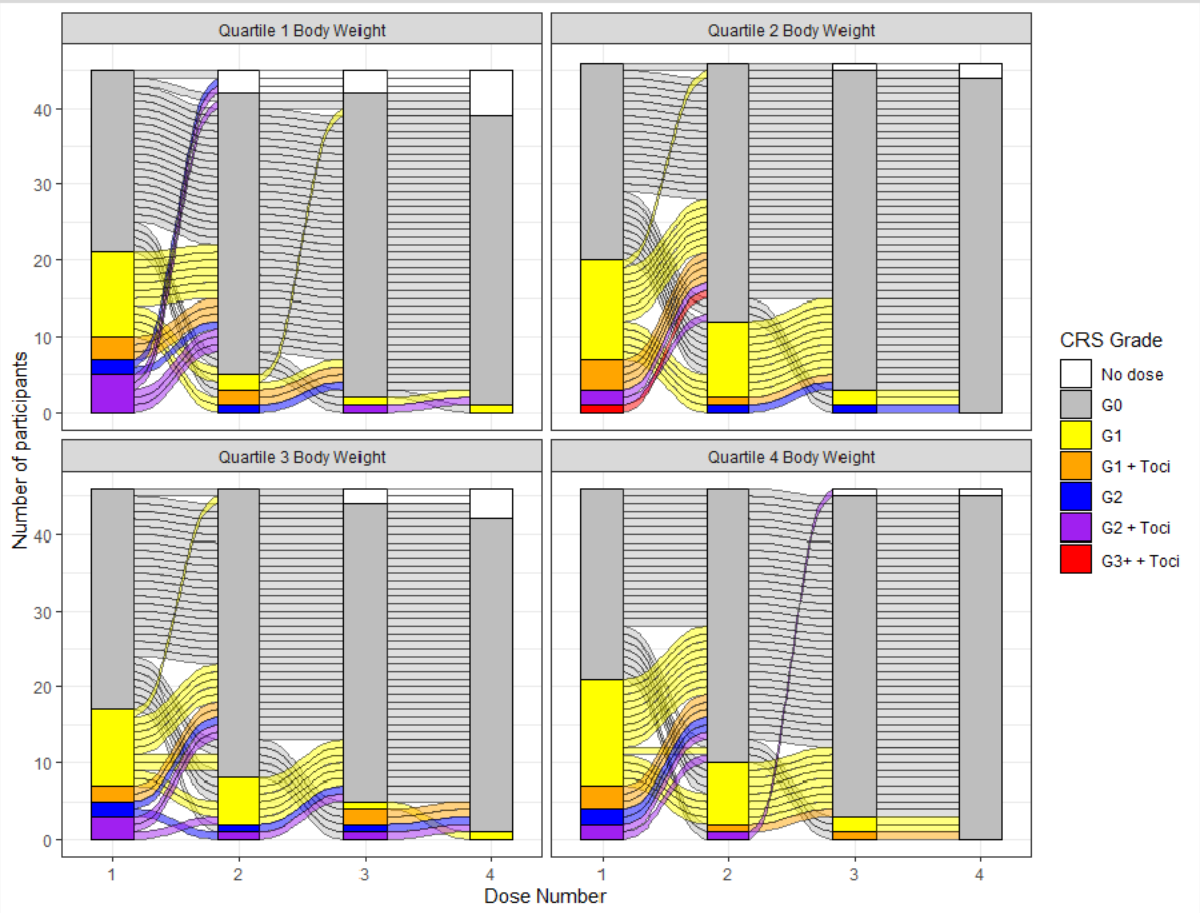
Figure 3: FDA – Sunburst Plot of CRS Events by Dose Event (Study C1071003, Safety Population, Cohorts A and B)



Source: Applicant's response to IR submitted on 5/2/2023, Figure 5

Additionally, no trends for CRS incidence or severity were observed across different body weight quartiles following the proposed 12/32/76 mg dosing regimen (APPEARS THIS WAY ON ORIGINAL Figure 4). The incidence of CRS of any Grade was 55.6%, 63%, 52.2%, and 60.9% for body weight quartiles 1 to 4, respectively. The incidence of CRS of Grade ≥ 2 was 20%, 8.7%, 17.4%, and 10.9% for body weight quartiles 1 to 4, respectively.

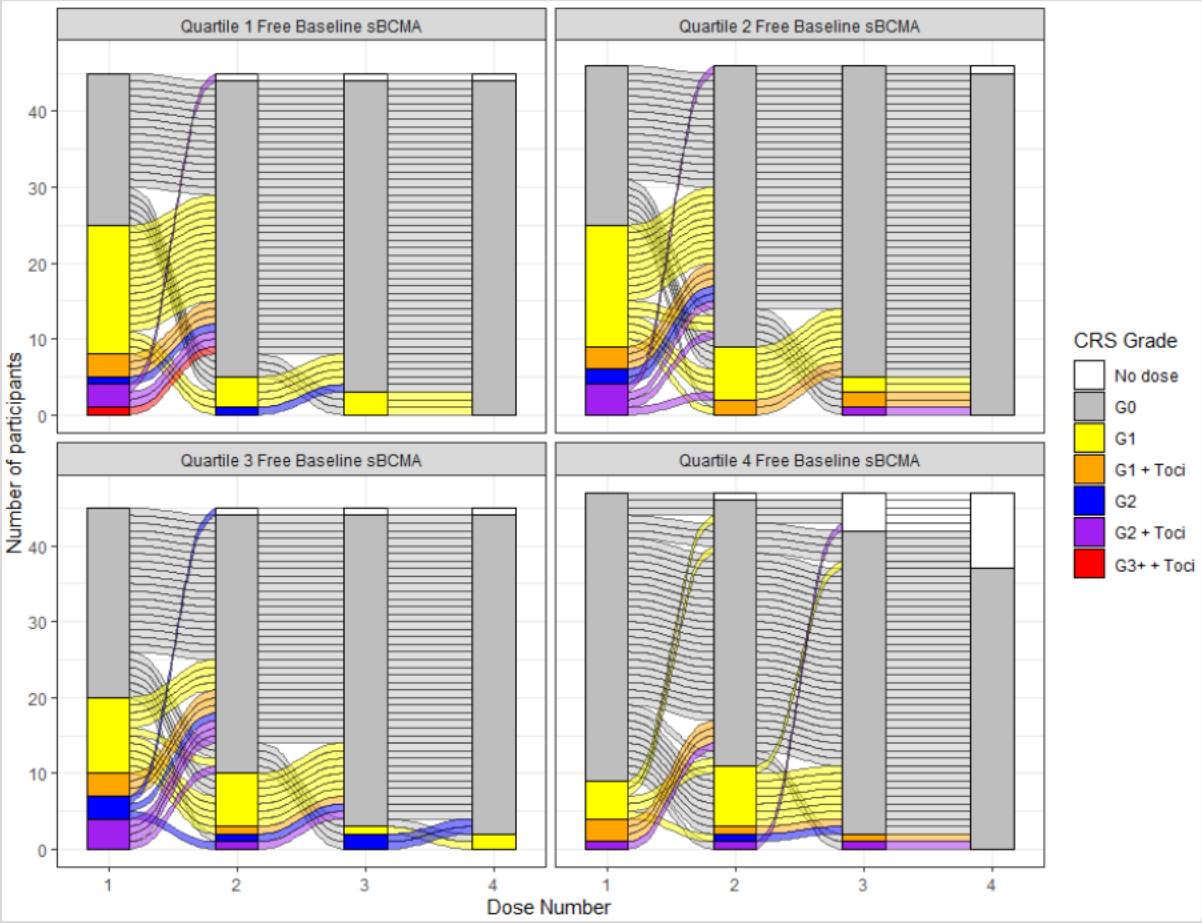
Figure 4: FDA – Sankey Plot for CRS Grade and Tocilizumab use by Body Weight Quartile Following the Proposed 12/32/76 mg Dosing Regimen (Study C1071003)



Source: Applicant's response to IR on March 10, 2023, Figure 2

A trend for lower incidence of any Grade CRS was observed for higher sBCMA quartiles (Figure 5). The incidence of CRS of any Grade was 68.9%, 65.2%, 52.2%, and 45.7% for baseline total sBCMA quartiles 1 to 4, respectively. However, this trend was not clinically relevant as Grade ≥ 2 CRS was generally comparable across the sBCMA quartiles.

Figure 5: FDA – Sankey Plot for CRS Grade and Tocilizumab use by Baseline sBCMA (Free) quartiles (Study C1071003)



Source: Applicant's response to IR on March 10, 2023, Figure 3

- *Treatment Dose*

The treatment dose of 76 mg is acceptable based on the following assessment:

1) Both ORR and CRR generally increased with increases of the full dose. The highest response rates were observed at the 76 mg full dose (Table 9).
2) Modeling and simulations including E-R analysis suggest that higher elranatamab exposure may be associated with higher ORR rates, and with a plateau of efficacy following the proposed dosage regimen 76 mg QW. The model also predicts that patients with a lower

number of prior lines of therapy (< 5 lines) and an absence of baseline extramedullary disease (EMD) seemed to correlate with higher responses (Figure 45).

3) The E-R safety analysis did not identify any safety concerns with the proposed dosage regimen. There are E-R safety trends for ≥ grade 2 overall AE, ≥ grade 3 overall AE, ≥ Grade 3 neutropenia, any grade CRS, and Grade ≥2 CRS. There were limited data for other AEs. Refer to Appendix 19.4.4.3 for detailed E-R safety analyses.

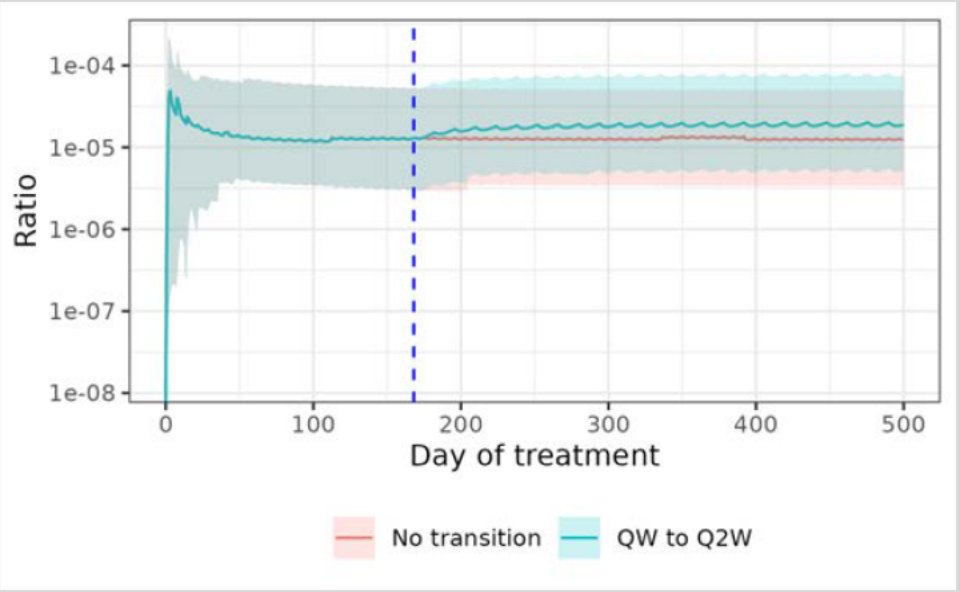
- *Change in Dosing Intervals*

The FDA agreed with Applicant's proposal on switching dosing frequency from 76 mg QW to Q2W dosing at week 25 in responders who have received at least 24 weeks of treatment with elranatamab and have achieved a response [partial response (PR) or better] and maintained this response for at least 2 months. Responses occurred early in pivotal study 1003 Cohort A. Median time to response was 1.22 months (range from 0.89 to 7.36) months). Among the 48 participants who had at least 3 months follow-up after switching to Q2W dosing, 94% of patients maintained or improved their responses. Among the 27 patients who had at least 6 months follow-up after switching to Q2W dosing, 85% of patients maintained or improved their responses. A similar trend was reported in Cohort B, in patients who received prior BCMA directed therapy. Among the 14 participants who had at least 3 months follow-up after switching to Q2W dosing, 100% of patients maintained or improved their responses. Among the 5 patients who had at least 6 months follow-up after switching to Q2W dosing, 80% patients showed maintenance or improvement of the response (Source: table 14.2.5.6.3 Applicant's response to IR on 3/10/2023).

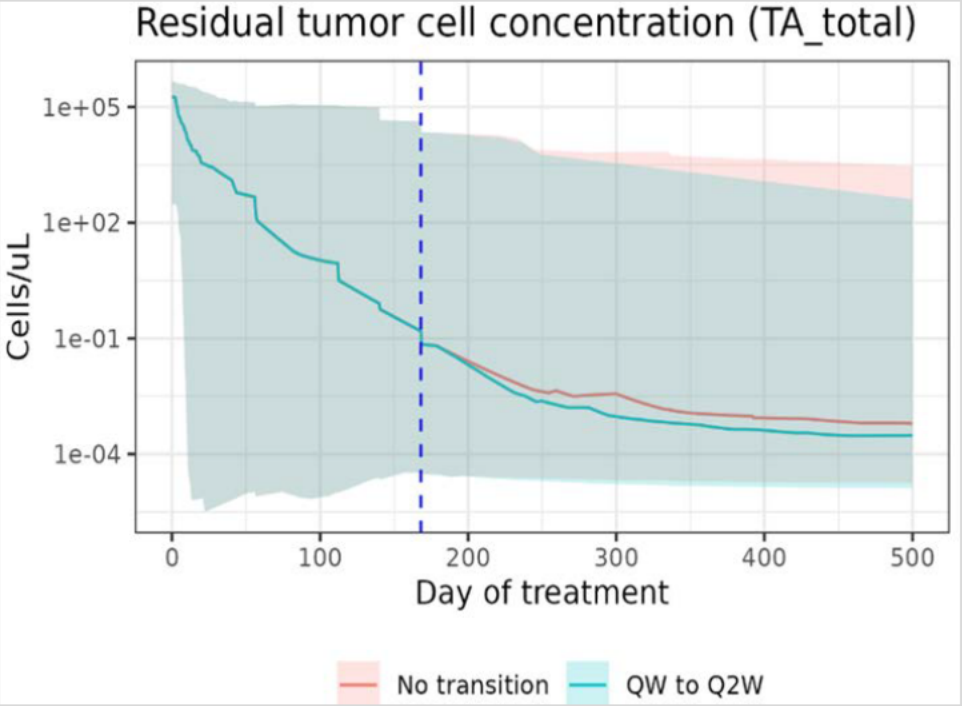
Due to the limited clinical data in patients with longer follow-up after the dosing switch in responders, the Applicant also conducted a mechanistic QSP simulation. The FDA agreed with Applicant that the mechanistic QSP simulations indicated that change of dosing interval from QW to Q2W in responders is not likely to result in decrease in efficacy. The CD3-elranatamab-membrane BCMA trimer to tumor ratio profiles, which serve as the driving force of target cell killing, and the resultant residual target cell concentration profiles was predicted to be comparable in virtual responders who switched from 76 mg QW to 76 mg Q2W dosing and who maintained 76 mg QW dosing (Figure 6). See section 19.4.5 for additional detail on the QSP simulation.

Figure 6: FDA – QSP Model Predicted in Responders who had no Transition and Those who Transitioned from QW-to-Q2W regimens

(A) Trimer Concentration Normalized by Tumor Cell Concentration Profiles



(B) Residual Target Cell Concentration Profiles



Source: Figures 3 of the Applicant's QSP IR Response dated 5/2/2023

6.2.2.2 Therapeutic Individualization

Data:

Impact of individual baseline characteristics of study participants on elranatamab exposure, efficacy and safety were assessed in the PopPK and ER-efficacy and safety analyses (Section 19.4).

The covariate analysis indicated that sex on clearance, age on rate of absorption, and body weight on central volume of distribution were statistically significant covariates, however, none of these resulted in clinically relevant differences in exposure. Body weight was not a statistically significant covariate in exposure-efficacy or safety analyses. Given the lack of clinically relevant impact of body weight on exposure, efficacy, or safety, fixed-dosing approach of elranatamab is supported. All other assessed covariates including race, baseline albumin, AST, bilirubin, and eGFR were not considered statistically significant covariates in the final model.

ER-efficacy analyses showed that baseline sBCMA level, presence of EMD at baseline, and >5 prior lines of therapy were inversely associated with ORR. No clinically relevant covariates were identified in ER-safety analyses for the evaluated safety events (Grade ≥3 neutropenia, Grade ≥3 infections, and Grade ≥2 peripheral neuropathy).

The Applicant's Position:

PopPK, ER-efficacy and safety analyses, and QSP simulations support the recommended 2 step-up priming dose regimen, the 76 mg QW full treatment dose, and the switch of dosing interval from QW to Q2W after 24 weeks for responding participants. No dose adjustment is needed based on intrinsic factors including body weight, age, sex, race, mild hepatic impairment, and mild or moderate renal impairment.

The FDA's Assessment:

The FDA agrees with the Applicant's position. The Applicant's population PK analysis of elranatamab is acceptable for the purpose of supporting the analysis objectives. Covariate analysis showed that age (36 to 89 years), sex, and body weight (37 to 160 kg) had statistically significant effects on elranatamab exposure, but the impact of these covariates on exposure was not considered clinically relevant.

Race [193 (71%) White, 49 (18%) Asian, or 29 (11%) Black], mild or moderate renal impairment (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 1 to ≤1.5 x ULN or any AST greater than ULN), extramedullary disease [yes 113 (35%), no 173 (54%)] did not have a statistically significant effect on elranatamab exposure.

The effects of severe renal impairment (eGFR 15 to 29 mL/min), end-stage renal disease (eGFR <15 ml/min), moderate to severe hepatic impairment (total bilirubin >1.5 times ULN and any AST) or ethnicity (e.g., Hispanic or Latino) on the PK of elranatamab are unknown.

The FDA agrees with the Applicant's position that modeling and simulation appeared to support the proposed 2 step-up dose regimen, the 76 mg QW full treatment dose. E-R efficacy suggest a potential trend of higher elranatamab exposure with higher ORR, the response however plateaued at 76 mg QW full treatment dose. Exposure-response (E-R) safety analysis did not identify any safety concerns with exposure following the proposed dosage of 12/32/76mg.

6.2.2.3 Outstanding Issues

Data: Not applicable
The Applicant's Position: There are no outstanding issues.

The FDA's Assessment:
Not applicable.

6.3 Comprehensive Clinical Pharmacology Review

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

Data:
Elranatamab clinical pharmacology findings including PK, PD, exposure-response for efficacy and safety, and immunogenicity analyses support the recommended dosing regimen and the following conclusions:

Pharmacokinetic Characteristics:

a. Elranatamab free and total PK were characterized by a semi-mechanistic target binding model that accounts for elranatamab binding to sBCMA in addition to a linear clearance and first order absorption. Based on population PK analysis, the population median clearance for free elranatamab ($CL_{elranatamab}$) and volume of distribution ($V_{c,elranatamab}$) were 0.324 L/day and 4.78 L, respectively. Model-predicted absolute bioavailability from SC route is ~56.2%. Median T_{max} after the first dose across dose levels for the SC route ranged from 3 to 7 days.

b. On average, total and free elranatamab exposure increased with dose in approximately dose-proportional manner over the dose range evaluated via SC route.

c. The calculated median accumulation ratio on week 24 of 76 mg QW dosing for total elranatamab AUC_{tau} and C_{max} was 8.0 and 4.8, respectively.

d. Patients who discontinue elranatamab after 24 weeks of 76 mg QW dosing are expected to have a 50% reduction from C_{max} of elranatamab at a median (5^{th} to 95^{th} percentile) time of 25 (9.6 to 70) days after T_{max} and a 97% reduction from C_{max} at a median time of 130 (43 to 275) days after T_{max}.

Effect of Intrinsic Factors:

a. Elranatamab dose adjustment for intrinsic factors (eg, body weight, age, gender, race, renal or hepatic function) is not required. Body weight (range: 37 – 160 kg) was not a statistically significant covariate on $CL_{elranatamab}$ and was retained as a statistically significant covariate on $V_{c,elranatamab}$. No clinically relevant differences in elranatamab exposure are expected

between patients with extreme body weights. Body weight was not a statistically significant covariate in exposure efficacy or safety analyses. Due to the lack of clinically relevant effect of body weight on the PK of elranatamab, a fixed dosing approach is supported.

b. No clinically meaningful differences in elranatamab exposure in participants with mild hepatic impairment, or mild to moderate renal impairment compared to participants with normal organ function. Limited data are available from participants with moderate and severe hepatic impairment and from participants with severe renal impairment.

Effect of Extrinsic Factors:

a. The risk of DDIs with elranatamab is low. Elranatamab administration transiently increased cytokine levels (eg, IL-6) which may result in temporary inhibition of CYP enzymes. Cytokine continued to decrease over the course of the first cycle. The highest risk of interaction is expected to be during the step-up dosing schedule. The median levels for peak cytokines appeared to be higher in participants experiencing CRS for some cytokines.

Immunogenicity

a. In participants assigned to receive 1000 µg/kg/76 mg monotherapy full dose SC, the incidence of ADA was 8.31% (20/240). The median titer was low (≤300) across all time points and there were no trends in ADA titer over time. ADA (overall and baseline status) was not identified to be a statistically significant covariate on elranatamab exposure, efficacy, or safety.

Exposure-Response Relationship

a. Exposure-efficacy relationship: Higher elranatamab exposure (both free and total) was associated with higher probability of ORR. For the analysis using total elranatamab exposure, baseline sBCMA had a significant, inverse association with ORR. Free elranatamab exposure was lower in patients with high baseline sBCMA. Baseline EMD and number of prior lines >5 were inversely associated with ORR. The 76 mg QW regimen achieves the highest free elranatamab exposure at a given baseline sBCMA level in the dose range evaluated, and results in higher probability of achieving an objective response vs lower doses, with no expected impact on safety.

b. Exposure-safety relationship for AEs of CRS: A significant association between early elranatamab exposure ($C_{max, 24}$ after first dose [both free and total]) with any Grade CRS and Grade ≥2 CRS was observed. For the analysis using total elranatamab exposure, baseline sBCMA was inversely associated with any Grade CRS but was not a predictor for Grade ≥2 CRS.

c. Exposure-safety relationship for Grade ≥3 neutropenia, Grade ≥3 infections, and Grade ≥2 peripheral neuropathy: No statistically significant or clinically meaningful relationship was observed between elranatamab exposure and these AEs.

d. PK-QTc interval prolongation: Total and free elranatamab concentration had no effect on the QT interval corrected for heart rate.

Quantitative Systems Pharmacology

a. A simulation-based approach for evaluation of virtual patient efficacy supported the recommended dosing regimen (76 mg QW) which is projected to provide meaningful clinical benefit in the majority of RRMM patients, including those with relatively high sBCMA levels.

b. Virtual patient simulations indicated maintenance of response upon transitioning the dosing regimen for responding participants from QW to Q2W after Week 24 compared to 76 mg QW continuously.

The Applicant's Position:

The totality of clinical pharmacology findings support the recommended 2 step-up priming dose regimen, the 76 mg QW full treatment dose, and the switch of dosing interval from QW to Q2W after at least 24 weeks for patients who have achieved a response.

The FDA's Assessment:

General pharmacology and PK characteristic of elranatamab based on FDA assessment are summarized in Table 11. PK characteristics are reported based on elranatamab free drug concentration and the recommended SC dosing regimen with PPK model unless otherwise noted in Table 11.

Table 11: FDA – Elranatamab General Pharmacology and Pharmacokinetic Characteristics

General Information	
PK Bioanalytical assay	To detect elranatamab, an electrochemiluminescent (ECL) assay was implemented. An acid dissociation step was used to dissociate drug-target complexes, followed by neutralization with a solution consisting of biotin-labeled anti-CD3, RN327 (anti-BCMA homodimer used as a target blocker), and goat anti-hBCMA IgG polyclonal antibody (used as a target blocker). Elranatamab is captured on a streptavidin plate via the biotin-labeled anti-CD3 moiety, and detected with ruthenium-labeled mouse anti-BCMA. The ECL signal is detected using the MSD SECTOR Imager 6000 or SECTOR S 600. See section 19.4.6 for detail summary on validated range, accuracy, precision, and stability of the PK assay.
Pharmacokinetic (PK) Characteristics	
Steady-state exposure at the proposed dosing regimen	Maximum elranatamab exposure is expected on week 24. The calculated median accumulation ratio was 11.2 on week 24 of 76 mg QW dosing for free elranatamab AUC_{tau}.
Dose proportionality	Elranatamab exhibits dose proportional pharmacokinetics overdose range from 6 to 76 mg (0.079 to 1 times the approved recommended dosage).

Absorption	The mean bioavailability of elranatamab was 56.2% when administered subcutaneously. The median (min, max) Tmax after elranatamab SC administration was 7 (3 to 7) days. According to Study C1071003 Protocol, injections to the abdomen are preferred. In agreement with the protocol instructions, 183 participants received all their doses in the abdominal region. There were 4 participants received dosing in thigh with at least 1 dose (range: 1 to 15), and no injections were reported in the upper extremities. The conclusion of PK comparability cannot be made due to limitation of sample size.
Distribution	The steady state volume of distribution of elranatamab was 7.76 L (33%)
Elimination	The half-life of elranatamab was 22 (64%) days at the 76 mg dosage, with apparent clearance of 0.324 L/day (100%) following 24 weeks dosing.
Specific Population	
Intrinsic Factor	There were no clinically significant differences in the PK of elranatamab based on age (36 to 89 years), sex, race (White, Asian, or Black), body weight (37 to 160 kg), mild or moderate renal impairment (eGFR by MDRD method: 30 to 89 mL/min), or mild hepatic impairment (total bilirubin 1 to ≤1.5 x ULN or any AST greater than ULN). Although bodyweight was identified as a statistically significant covariate on central volume of distribution (Vc), its impact on elranatamab exposure was not considered clinically relevant. Simulation showed the exposure between patients with extreme values of body weight (10^{th} and 90^{th} percentile) did not differ when compared to exposure for patient with median body weight (Figure 34). Therefore, the result supported the Applicant's proposed fixed dosing of elranatamab.
Immunogenicity	
	In Study 1003, of the 168 participant who received the recommended step-up and full dosage of elranatamab-bcmm for up to 24 months and were evaluable for presence of ADA against elranatamab, 8.9% (15/168) of patients tested positive for anti-elranatamab antibodies. Among the 15 patients who tested positive for ADAs, 60% (9/15) tested positive for neutralizing antibodies against elranatamab-bcmm. The effect of these antibodies on the PK, PD, safety, and/or effectiveness of

	elranatamab products is unknown.
Pharmacodynamic (PD) Characteristics	
Pharmacodynamics	Transient elevations of circulating cytokines IL-2, IL-6, IL-8, IL-10, TNF-α, and IFN-γ was observed at dosage levels of 215 µg/kg (0.215 times the approved recommended dosage) and above. After administration of the approved recommended dosage of ELREXFIO, the highest elevation of cytokines was generally observed within 72 hours after first elranatamab-bcmm dose at 12 mg on week 1 Day 1, and generally returned to baseline prior to the administration of the first full dose 76 mg on Day 8. Declines in free sBCMA concentrations were observed in responders on cycle 2 day 1. In contrast, free sBCMA in non-responders remained largely unchanged or increased in some patients. For additional information on soluble BCMA. Refer to Section 19.4.2 Pharmacodynamics summary for detail.
Exposure-Response for Efficacy	Higher free elranatamab exposure (i.e., $C_{avg,28days}$) was associated with higher ORR in study 1003 patients with RRMM. The efficacy reached a plateau at the higher exposures of 76 mg QW. The E-R efficacy analysis supported the 76mg QW regimen in the proposed patient population.
Exposure-Response for Safety	Higher free elranatamab exposure (i.e., AUCss) are associated with higher incidences of ≥ grade 2 overall AE, ≥ grade 3 overall AE and ≥ Grade 3 neutropenia. There are limited data for other AEs to allow for a full analysis. E-R safety analysis did not identify any major safety concern in the proposed regimens. The E-R safety analysis supports the proposed 76 mg QW regimen.
Quantitative Systems Pharmacology (QSP)	The QSP analysis described the pharmacokinetic profiles of elranatamab and dynamics of biomarkers (i.e., integrated paraproteins, sBCMA) and the biochemical response rate (BRR) after elranatamab treatment. It provided supportive evidence for the recommended dosing regimen of 76 mg QW SC with a step-up regimen and a QW to Q2W dosing interval change after 6 Cycles with weekly dosing for participants with responses of partial response (PR) for at least 2 Cycles. Refer to section **Error! Reference source not found.** for additional information.

Formulation Effect	In the PPK model, the drug product formulation (10 mg/mL versus 40 mg/mL) was evaluated as a covariate and no other significant relationships were identified with elranatamab absorption rate constant, CL, or V.

Additional Pharmacokinetics Summary

The population PK analysis of elranatamab was performed using pooled data from 321 participants who received elranatamab monotherapy in Studies 1001, 1002, 1003, and 1009. Based on the PK simulation, PK parameters of elranatamab are summarized in Table 24. PK profiles of elranatamab following other dosing schedules are presented in section **Error! Reference source not found.**. The popPK stimulated elranatamab PK is presented in Figure 32.

Table 12 presents the PopPK model predictions of PK of the free elranatamab in responders and nonresponders. The difference between responders and nonresponders can be seen as early as the first full dose. The median predicted C_{trough} concentration in responder is 5.5 µg/mL whereas in non-responders, it is 2.1 µg/mL. The concentration of 76 mg QW at end of Cycle 6 (week 24) by response status indicates a 5-6-fold higher exposure in responders when compared to nonresponders. The higher free elranatamab concentrations stimulated in responders, especially during later cycle, may attribute to reduced tumor burdens, which in turn translate to less receptor saturation and higher free elranatamab concentration when compared to those of the nonresponders.

Given the significant concentration difference between responders and nonresponders at later cycles of the QW treatment, and that Q2W dosing schedule only apply to responders, the following elranatamab exposure parameters (i.e., C_{ave}, C_{max} and C_{trough}) were included in ELREXFIO USPI. The elranatamab exposure parameters from all patients (including nonresponders and responder) were reported following first full dose. The elranatamab exposure parameters from responders were reported at end of weekly dose (week 24) and steady state following biweekly dosing.

Table 12: FDA – Free Elranatamab PK Parameters by Response Status

Timepoint	Group	Parameter		
		C_{avg} (µg/mL)	C_{max} (µg/mL)	C_{trough} (µg/mL)
First Full 76mg Dose	Responders (151)	4.7 (73%)	5.8 (71%)	5.5 (67%)
	Non-responders (173)	2.1 (82%)	2.6 (82%)	2.1 (89%)
	All (324)	3.1 (94%)	3.8 (94%)	3.3 (102%)
76mg QW on Cycle 2 Day 1 (Week 5)	Responders (151)	14.4 (51%)	15.3 (51 %)	14.2 (50 %)
	Non-responders (173)	4.9 (89%)	5.5 (85%)	4.3 (101%)
	All (324)	8.1 (101%)	8.8 (97%)	7.5 (115%)
76mg QW on Cycle 3 Day 1 (Week 9)	Responders (151)	22.2 (46%)	23.0 (46%)	21.5 (47%)
	Non-responders (173)	6.4 (103%)	7.0 (97%)	5.5 (118%)
	All (324)	11.4 (116%)	12.2 (110%)	10.4 (133%)
76mg QW on Cycle 4 Day 1 (Week 13)	Responders (151)	26.9 (46%)	27.8 (46%)	25.8 (48%)
	Non-responders (173)	7.0 (113%)	7.7 (106%)	6.0 (128%)
	All (324)	13.0 (129%)	14.0 (121%)	11.9 (146%)
76mg QW on Cycle 5 Day 1 (Week 17)	Responders (151)	29.9 (47%)	30.7 (47%)	28.5 (49%)
	Non-responders (173)	7.3 (119%)	8.0 (112%)	6.3 (135%)
	All (324)	14.1 (137%)	15.0 (128%)	12.7 (155%)
76mg QW on Cycle 6 Day 1 (Week 21)	Responders (151)	31.7 (48%)	32.6 (48%)	30.3 (50%)
	Non-responders (173)	7.5 (123%)	8.2 (115%)	6.4 (140%)
	All (324)	14.7 (142%)	15.7 (134%)	13.2 (162%)
76 mg QW End of Cycle 6 (week 24)	Responders (N = 151)	32.7 (49%)	33.6 (48%)	31.2 (50%)
	Non-responders (N = 173)	7.6 (125%)	8.3 (117%)	6.5 (142%)
	All (N = 324)	15.0 (145%)	15.9 (136%)	13.5(165%)
Steady state (every two weeks dosing)	Responders (N = 151)	18.4 (57%)	20.1(55%)	15.9 (64%)

Source: Applicant's simulation submitted on 7/3/2023 and dataset code submitted on 7/06/2023

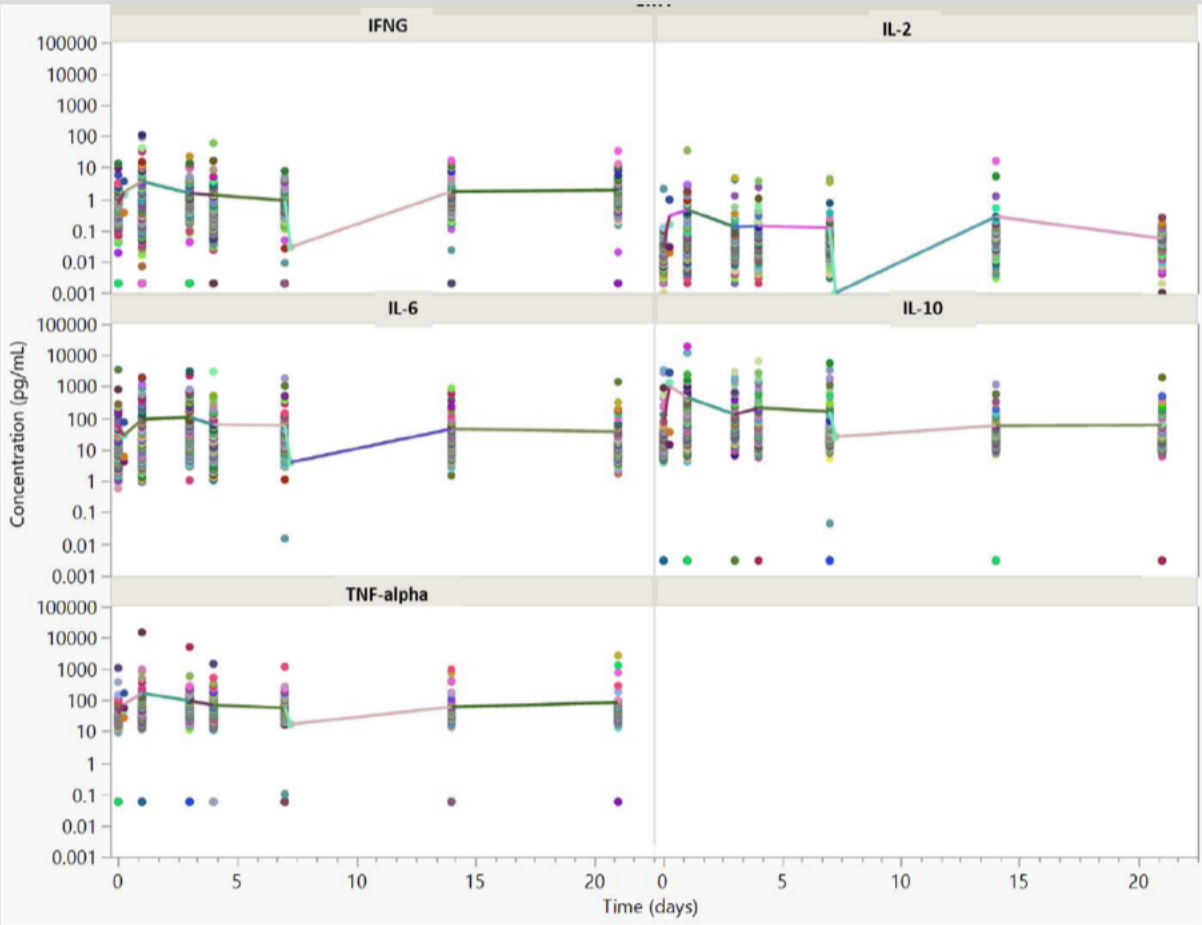
Cytokine levels

In Study 1003, blood samples for cytokine analysis were collected as predose and 24 hr. post-dose on C1D1 and C1D4, and predose only on C1D8, C1D15, C1D22. Cytokine levels were transiently elevated and mostly peaked around 72 hours after the first priming dose (12 mg) on week 1 day 1 and returning to baseline around the next full dose administration on week 2 day 1. Cytokine release profiles including interferon gamma (IFNG), interleukin 2(IL-2), interleukin 5(IL-5), interleukin 10(IL-10), and tumor necrosis factor alpha (TNF-alpha) in peripheral blood over time in study 1003 are displayed in

Figure 7. Similar time course of cytokine concentration was also observed for these cytokines. The concentration summary of IL-6 for the total samples, samples without tocilizumab and sample with tocilizumab was also included in

Table 13. Cytokine release profiles of elranatamab in patient without tocilizumab use and following other dosing schedules are present in section 19.4.2.

Figure 7: FDA - Observed Cytokine Levels Over Time Following RP2D (12/32/76 mg) (Study C1071003)



Each point represents a patient. Lines represent arithmetic mean value. Lines represent arithmetic mean value. IFNG represents interferon gamma (IFN-γ); IL-2 represents interleukin 2; IL-6 represents interleukin 6; IL-10 represents interleukin 10; TNF represents tumor necrosis factor-alpha (TNFα).
Source: FDA Reviewer's analysis created from poppk1 dataset

Table 13: FDA – Summary of IL-6 by Cycle Day (Study C1071003)

Cycle	Dose (mg)	Timepoint	N	Mean (SD)	Median	(25^{th}, 75^{th} percentile)	(2.5^{th}, 97.5^{th} percentile)	Range
C1D1	12	Pre-dose	162	45.1 (285)	7.32	(3.85, 15.5)	(1.1, 231)	0.58 – 3519
		Pre-dose: Without toci	162	45.14 (285)	7.32	(3.85, 15.5)	(1.1, 232)	0.58 – 3519
		Pre-dose: With toci	0	NA	NA	NA	NA	NA
		6 hr. post-dose	4	28.3 (32.5)	17.4	(5.6, 40.1)	(4.32, 70.7)	4.18 – 74.1

Cycle	Dose (mg)	Timepoint	N	Mean (SD)	Median	(25^{th}, 75^{th} percentile)	(2.5^{th}, 97.5^{th} percentile)	Range
		6 hr. post-dose: Without toci	4	28.3 (32.5)	17.4	(5.6, 40.1)	(4.32, 70.7)	4.18 – 74.1
		6 hr. post-dose: With toci	0	NA	NA	NA	NA	NA
C1D2		20-24 post-dose	150	124.7 (342)	14.7	(5.4, 59.2)	(1.31, 1292)	0.95 -2003
		20-24 Without toci	142	93.2 (277)	13.3	(5.19, 49.9)	(1.3, 885)	0.95 -1986
		20-24 post-dose: With toci	8	684 (750)	244	(156, 1230)	(66.3, 1911)	49.6 - 2003
C1D4	32	Pre-dose	156	191 (487)	25.3	(10.8, 76.9)	(3.21, 1906)	1.07 - 3128
		Pre-dose: Without toci	139	107 (348)	20.68	(9.62, 48.4)	(3.15, 697)	1.07 - 3099
		Pre-dose: With toci	17	875 (836)	748	(183, 1016)	(26.7, 2700)	23.6 - 3128
C1D5		20-24 post-dose	131	181 (617)	12.51	(5.83, 52.4)	(1.53, 3020)	1.03 - 3533
		20-24 post-dose Without toci	114	63.1 (291)	10.7	(5.35 -34.0)	(1.49, 295)	1.03 - 3043
		20-24 post-dose: With toci	17	969 (1320)	236	(76.8, 1374)	(10.0, 3382)	7.26 - 3533
C1D8	76	Pre-dose	146	134 (448)	20.3	(10.0, 67.4)	(3.06, 1120)	0.02 -3894
		Pre-dose: Without toci	122	59.0 (200)	15.9	(8.44, 31.8)	(2.94, 375)	0.02 -1857
		Pre-dose: With toci	24	514 (935)	125	(86.1, 372)	(33.1 3314)	28.9 - 3890
		6 hr. post-dose	4	69.0 (59.5)	68.1	(28.8, 108)	(6.48, 133)	3.99 - 136
		6 hr. post-dose: Without toci	1	3.99 (NA)	3.99	(3.99, 3.99)	(3.99, 3.99)	3.99 – 3.99
		6 hr. post-dose: With toci	3	90.6 (49.9)	99.0	(68.1, 117)	(40.2, 134)	37.1 - 136
C1D15	76	Pre-dose	145	126 (448)	17.5	(9.74, 72.0)	(3.12, 866.97)	1.13 - 3710
		Pre-dose: Without toci	118	45.7(118)	14.7	(8.21, 27.9)	(3.21, 381)	1.52 - 897
		Pre-dose: With toci	27	475(945)	135	(92.6, 255)	(16.4, 3544)	1.13 - 3709
C1D22	76	Pre-dose	136	126 (440)	13.5	(7.09, 52.19)	(2.89, 1110)	1.06 - 3371
		Pre-dose: Without toci	109	37.6(143)	10.2	(6.2, 22.0)	(3.02, 182)	1.73 - 1443
		Pre-dose: With toci	27	484(869)	148	(80.9, 399)	(8.70 – 2957)	1.06 - 3371

Source: Applicant's response to IR on 6/09/2023, Table 1.

Soluble BCMA

The FDA analysis concurs with the Applicant's assessment of sBCMA levels regarding the response to elranatamab. The FDA analysis of study 1003 further showed that free sBCMA levels cycle 2 day 1 (C2D1) was significantly ($p<0.001$) associated with the level of response to elranatamab. The non-responder group had higher free sBCMA levels at baseline and C2D1 than the responder group (Table 14). Notably, the median free sBCMA levels at C2D1 did not significantly change from baseline in the non-responder group. However, the median free sBCMA levels at C2D1 significantly ($p<0.001$) changed from baseline in the responder group (Table 14). See additional discussion in section 19.4.2.

Table 14: FDA – Statistical Summary of Baseline and Cycle 2 Day 1 sBCMA by Response Status (Study C1071003, Cohorts A and B)

Baseline sBCMA (ng/mL)				
Study Cohorts	**Response Status (N)**	**Mean (SD)**	**Median (Ranges)**	**95% CI**
Cohort A	No-Responder (45)	176.0(142)	131 (6.92 -511)	133.4 - 218.5
	Responders (70)	45.0(63)	19.3 (2.27 - 389)	30.1 - 59.9
Cohort B	No-Responder (33)	128.1(127)	115 (0.274 - 606)	83.0 - 173.1
	Responders (26)	39 (51)	19.3 (1.95 -230)	18.5 - 59.7
Cycle 2 Day 1 sBCMA(ng/mL)				
Cohort A	No-Responder (31)	181.4(158.9)	147 (0 - 602)	123.1 - 239.7
	Responders (64)	6.2(17.7)	0.129 (0 - 101)	1.7 - 10.6
Cohort B	No-Responder (16)	100.0(100.8)	42.6 (0- 265)	46.3 - 153.7
	Responders (22)	7.4(11.2)	0.151 (0-31.3)	2.4 - 12.4

Source: Reviewer's analysis created from the Applicant's response to IR 4/27/2023, dataset titled 'C107_COMBINED_EFFICACY_IR_21MAR2023.csv'

Immunogenicity

- In the Study C1071003, of the 168 participants who received the recommended step-up and full dosage of elranatamab for up to 24 months and are evaluable for presence of ADA against elranatamab-bcmm, 8.9% (15/168) of patients tested positive for anti-elranatamab-bcmm-antibodies. Among the 15 patients who tested positive for ADAs, 60% (9/15) tested positive for neutralizing antibodies against elranatamab.
- The majority of ADA were treatment-induced, eleven out of fifteen patients were negative at baseline and development of ADA occurred while on study. The time for treatment induced ADA onset ranges from day 28 to day 88 (
- Because the low occurrence (8.9%) of anti-drug antibodies, effect of these antibodies on pharmacokinetic, safety, and effectiveness of elranatamab cannot be evaluated.

- Table 15).

- Four patients (3.5%) were positive at baseline and had at least one subsequent positive ADA sample.
- Because the low occurrence (8.9%) of anti-drug antibodies, effect of these antibodies on pharmacokinetic, safety, and effectiveness of elranatamab cannot be evaluated.

Table 15: FDA – Summary of Anti-Drug Antibody Incidence (Study C1071003)

	Cohort A (BCMA naïve)	Cohort B (BMCA exposed)
Overall Incidence	12/113 (10.6)	3/55 (5.5)
Treatment induced	8/113 (7.1%)	3/55 (5.5%)
Treatment-boosted	4/113 (3.5%)	0
Median onset (range) (days)	58.0 (28, 84)	29.0 (28, 88)

Source: CRS study C1071003

6.3.2 Clinical Pharmacology Questions

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

Data:

The exposure-response for efficacy analyses were based on participants with available PK and ORR data who received elranatamab as monotherapy in Studies C1071001 monotherapy cohorts (IV cohorts ranging 0.1 to 50 μg/kg and SC cohorts ranging 80 to 1000 μg/kg), C1071002, C1071003, and C1071009 Part 1 (total of 297 participants). A significant association between elranatamab exposure (both free and total) was observed with ORR. For the analysis using total elranatamab exposure, baseline sBCMA was inversely associated with ORR. Free elranatamab exposure was lower in patients with high baseline sBCMA.

The Applicant's Position:

Exposure-response analysis support the full treatment dose of 76 mg QW regimen aiming to saturate sBCMA and maximize elranatamab free drug exposure to increase the probability of ORR with no expected impact on safety given the relatively flat exposure-safety relationship.

The FDA's Assessment:

The FDA agrees with the Applicant's position that clinical pharmacology analysis support evidence of efficacy following the proposed dosage regimen. The Applicant explored dose levels ranging from 0.1 to 1000 μg/kg including fix dose and step-up dose. Highest efficacy was reported at 1000 μg/kg or the equivalent of fixed dose of 76 mg. Model and simulation suggested a potential trend of higher elranatamab exposure associated with higher ORR, which plateaued at the 76 mg dosage. There were E-R safety trends observed for ≥ grade 2 overall AE≥ grade 3 overall AE as well ≥ Grade 3 neutropenia. The data was limited for other AEs. E-R safety analysis did not identify any major safety concern in the proposed regimens. The results of the

exposure-efficacy and safety analyses appeared to support the recommended full treatment dosing regimen of 76 mg QW.

Significant CRS including Grade ≥ 2 CRS in patients with RRMM was observed with dosages of 50 ug/kg and above. The Applicant performed dose optimization of the step-up dosing and first evaluated a single step-up dosing of 44 mg, which could not resolve the CRS risk. Grade 2 CRS was 47% in patients with RRMM following the 44/76 mg single step-up regimens. The inclusion of an initial lower dose of 12 mg before the intermediate dose of 32 mg in study 1003 reduced the risk of CRS. Grade 2 CRS was 13.7% in patients with RRMM following 12/32/76 mg two step-up regimen. The Applicant also explored the addition of a lower initial dose of 4 mg followed by an intermediate dose of 20 mg. Although lower initial dose of 4 mg also resulted in comparable grade 2 CRS incidence rate of 13.7% as the 12/32 mg priming regimen, CRS events were equally distributed across first, second, third or later doses with 13% of grade 1 CRS rate for third dose and later (Table 10). The RP2D priming regimen of 12/32 mg resulted in a more favorable CRS profile with any CRS occurring primarily after first (44%) and second step-up dose (19%) and only 1.6% of CRS events for the fourth dose (second full treatment dose of 76 mg QW) and later (Table 10). Overall, based on a lower incidence of any Grade and Grade ≥2 CRS, as well as the favorable CRS profile, the Applicant's proposed 12/32 mg step-up dosing regimen appears to be reasonable.

Refer to section 6.2.2.1 for details regarding justification for the step-up doses and full doses and refer to section 19.4.4.1 for details regarding the exposure-response relationship for efficacy and safety.

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

Data:

Results of PopPK, ER analyses for efficacy (ORR and DoR), and safety (AEs of CRS, Grade ≥3 neutropenia, Grade ≥3 infections, and Grade ≥2 peripheral neuropathy, and QT prolongation) using pooled data from Studies C1071001, C1071002, C1071003, and C1071009 in participants with RRMM were summarized in Section 6.3.1.

The Applicant's Position:

The totality of clinical pharmacology findings supports the recommended 2 step-up priming dose regimen, the 76 mg QW full treatment dose, and the switch of dosing interval from QW to Q2W after at least 24 weeks for patients who have achieved a response.

The 2 step-up priming dose regimen of 12 mg/32 mg with premedications was supported by a) exposure-CRS analyses indicating that a lower initial dose is expected to be associated with lower rate and severity of CRS, b) the predictable profile observed with this regimen compared to regimens with lower initial priming doses, c) sufficient stimulation of cytokines with the first dose of 12 mg.

The 76 mg QW full treatment dose regimen is supported by the results of the exposure-response analyses indicating that higher elranatamab is associated with higher probability of ORR and is expected to provide clinical benefit in RRMM including those with high baseline sBCMA, with no expected impact on safety given the relatively flat exposure-safety relationship.

The switch to Q2W dosing after 24 weeks for responding patients is supported by a) maintained and/or deepening clinical benefit with this regimen in Study C1071003, b) pharmacodynamics data showing rapid and deep declines in free sBCMA concentrations suggesting reduced disease burden and/or saturation of sBCMA, c) lack of association between elranatamab exposure and Q2W switch on DOR, and d) mechanistic QSP simulations indicating maintenance of responses with the proposed switch to Q2W.

The FDA's Assessment:
FDA agrees with Applicant's position that the proposed dose and schedule of 12/32/76 mg of elranatamab is appropriate for the general patient population for which the indication is being sought. See detailed discussion in section 6.2.2.1.

6.3.2.3 Dosage Recommendations for Restarting Therapy after Dose Delay

The FDA's Assessment:
Although CRS associated with elranatamab treatment occurs primarily within the first three doses of treatment, risk of CRS re-emerged when a patient is off treatment for a prolong period. This is due to re-sensitization of the immune system and potential rebound of the target cells. The proposed re-priming recommendations were not part of the clinical study protocol. In Study 1003, there were only three episodes of repriming with the 32 mg regimen; 2 episodes occurred after the fourth dose during QW dosing of 76 mg, and one episode occurred after fourth dose during Q2W dosing of 76 mg. All three repriming episodes occurred after a dose delay > 56 days. No CRS was reported in any of these episodes of repriming.

FDA disagrees with the Applicant's proposal (b) (4)

Based on the available clinical data and PK simulation data, FDA revised the recommendation to allow prescribers to proceed with the next planned dose if dose delay of any full treatment dose is ≤ 42 days.

Table 16 presents the updated recommendations for restarting therapy after dose delay after incorporating FDA recommendations.

Table 16: FDA – Recommendations for Restarting Therapy After Dose Delay

Last Dose Administered	Time Since the Last Dose Administered	Action for Next Dose
Step-up dose 1 (12 mg)	2 weeks or less (≤14 days)	Restart ELREXFIO at step-up dose 2 (32 mg). [a] If tolerated, increase to 76 mg 4 days later.
	Greater than 2 weeks (>14 days)	Restart ELREXFIO step-up dosing schedule at step-up dose 1 (12 mg). [a]
Step-up dose 2 (32 mg)	2 weeks or less (≤14 days)	Restart ELREXFIO at 76 mg.
	Greater than 2 weeks to less than or equal to 4 weeks (15 days to ≤28 days)	Restart ELREXFIO at step-up dose 2 (32 mg).[a] If tolerated, increase to 76 mg 1 week later.
	Greater than 4 weeks (>28 days)	Restart ELREXFIO step-up dosing schedule at step-up dose 1 (12 mg).[a]
Any treatment dose (76 mg)	6 weeks or less (≤42 days)	Restart ELREXFIO at 76 mg.
	Greater than 6 weeks to less or equal to 12 weeks (43 days to ≤84 days)[b]	Restart ELREXFIO at step-up dose 2 (32 mg).[a] If tolerated, increase to 76 mg 1 week later.
	Greater than 12 weeks (>84 days)[b]	Restart ELREXFIO step-up dosing schedule at step-up dose 1 (12 mg).[a]

a. Administer pre-treatment medications
b. Consider benefit-risk of restarting ELREXFIO in patients who require a dose delay of more than 42 days due to an adverse reaction.
Source: Table 2, elranatamab USPI.

The FDA assessment on the adequacy of the proposed recommendations for restarting therapy after dose delay, as detailed below, include evaluations of observed CRS data after dose delay and PK simulations following different dosing delay scenarios indicated that the recommendations of step-up dose 1 and 2 in Table 16 are supported by the observed dose delay data (Table 17). Evaluation of CRS events following dose delay in study 1003 indicated that no increase in the risk of CRS following dose delays that were less than the proposed cut-offs for re-priming when compared to overall RP2D expansion cohorts (i.e., Cohort A and Cohort B). However, there is limited clinical data to support the evaluation of a dosing interval of ≤ 8 weeks or 56 days following treatment doses of 76 mg given that 95% of dose delay episodes following treatment doses of 76 mg are ≤ 4 weeks or 28 days. Nineteen (19) patients experienced a dose delay ranging from 29 to 42 days, and none of these patients developed CRS during the next full treatment dose (source: IR response on June 09, 2023, table 16.2.5.1.4). Four patients reported dose delays of 43 days, 48 days, 48 days and 55 days respectively following the full treatment doses. CRS was not reported in these patients. Only three patients reported dose delays of 63 days, 77 days, and 83 days or 9 weeks, 11 weeks and 11.9 weeks respectively. All patients received a repriming at 32 mg and CRS was not reported in these patients.

Table 17: FDA – Summary of CRS Events Following Dose Delays (Study C1071003, Cohorts A and B)

Duration	Delayed Dose	No CRS	Grade 1 CRS	Grade 2 CRS
CRS Following Dose Delays Less than or Equal to the Proposed Re-Priming Cut-Offs	**Step-up Dose 1 Delay**	**≤14 days between step-up dose 1 and step-up dose 2**		
		41(80%)	9 (18%)	1(2%)
	Step-up Dose 2 Delay	**≤14 days between step-up dose 2 and first full dose**		
		54 (93%)	2(3.4%)	2(3.4%)
	Full Dose Delay	**≤56 days between full doses** *		
	First 76 mg QW dosing	45(98%)	1 (2.5%)	0
	Second 76 mg QW dosing	27(100%)	0	0
	Third 76mg QW dosing	36(100%)	0	0
	Forth or later 76mg QW dosing	235(100%)	1 (6.7%)	0
	Fourth or later 76 mg dose (Q2W)	111(100%)	0	0
CRS Following Dose Delays Greater than the Proposed Re-Priming Cut-Offs	**Step-up Dose 2 Delay**	**>14d ays between step-up dose 1 and step-up dose 2**		
		0	0	0
	First Full Dose Delay	**>14 days between step-up dose 2 and first full dose**		
		0	1(100%)	0
	Full Dose Delay	**>56 days between full doses** &		
	Third 76 mg dose	1 (100%)	0	0
	Fourth or later 76 mg dose (Q2W)	2 (100%)	0	0

*95% of dose delay episodes are ≤ 28 days
&All three patients with >56 days of dose delay received a re-priming dose at 32 mg
Source: IR response received on June 09, 2023, table 14.4.1.5.5.1. Table 16.2.5.1.1 to Table 16.2.5.1.4

PK simulation

The dosage recommendation for restarting the doses or repeating doses were also assessed based on PK simulation. Elranatamab exposure based on free drug concentrations after each dose delay scenario was simulated using the elranatamab PPK model and compared elranatamab exposure after the recommended dose schedule. The C_{trough} at the maximum allowed dose delay interval should be no more than 20% lower when compared to the C_{trough} of the next lower dose level (e.g., the step-up doses) to avoid the risk of CRS. There is no concern of the rebound CRS if C_{trough} at the maximum allowed dose delay interval is higher than the reference C_{trough}. Simulated elranatamab exposures under the dose restart recommendations are summarized in Table 18.

Table 18: FDA – Simulated Elranatamab C_{trough} for Dose Delay Scenarios

Last Dose Administered	Time Since the Last Dose Administered	Action for Next Dose	Simulated Ctrough (ng/mL) at End of Dose Delay	Reference Ctrough (ng/mL)
Step-up dose 1 (12 mg) on C1D1	2 weeks or less (≤14 days)	Continue at step-up dose 2 (32 mg)	186 (LLOQ, 699)	207 (64, 681)
Step-up dose 2 (32 mg) on C1D4	2 weeks or less (≤14 days)	Continue at 76 mg	786 (130, 2084)	1038 (317, 3641)
	< 2 to ≤ 4 weeks (15 days to ≤28 days)	Restart at step-up dose 2 (32 mg).	430 (LLOQ-1868)	207 (64, 681)
Frist treatment dose (76 mg) on C1D8	6 weeks or less (≤42 days)	Continue at 76 mg	861 (LLOQ-4155)	1037 (317, 3641)
	8 weeks or less (≤56 days)	Continue at 76 mg	529 (LLOQ-3295)	1037 (317, 3641)
	< 8 to ≤ 12 (56 days to ≤84 days)	Restart at step-up dose 2 (32 mg)	226 (LLOQ-2177)	207 (64, 681)
76 QW C1D15 and onward and Q2W C7D1 and onward	8 weeks or less (≤56 days)	Continue at 76 mg	1188 (LLOQ-5950) or higher	1037 (317, 3641)
	< 8 to ≤ 12 weeks (56 days to ≤84 days)	Restart at step-up dose 2 (32 mg)	388 (LLOQ-3594) or higher	207 (64, 681)

C_{trough} = trough concentration; QW = every week; Q2W = every 2 weeks; LLOQ: 50 ng/mL
Source: IR Response received 16 June 2023, Tables 2-12

The PK-based criterion was met for all but two dose delay scenarios:

- Continuation of 76 mg after a 2 weeks (14 days) dosing interval following step-up dose 2 (32 mg) on C1D4 failed to meet the PK-based criterion and the predicted C_{trough} was approximately 75% of reference value. Such dose delay scenario was supported by safety data observed in clinical trial (Table 17).
- Continuation of 76 mg after a 8 weeks (56 days) dosing interval following the first treatment dose of 76 mg also failed to meet the PK-based criterion and the predicted Ctrough was approximately 50% of reference value, while PK simulations suggested that a 6 weeks (42 days) dosing interval can meet the PK-based criterion and the predicted C_{trough} was approximately 83% of reference value(Table 18). Based on the totality of data including PK simulation and clinical data, FDA recommended a more conservative approach, to allow patients to proceed with the next planned treatment doses after any treatment dose at 76 mg if dose delay is ≤ 42 days. Due to limited clinical data (7 patients) for a dose interval ≥ 42 days between any full treatment doses of 76 mg, FDA also provided a statement for prescribers to consider the benefit-risk of restarting elranatamab for a dose delay of more than 42 days due to an adverse reaction.

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

Data:

Effects of intrinsic factors were summarized in Section 6.3.1.

The results of the population PK analysis indicated no clinically meaningful differences in elranatamab exposure based on body weight, age, sex, and race. Similar elranatamab exposure is expected in participants with mild hepatic impairment and participants with mild or moderate renal impairment compared to participants with normal organ function. Limited data are available from participants with moderate and severe hepatic impairment and participants with severe renal impairment.

The Applicant's Position:

No dose adjustment is needed based on intrinsic factors including body weight, age, sex, race, mild hepatic impairment, and mild or moderate renal impairment.

The FDA's Assessment:

The FDA agrees with Applicant's position that there is no need for dose adjustment for the currently proposed indication observed based on age (36 to 89 years), sex, race (White, Asian, or Black), body weight (37 to 160 kg), mild or moderate renal impairment (eGFR 30 to 89 mL/min), or mild hepatic impairment (total bilirubin 1 to ≤1.5 x ULN or any AST greater than ULN).

The effects of severe renal impairment (eGFR 15 to 29 mL/min), end-stage renal disease (eGFR <15 ml/min), or moderate to severe hepatic impairment (total bilirubin > 1.5 times ULN and any AST) on the PK of elranatamab are unknown. No impact of organ impairment on PK is expected given elranatamab is a large, targeted protein and bispecific antibody.

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

Data:

Elranatamab is not metabolized via CYP enzymes. No formal drug interaction studies have been conducted with elranatamab. A food effect is not anticipated as elranatamab is a biologic that is administered through SC route.

The initial release of cytokines associated with the start of elranatamab treatment could suppress CYP450 enzymes. The highest risk of interaction is expected to be during the step-up dosing schedule as the increases in cytokine levels (eg, IL-6) in vivo in monkeys and humans were transient.

The Applicant's Position:

The risk of PK drug-drug interaction from elranatamab on CYP enzyme substrates is considered transient. During the step-up dosing period, toxicity or drug concentrations should be monitored in patients who are receiving concomitant CYP450 substrates with a narrow

therapeutic index. The dose of the concomitant medicinal product should be adjusted as needed.

The FDA's Assessment:
The FDA agrees with Applicant that no food effect is anticipated given elranatamab is administered through SC route.

The FDA disagrees with the Applicant's position regarding concomitant treatment with other drugs. Elranatamab caused release of cytokines that may suppress activity of CYP enzymes. The Applicant's proposal (b) (4) may be insufficient for sensitive CYP substrates with narrow therapeutic index. Cytokine levels peaked 3 days after the first dose administration. The highest IL-6 observed is pre-dose C1D4 with median concentration around 190.55 pg/mL (APPEARS THIS WAY ON ORIGINAL Table 13).

Based on FDA's evaluation of available clinical data in the literature and understanding of postulated mechanism of IL-6 mediated CYP suppression and estimated time of CYP recovery, FDA recommends monitoring for drug interaction risk after the first step-up dose 12 mg on Cycle 1 Day 1 and for 2 weeks after the first 32 mg dose on Cycle 1 Day 4, and during and after any CRS. Refer to section 6.3.1 and 19.4.2 for review of the cytokine analysis and detailed discussion.

X X

Primary Reviewer	Team Leader
Yue Xiang	Xiling Jiang
Hongshan Li	Jiang Liu
Joseph Roman	Jeffrey Kraft
Guansheng Liu	Yuching Yang

7 Sources of Clinical Data

7.1 Table of Clinical Studies

Data:

Table 19: Applicant – Clinical Studies Supporting the Current Submission

Protocol & NCT No.	Study Design and Endpoints	Treatment Groups	No. of Patients	Demographics (No. of Subjects)	Duration of Treatment	Study Information[a]
C1071003 (Data cut-off: 10/14/2022) NCT04649359 Active, not recruiting	Phase 2, OL, multicenter, nonrandomized study of elranatamab monotherapy in participants with MM who are refractory to ≥1 PI, 1 IMiD, & 1 anti-CD38 mAb Primary endpoints: Efficacy of elranatamab in Cohort A and Cohort B, ORR by BICR	Elranatamab monotherapy SC QW at 76 mg starting Day 8 with a 2 step-up priming dose of 12 mg on Day 1 and 32 mg on Day 4. Cohort A (pivotal): Naive to BCMA-directed treatment Cohort B (supportive): Received prior BCMA-directed treatment (ADC and/or CAR-T)	N = 187 Cohort A: 123 Cohort B: 64	Total Sex: 98 (52.4%) M 89 (47.6%) F Age (yrs) Mean (SD)=66.6 (9.43) Median (range): 68.0 (36-89) Race: W/B/A/U/NR: 116 (62.0%)/ 11 (5.9%)/ 17 (9.1%)/ 3 (1.6%)/ 40 (21.4%)	Total Mean (SD)=5.725 (4.7863) months Median (Range)=4.370 (0.03, 19.81) months	• FSFV: 2/2021 • PCD: 6/2022 • Ongoing • Final CSR • No. of Centers and Countries: 53 centers across 10 countries
C1071001 (Data cut-off: 6/22/2022) NCT03269136 Active, not recruiting	Phase 1, OL study to evaluate the safety, PK, PD and clinical activity of elranatamab, a BCMA CD3 bispecific antibody, as a single agent and in combination with immunomodulatory agents	Part 1 single agent elranatamab administration (Route: IV; 0.1, 0.3, 1, 3, 10, 30, and 50 µg/kg) QW Part 1 single agent elranatamab administration (Route: SC; 80, 130, 215, 360, 600, and 1000 µg/kg) QW	N=101 Part 1 IV Cohorts Total: 23 Part 1 SC Cohorts Total: 30	Total Sex: 54 (53.5%) M 47 (46.5%) F Mean/Median Age (range): 63.7/64.0 (32-86) yrs Race: W/B/A/N:	Total Mean/Median (Range) 6.56/2.17 (0-28.8) months	• FSFV: 11/2017 • Ongoing • Interim CSR • No. of Centers and Countries: 14 centers

Table 19: Applicant – Clinical Studies Supporting the Current Submission

Protocol & NCT No.	Study Design and Endpoints	Treatment Groups	No. of Patients	Demographics (No. of Subjects)	Duration of Treatment	Study Information[a]
	in patients with advanced RRMM Primary endpoints: Part 1: DLTs Part 2: ORR and DOR	Part 1.1 single agent elranatamab administration (Route: SC; 600 µg/kg priming dose to 1000 µg/kg full dose) QW or Q2W Part 2 single agent elranatamab administration (Route: SC; 44 mg priming dose to 76 mg full dose) QW Part 1 combinations: PF- 06863135 (32 mg priming to 44 mg full dose; SC QW) + Pomalidomide 4 mg; QD Oral, Days 1-21 of 28-day cycle PF- 06863135 (32 mg priming to 44 mg full dose; SC QW) + Lenalidomide 25 mg; QD Oral, Days 1-21 of 28-day cycle	Part 1.1 SC Priming Dose Cohorts Total: 20 Part 2A SC Dose Expansion: 15 Part 1C Elranatamab + Lenalidomide: 4 Part 1D Elranatamab + Pomalidomide: 9	71 (70.3%)/ 19 (18.8%)/ 6 (5.9%)/ 5 (5.0%)		across 2 countries (USA and Canada)
C1071002 (Data cut-off: 5/27/2022) NCT04798586 Active, not recruiting	Phase 1, OL study to evaluate the safety and PK of elranatamab, a BCMA CD3 bispecific antibody, as a single agent in Japanese participants with advanced RRMM Primary endpoint: DLTs	Elranatamab 600 µg/kg priming dose and 1000 µg/kg full dose administered QW	N = 4	Total Sex: 3 (75.0%) M/ 1 (25.0%) F Mean/Median Age (min/max) in yrs: 64.0/68.5 (49/70) Race: A 4 (100%)	Total Mean/Median (Range): 43.46/42.21 (32.3/57.1) wks	• FSFV: 3/2021 • PCD: 5/2022 • Ongoing • No. of Centers and Countries: 2 sites in Japan

Table 19: Applicant – Clinical Studies Supporting the Current Submission

Protocol & NCT No.	Study Design and Endpoints	Treatment Groups	No. of Patients	Demographics (No. of Subjects)	Duration of Treatment	Study Information[a]
C1071009 (Data cut-off: 7/29/2022) NCT05014412 Recruiting	Phase 1b/2, OL, multicenter study to evaluate a dosing regimen with 2 step-up priming doses and longer dosing intervals of elranatamab monotherapy in participants with RRMM Primary endpoint: Grade ≥2 CRS rate during C1	Elranatamab monotherapy SC QW with 2 step-up priming dose of 4 mg (C1D1) and 20 mg (C1D4), then 76 mg (C1D8) followed by: Part 1: 76 mg QW C2-C6, then 76 mg Q2W C7+ (PR or better) Part 2A (Dose Determination; C2 is DLT period): DL1: • 116 mg Q2W C2-C6 • 116 mg Q4W C7+ (PR or better) *If tolerated begin DL2:* • 152 mg Q2W C2-C6 • 152 mg Q4W C7+ (PR or better) MTD/RP2D determined. Proceed to Part 2B and if both DLs tolerated, Part 2C Part 2B (Dose Expansion): • MTD/RP2D Q2W C2-C6 • MTD/RP2D Q4W C7+ (PR or better) Part 2C (Dose Intensity Exploration, C2 is DLT period)	Projected Participant Numbers: N = 76 Part 1: 30 Part 2A DL1: 8 DL2: 8 Part 2B: 22 Part 2C: 8	Total (based on 45 participants enrolled and treated in Part 1 (33) and Part 2A DL1 (12)) **Part 1:** Sex: 22 (48.9%) M 23 (51.1%) F Mean/Median Age (min/max): 60.4/63.0 (36/79) yrs Race: W/B/A/U/NR: 11 (33.3%)/ 2 (6.1%)/ 19 (57.6%)/ 0/ 1 (3.0%) **Part 2A DL1:** Sex: 8 (66.7%) M 4 (33.3%) F Mean/Median Age (min/max): 64.0/66.0 (49/78) yrs Race: W/B/A/O/U:	Total (based on 45 participants enrolled and treated in Part 1 (33) and Part 2A DL1 (12)) Part 1: Mean/Median (Range): 3.84/ 4.47 (0.49/7.92) mos Part 2A DL1: Mean/Median (Range): 1.55/ 1.58 (0.13/3.32) mos	• FSFV: 10/2021 • Ongoing • Interim CSR • No. of Centers and Countries: 24 sites across 4 countries.

Table 19: Applicant – Clinical Studies Supporting the Current Submission

Protocol & NCT No.	Study Design and Endpoints	Treatment Groups	No. of Patients	Demographics (No. of Subjects)	Duration of Treatment	Study Information[a]
		• 116 or 152 mg QW C2-C3 • 116 or 152 mg Q2W C4-C6 (PR or better) • 116 or 152 mg Q4W C7+ (PR or better)		6 (50.0%)/ 0/ 5 (41.7%)/ 0/ 1 (8.3%)		

Note: Terms "patients", "participants", and "subjects" are interchangeable in this AAid. For Race: A=Asian; B=Black; NR=not reported; O=Other; U=Unknown; W=White.

a. Study Initiation Date/Completion Date/Status/CSR (interim or final CSR to be submitted at time of authorization application indicated in respective rows of individual studies)/No. of Centers and Countries.

The Applicant's Position:

The overview of efficacy and safety for this submission focuses on the statistically significant and clinically meaningful results from pivotal Study C1071003 Cohort A and supportive Studies C1071003 Cohort B, C1071001 and C1071009 that were conducted by the applicant/designee (b) (4)

The FDA's Assessment:

The FDA agrees that Study C1071003 (MAGNETISSM-3) is the pivotal trial supporting this BLA. Additional studies, Studies C1071001 and C1071009 are supportive. The initial efficacy analysis supporting this application was based on the results from Study C1071003 Cohort A (no prior BCMA-directed therapy). However, the FDA's analysis of efficacy was based on the indicated patient population from Study C1071003 Cohort A (i.e., patients who had received at least 4 prior lines of therapy including a PI, IMiD, and anti-CD38 antibody).

The FDA does not agree (b) (4) Based on the data submitted, the FDA concluded that the safety and efficacy data provided to date supports accelerated approval based on response rate and durability of response in the indicated patient population (patients with RRMM who have received at least 4 prior lines of therapy including a PI, IMiD, and anti-CD38 antibody). However, this is contingent upon verification of clinical benefit in the ongoing confirmatory trial (Study C1071005).

8 Statistical and Clinical Evaluation

8.1 Review of Relevant Individual Trials Used to Support Efficacy

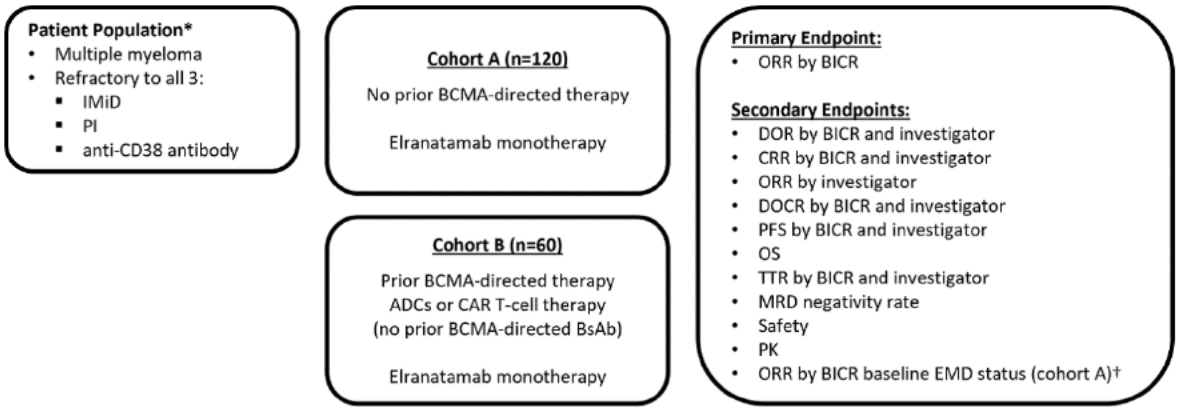
8.1.1 Study C1071003

- An Open-Label, Multicenter, Non-Randomized Phase 2 Study of Elranatamab (PF-06863135) Monotherapy in Participants With Multiple Myeloma Who Are Refractory To At Least One Proteasome Inhibitor, One Immunomodulatory Drug And One Anti-CD38 Antibody

Trial Design

Basic study design and Trial location:

Figure 8: Applicant – Study C1071003 Schema



*allow other prior therapies like selinexor
† Key Secondary Endpoint
PI = proteasome inhibitor; IMiD=immunomodulatory drug; BICR=blinded independent central review

Study information, including study primary endpoints and site locations, is presented in Table 19. Study activities were conducted per protocol.

Screening assessments (e.g., informed consent, demography/medical history, disease characteristics, treatment history, ECOG PS) were completed and reviewed to confirm that potential participants met all eligibility criteria.

Laboratory assessments for efficacy and safety were performed locally. Disease assessments were conducted every 28-days (±1 wk.) and continued until confirmed PD, withdrawal of consent, start of new anticancer therapy, lost to follow-up, death, or defined end of study (whichever occurred first). Disease response and status were evaluated according to IMWG criteria. MRD negativity (per IMWG) was assessed by a central laboratory.

All safety assessments were conducted according to the protocol. The time period for actively eliciting and collecting AEs and SAEs for each participant began at informed consent and continued through and including a minimum of 90 calendar days after the last administration of the study intervention. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Diagnostic criteria: See C1071003 Eligibility Criteria.

Study treatments and Choice of control group: Elranatamab was administered SC. Participants received step-up priming doses during the first week of treatment (12 mg on C1D1 and 32 mg on C1D4) followed by the first full dose (76 mg) on C1D8, then 76 mg QW thereafter. If a participant received QW dosing for ≥6 cycles and achieved IMWG response of PR or better persisting for ≥2 months, the dose interval was to be changed from QW to Q2W. If the participant subsequently had an increase in disease burden before qualifying as PD per IMWG criteria, dose intervals were to return to weekly dosing.

A single-arm design was chosen for Study C1071003 due to the lack of an established standard of care treatment for use as a control arm at the time the study was designed/initiated (February 2021), despite available therapies.

Dose selection: See Section 6.2.2.

Assignment to treatment and Blinding: The study enrolled 2 independent and parallel cohorts; one cohort with participants who have not previously received a BCMA-directed therapy (Cohort A) and one cohort with participants who have received previous treatment with BCMA-directed therapies (ADCs and/or CAR-Ts) (Cohort B).

The study was not blinded; however, efficacy endpoints (including the primary endpoint) were assessed by a blinded independent review committee who was blinded to response assessment by the investigator.

Dose modification, dose discontinuation: See Section 6.2.2.

Administrative structure: The study was managed by Pfizer Inc. (the sponsor) and conducted by investigators contracted by and under the direction of the sponsor. Study centers were monitored by Sponsor and CRO. The study used both a Steering Committee and a DMC. The Steering Committee (comprising members external to Pfizer) provided input on data analysis,

interpretation, and any other aspects of study design or conduct as requested by the Sponsor. The DMC was independent of the study team (comprised of only members external to Pfizer) and was responsible for ongoing monitoring of the safety of participants in the study according to the charter, and reviewed cumulative safety data during the study conduct as well as the interim futility and efficacy analyses.

Concurrent medications, Dietary restrictions, and Rescue medication: Participants were required to receive premedications (acetaminophen 650 mg or paracetamol 500 mg; diphenhydramine 25 mg; dexamethasone 20 mg) before administration of both priming doses and first full dose of elranatamab 76 mg. Concomitant treatment considered necessary for the participant's well-being could be given at the discretion of the investigator, including but not limited to, prophylactic antimicrobial agents and vaccines. Chronic systemic corticosteroid use for palliative/supportive purposes and additional anticancer therapies were not allowed; however, acute emergency administration of corticosteroids was allowed.

Treatment compliance: Participants were administered study intervention by investigator or qualified designee. The date/time of each dose administered in the clinic was recorded in source documents and recorded in the CRF.

Subject completion, Discontinuation, and Withdrawal: Each participant was able to receive study drug treatment until confirmed disease progression, unacceptable toxicity, withdrawal of consent, or study termination. Study completion will occur when the last enrolled participant has been followed for OS for ≥2 years from date of enrollment. Reasons for permanent study drug discontinuation included participant revoked consent, AE requiring discontinuation (eg, toxicity), PD per IMWG, lack of efficacy, participant pregnant/breastfeeding, noncompliance or significant protocol deviation per investigator discretion, lost to follow-up, participant completed study, death, and sponsor study termination.

The FDA's Assessment:

The FDA agrees with the Applicant's description of the Study design for Study C1071003 (MAGNETISSM-3). Study C1071003 is a phase 2 single-arm trial of elranatamab monotherapy in patients with relapsed or refractory multiple myeloma who are refractory to at least one PI, one IMiD, and one anti-CD38 monoclonal antibody. This study enrolled patients in two independent and parallel cohorts. Cohort A included patients who are naïve to BCMA-directed therapy with a planned enrollment of 120 patients. Cohort B included patients previously exposed to BCMA-directed therapy with a planned enrollment of 60 patients. Patients in Cohort A who received at least 4 prior lines of therapy including a PI, IMiD, and anti-CD38 monoclonal antibody are the primary efficacy population.

Cohort A initially started with a single step-up dosing regimen of 44 mg SC administered on Day 1 followed by the target dose of 76 mg. A total of four patients received this dosing regimen. The protocol was then modified to include a two-dose step-up regimen, which was continued throughout the duration of the study. All subsequent patients in both cohorts received elranatamab monotherapy with two step-up doses of 12 mg SC on Cycle 1, Day 1 and 32 mg SC on Cycle 1, Day 4, followed by the target dose of 76 mg SC once weekly starting on Cycle 1, Day 8 and

continuing through six cycles. Patients who received weekly dosing for at least six cycles and achieved a PR or better with a response persisting for at least two months, were changed to a dosing interval of every two weeks. Treatment continued for all patients until disease progression, unacceptable toxicity, or withdrawal of consent.

The primary endpoint was ORR by Blinded Independent Central Review (BICR).
As noted below (Table 22), there were nine amendments to Study C1071003.

Eligibility Criteria

The Applicant's Description:

The participants included in this study were age ≥18 years with diagnosis of MM as defined according to IMWG criteria and refractory to at least one PI, one IMiD, and one anti-CD38 antibody, and were relapsed or refractory to their last line of therapy. Participants had to have measurable disease based on IMWG criteria as defined by at least 1 of the following: 1) serum M-protein ≥0.5 g/dL by SPEP, 2) urinary M-protein excretion ≥200 mg/24 hrs. by UPEP, 3) serum immunoglobulin FLC ≥10 mg/dL (≥100 mg/L) and abnormal serum immunoglobulin kappa to lambda FLC ratio. Participants must not have received prior BCMA-directed therapy (Cohort A); have received prior BCMA-directed ADC or CAR T-cell therapy (Cohort B); have ECOG score ≤2; and resolved acute effects of any prior therapy to baseline severity or CTCAE Grade ≤1; not pregnant and willing to use contraception. Participants were excluded from enrollment for any of the following: Smoldering MM, active plasma cell leukemia, amyloidosis, POEMS syndrome, recent stem cell transplant (≤12 weeks before enrollment), Active infection (eg, HBV, HCV, SARS-CoV-2, HIV) or any active, uncontrolled bacterial, fungal, or viral infection; Any other active malignancy within 3 years before enrollment (except adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ); Previous administration with an investigational drug within 30 days or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).

The FDA's Assessment:

The FDA agrees with the Applicant's description of the key eligibility criteria for Study C1071003. The full eligibility criteria are noted in Appendix 0.

Study Endpoints

The Applicant's Description:

Regulatory history: See Section 3 for information on Regulatory interactions regarding Study C1071003.

Primary and selected secondary endpoints:

Table 20: Applicant – Study C1071003 Primary and Secondary Endpoints

Endpoint	Description		Analyses
Primary			
ORR by BICR	Proportion of participants with confirmed objective response by BICR per IMWG criteria.		Point estimates of ORR calculated along with corresponding 2-sided exact 95% CIs using the Clopper-Pearson method.
Secondary			
Time to Event	DOR[a]	Time from first documentation of objective response by BICR that is	K-M estimates and median DOR time with 2-sided 95% CIs.

Table 20: Applicant – Study C1071003 Primary and Secondary Endpoints

Endpoint	Description		Analyses
		subsequently confirmed, until confirmed PD per IMWG criteria, or death due to any cause, whichever occurred first, or censoring.	
	TTR[a]	Time from date of first dose to first documentation of objective response by BICR that is subsequently confirmed.	Summarized using descriptive statistics.
MRD negativity rate[b]	Proportion of participants with negative MRD (assessed by central lab) per IMWG sequencing criteria by BMA from date of first dose until confirmed PD, death or start of new anticancer therapy, whichever occurred first.		Defined by a threshold of 10^{-5} by next generation sequencing. Calculated along with 2-sided 95% CI using Clopper-Pearson method.

a participants with an objective response per IMWG criteria
b participants with a sCR/CR per IMWG criteria

The FDA's Assessment:
FDA agrees with the Applicant's description of the primary and selected secondary endpoints and analyses methods.

Statistical Analysis Plan and Amendments

The Applicant's Description:
The Study C1071003 original SAP had 8 amendments. The modifications to the original SAP are not considered to have had an impact on the integrity of the trial or the interpretation of the results.

The Statistical Analysis Plan (SAP) for Study C1071003 was finalized on 14 April 2022 prior to the 14 April 2022 database snapshot (23 March 2022 data cutoff) for BICR for the interim analysis for Cohort A. The SAP was amended on 08 July 2022 prior to the 20 July 2022 database snapshot (17 June 2022 data cutoff [PCD]) for BICR for the final analysis for the primary endpoint for both cohorts for additional COVID-19 related analyses and subgroup analyses for Cohort B (ADC vs CAR-T). The SAP was last amended on 26 October 2022 prior to the 27 October 2022 database snapshot (14 October 2022 data cutoff) for the 9-month follow-up analysis per FDA request to clarify the primary analysis population for the efficacy analyses. The study SAP reflected changes in the protocol (via protocol amendments) such as additional or updated analyses as deemed clinically relevant and/or statistically appropriate based on emerging data.
The sample size for Cohort A (approximately 120) and Cohort B (approximately 60) was calculated to provide adequate power for testing the statistical hypotheses regarding the primary endpoint of ORR independently in the 2 cohorts using a 2-stage design based on the exact binomial distribution.

The primary analysis for all efficacy endpoints was performed separately by cohort and based on the BICR assessment of disease status using the safety analysis set (same as the final analysis evaluable set, N=123 for Cohort A and N=64 for Cohort B), which is all enrolled participants who received ≥1 dose of study drug. All enrolled participants received at least one dose of study drug.

The primary endpoint was ORR, defined as the proportion of subjects who achieved a PR or better according to the IMWG response criteria (Kumar et al, 2016), as assessed by BICR. The ORR and its 2-sided 95% Clopper-Pearson exact confidence interval (CI) were presented, with the

corresponding null ORR ≤30% for Cohort A and null ORR ≤15% for Cohort B. The study was to be considered successful if the lower bound of the 95% confidence interval exceeds 30% and 15%, respectively. Sensitivity analyses of ORR were performed using disease response based on a computerized algorithm according to the IMWG response criteria (Kumar et al, 2016).

The secondary endpoints of CR or better rate and MRD negativity rate were analyzed similarly. DOR was estimated using the Kaplan-Meier method. Time to response was analyzed using descriptive statistics. Subgroup analyses for ORR included (but were not limited to) age, gender, and race.

Table 21: Applicant – Study C1071003 Rationale for SAP Amendments

Version/ Issue Date	Overall Rationale for Amendment
1 / 19 Nov 2020	N/A – Original SAP
2 / 30 Mar 2021	Health Authority input
3 / 29 Jun 2021	Health Authority input
4 / 20 Oct 2021	Blinded Data Review
5 / 07 Jan 2022	Health Authority input
6 / 04 Apr 2022	Blinded Data Review
7 / 14 Apr 2022	External environment (align with evolving MM landscape)
8 / 08 Jul 2022	Blinded Data Review
9 / 26 Oct 2022	Health Authority input

The FDA's Assessment:

In general, FDA agrees with the Applicant's description of the SAP, including the SAP revisions. The amendments to the original SAP did not affect the evaluation of the study or have impact on the study conclusions. For the secondary endpoints, FDA considers time-to-event endpoints such as progression-free survival (PFS) and overall survival (OS) to be largely uninterpretable in single-arm trials. Therefore, the analyses of PFS and OS results are considered exploratory.

The prespecified analysis population in Cohort A, as stated in the protocol, included all enrolled participants who received at least one dose of the study intervention. However, FDA modified efficacy population to include the indicated patient population from study C1071003 Cohort A, which included patients who had received at least 4 prior lines of therapy including a PI, IMiD, and an anti-CD38 antibody.

For response rates and the MRD negativity rate, frequency counts and percentages were summarized, and exact 95% CIs for the rates were calculated using the Clopper-Pearson method. For Kaplan-Meier analyses, the Brookmeyer-Crowley method was used to construct the 95% CI for

the median DOR. Median follow-up for DOR was estimated using the reverse Kaplan-Meier method. TTR was summarized using descriptive statistics.

In Cohort A, the study was planned to test the null hypothesis that the ORR by BICR as defined by IMWG is ≤30% versus the alternative hypothesis that the ORR by BICR as defined by IMWG is >30%. In Cohort B, the study was planned to test the null hypothesis that the ORR by BICR as defined by IMWG is ≤15% versus the alternative hypothesis that the ORR by BICR as defined by IMWG is >15%.

The protocol stated that the sample size for Cohort A and Cohort B was calculated to provide adequate power for testing the statistical hypotheses regarding the primary endpoint of ORR independently in the two cohorts using a two-stage design based on exact binomial distribution. A total of 120 participants enrolled and treated in Cohort A provides approximately 98% power to detect a true ORR by BICR of 48% to reject the null hypothesis, with a 1-sided significance level of 0.025. Similarly, a total of 60 participants enrolled and treated in Cohort B provides approximately 91% power to detect a true ORR by BICR of 34% to reject the null hypothesis, with a 1-sided significance level of 0.025. FDA notes these terms of "hypotheses testing" for the single-arm trial were for sample size calculation purposes. In a single- arm trial, FDA does not consider any inferential procedures to evaluate the trial results. Instead, the efficacy decision is based on the lower limit of a 95% confidence interval to exceed a clinically relevant response rate. Comparison of response rate from single-arm trials against a historical rate is challenging because the historical benchmark is difficult to verify. Due to difference in population, trial design and other possible unknown confounders, the historical estimation is likely subject to biases which cannot be resolved.

Protocol Amendments

The Applicant's Description:

STUDY C1071003 PROTOCOL: There were 9 amendments to the original protocol. Important modifications to the C1071003 protocol are outlined in Table 22. Overall, modifications to the protocol were intended to increase patient safety and improve interpretation of study results.

Table 22: Applicant – Study C1071003 Protocol Important Modifications

Version/ Issue Date	Overall Rationale for Amendment
Original / 07 Oct 2020	N/A
1 / 07 Jan 2021	• Changed power from 80% to 90% to detect ORR of 48% (previously 45%) in Cohort A and 34% (previously 31%) in Cohort B. • Added interim safety assessment section and clarified that study will not be stopped for efficacy at IA.
2 / 14 Feb 2021	• Added elranatamab as investigational drug generic name. • Added IA and PRO analysis sets. • Revised criteria for temporary enrollment hold (required regulatory change).
3 / 24 Mar 2021	• Country-specific: Belgium, Germany, Poland, Spain for VHP procedure (review of PA 1)
4 /	• Country-specific: United Kingdom per MHRA (review of PA 1)

Table 22: Applicant – Study C1071003 Protocol Important Modifications

Version/ Issue Date	Overall Rationale for Amendment
09 Apr 2021	
5 / 02 May 2021	• Incorporates changes previously included in PA 2 (which was based on PA 1) and country-specific PA 3 and PA 4 (which were also based on PA 1); therefore PA 5 brings all the amendments into 1 document. • Included safety mitigation information for CRS and ICANS.
6 / 30 May 2021	• Revisions to enrollment hold, EC, and dose modifications were made per US FDA regulatory requirements.
7 / 11 Nov 2021	• Revised number of participants (from 150 to 180) and revised interim analyses (increased N from 60 to 90 for Cohort A) to allow for more robust datasets; updated power/sample size calculations. • Added efficacy IA for Cohort B. IAs based on actual number with adequate follow-up at time of IA. • The follow-up period for final analysis was revised. • Revised assessments for better alignment with global clinical practice (BMB sampling, immunofluorescence and flow cytometry)
8 / 23 Dec 2021	• Adjusted posterior probability threshold for interim analysis safety assessments.
9 / 29 July 2022	• Efficacy was further evaluated (addition of key secondary endpoint, ORR by BICR baseline EMD status, Cohort A) and updated elranatamab clinical results including frequency of infections with the addition of more detailed recommendations for prophylaxis to mitigate infection risk.

The FDA's Assessment:
The FDA agrees with the Applicant's summary of the protocol amendments for Study C1071003.

8.1.2 Study Results: C1071003

Compliance with Good Clinical Practices

The Applicant's Position:
The study was conducted in accordance with consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines, applicable ICH GCP guidelines, and applicable laws and regulations, including applicable privacy laws.

The FDA's Assessment:
FDA agrees with the Applicant's position. Study C1071003 was compliant with Good Clinical Practices and no issues were identified that indicate a significant risk to the data quality.

Financial Disclosure

The Applicant's Position:
The integrity of the Study C1071003 data was not affected by the financial interest of the investigators. Financial information is provided in the Financial Disclosure section in Appendix 19.2.

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

Patient Disposition

Data:

At the data cutoff date (14 October 2022), the median (range) duration of follow-up from initial dose was 10.38 months (range: 0.23, 20.14) in Cohort A and 9.22 (0.33, 12.32) in Cohort B.

Table 23: Applicant – Disposition Events Summary - End of Treatment and End of Study (Safety Analysis Set) (Protocol C1071003)

Participants n (%)	Naïve to BCMA-directed therapy (Cohort A) (N=123)	Received prior BCMA-directed therapy (Cohort B) (n=64)	Total (N=187)
End of Treatment			
Participants Entered:	123 (100.0)	64 (100.0)	187 (100.0)
Discontinued	71 (57.7)	46 (71.9)	117 (62.6)
Adverse event	13 (10.6)	5 (7.8)	18 (9.6)
Death	8 (6.5)	8 (12.5)	16 (8.6)
Lack of efficacy	3 (2.4)	1 (1.6)	4 (2.1)
Progressive disease	40 (35.0)	27 (42.2)	70 (37.4)
Withdrawal by subject	4 (3.3)	4 (6.3)	8 (4.3)
Refused Further Study Procedures	0	1 (1.6)	1 (0.5)
Ongoing	52 (42.3)	18 (28.1)	70 (37.4)
End of Study			
Discontinued	48 (39.0)	33 (51.6)	81 (43.3)
Death	41 (33.3)	26 (40.6)	67 (35.8)
Withdrawal by subject	7 (5.7)	7 (10.9)	14 (7.5)
Ongoing	75 (61.0)	31 (48.4)	106 (56.7)

The Applicant's Position:

The overall proportion of participants who discontinued from treatment due to disease progression (37.4%) and adverse events (9.6%), and the proportion of participants who discontinued from study due to death (35.8%) is consistent with what is expected in RRMM population.

The FDA's Assessment:

In general, FDA agrees with the Applicant's description of the disposition in the Applicant's defined primary safety and efficacy populations based on the clinical cutoff date of October 14, 2022, except that in Table 23, the number of patients with discontinuation of treatment due to progressive disease in Cohort A should be reported as 43 (35%).

In addition, the Agency's primary analysis population was based on the indicated patient population from Study C1071003 Cohort A (i.e., patients who had received at least 4 prior lines of therapy including a PI, IMiD, and anti-CD38 antibody). A summary of the disposition for the patients who had received at least 4 prior lines of therapy is included in Table 24 below.

Table 24: FDA – Disposition Summary - End of Treatment and End of Study (Study C1071003)

Participants n (%)	Naïve to BCMA-directed therapy (Cohort A) (N=97)	Received prior BCMA-directed therapy (Cohort B) (N=63)	Total (N=160)
End of Treatment			
Participants Entered:	97 (100.0)	63 (100.0)	160 (100.0)
Discontinued	60 (61.9)	46 (73.0)	106 (66.3)
Adverse event	12 (12.4)	5 (7.9)	17 (10.6)
Death	8 (8.3)	8 (12.7)	16 (10)
Lack of efficacy	2 (2.1)	1 (1.6)	3 (1.9)
Progressive disease	34 (35.1)	27 (42.9)	61 (38.1)
Withdrawal by patient	4 (4.1)	4 (6.4)	8 (5)
Refused Further Study Procedures	0	1 (1.6)	1 (0.6)
Ongoing	37 (38.1)	17 (27)	54 (33.8)
End of Study			
Discontinued	42 (43.3)	33 (52.4)	75 (46.9)
Death	36 (37.1)	26 (41.3)	62 (38.8)
Withdrawal by patient	6 (6.2)	7 (11.1)	13 (8.1)
Ongoing	55 (56.7)	30 (47.6)	85 (53.1)

Source: FDA Reviewer generated from ADSL dataset

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 January 12, 2023, 70.5% of participants had discontinued treatment, and 29.5% of remained on treatment. The reasons for treatment discontinuation included progressive disease (41.5%), adverse event (12.6%), death (9.8%), withdrawal by patient (3.8%), lack of efficacy (2.2%), and no longer clinically benefitting (0.5%).

Protocol Violations/Deviations

Data:

Overall, a total of 148 (79.1%) participants had ≥1 important protocol deviation. The protocol deviation categories with the highest frequency (≥20%) were Procedures/Tests (30.5%), Safety Reporting (29.9%), Informed Consent (29.4%), Investigational Product (28.3%), and Visit Schedule (27.8%). The majority of COVID-19 related IPDs were in the category of Visit Schedule; among participants with a missed visit, 20/52 were due to COVID-19.

The Applicant's Position:

In Study C1071003, the type/number of protocol deviations observed were not expected to affect the outcomes or interpretation of the study results or impact participant safety. There was minimal impact on conduct of the studies due to the COVID-19 pandemic, although there was a significant impact on the safety profile (Table 41). None of the minor deviations led to exclusion of safety or efficacy data.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. However, FDA notes that the percentage of patients in the safety population with Important Protocol Deviations in Study C1071003 is relatively high (78%). A summary of the important protocol deviations is provided in Table 25 below.

Further evaluation was done to determine the specific reasons for protocol deviations in the categories with the highest number of deviations. Under the category of "Procedures/Tests", 46 patients (24.6%) had deviations related to the disease assessment not being done/not completely done, including any component of assessment as required per protocol (i.e., SPEP, SIFE, FLC, bone marrow evaluation, or imaging). A total of 13 patients (7.0%) had deviations related to procedures for contraception counseling/contraception requirements not being followed. Under the category of Safety Reporting, 56 patients (29.9%) had deviations related to SAEs not being reported to the Sponsor within the specified timeframe. Under the category of Visit Schedule, 52 patients (27.8%) had deviations for the reason "visit not done". Under the category of Informed Consent, 35 patients (18.7%) had deviations related to the Informed Consent not being signed at the first patient visit after a revised/approved Informed Consent document was available at the site. Notably, under the category of Investigational Product, 43 patients (23.0%) had protocol deviations related to the product being administered without following dosage modification guidelines for hematologic and non-hematologic toxicity, as defined in the protocol

Despite the high number of protocol deviations, FDA agrees with the Applicant's conclusion that the type/number of protocol deviations observed were not likely to affect the outcomes or interpretation of the study results or impact participant safety.

Table 25: FDA – Summary of Important Protocol Deviations (Study C1071003)

Protocol Deviation Category	Cohort A N=123 n(%)	Cohort B N=64 n(%)	Total N=187 n(%)
Patients with Any Important Protocol Deviation	**96 (78)**	**52 (81)**	**148 (79)**
Procedures/Tests	34 (28)	23 (36)	57 (31)
Safety Reporting	35 (29)	21 (33)	56 (30)
Informed Consent	40 (33)	15 (23)	55 (29)
Investigational Product	30 (24)	23 (36)	53 (28)
Visit Schedule	31 (25)	21 (33)	52 (28)
Inclusion/Exclusion Criteria	4 (3.3)	5 (7.8)	9 (4.8)
Laboratory	2 (1.6)	1 (1.6)	3 (1.6)
Concomitant Medications	4 (3.3)	0	4 (2.1)

Source: Adapted from Study C1071003 CSR, Table 8.

Table of Demographic Characteristics

Data:

Table 26: Applicant – Demographic Characteristics (Safety Analysis Set) (Protocol C1071003)

Participants n (%)	Naïve to BCMA-directed therapy (Cohort A) (N=123)	Received prior BCMA-directed therapy (Cohort B) (n=64)	Total (N=187)
Age (Years)			
Median (range) years	68.0 (36, 89)	67.0 (41, 84)	68.0 (36, 89)
18 - <65 (n (%))	43 (35.0)	28 (43.8)	71 (38.0)
≥65 - <75 (n (%))	56 (45.5)	24 (37.5)	80 (42.8)
≥75 (n (%))	24 (19.5)	12 (18.8)	36 (19.3)
Gender, n (%)			
Male	68 (55.3)	30 (46.9)	98 (52.4)
Female	55 (44.7)	34 (53.1)	89 (47.6)
Race, n (%)			
White	72 (58.5)	44 (68.8)	116 (62.0)
Black or African American	9 (7.3)	2 (3.1)	11 (5.9)
Asian	16 (13.0)	1 (1.6)	17 (9.1)
Unknown	2 (1.6)	1 (1.6)	3 (1.6)
Not reported	24 (19.5)	16 (25.0)	40 (21.4)

Table 27: Applicant – Demographic Characteristics (Safety Analysis Set – USA Population) (Protocol C1071003)

Participants n (%)	Naïve to BCMA-directed therapy (Cohort A) (N=47)	Received prior BCMA-directed therapy (Cohort B) (n=35)	Total (N=82)
Race, n (%)			
White	34 (72.3)	33 (94.3)	67 (87.1)
Black or African American	8 (17.0)	2 (5.7)	10 (12.2)
Asian	3 (6.4)	0	3 (3.7)
Unknown	0	0	0
Not reported	0	0	0

The Applicant's Position:

Participant demographic characteristics were consistent with the target indication population of MM participants who were refractory to at least 1 PI, 1 IMiD, and 1 anti-CD38 mAb with regard to gender (slightly more common in men) and age (most cases diagnosed in persons age ≥65 years (American Cancer Society, 2022). MM is more common in the African American/Black population than in White American population. African American/Black participants were underrepresented in the overall Study C1071003 population (5.9%). However, because of targeted diversity enrollment activities for study sites within the US, 12.2% of participants overall (17.0% in Cohort A) enrolled at US study sites were Black/African American. The Diversity Plan was successfully implemented in pivotal Cohort A and enrolled the targeted percentage of Black/African American participants in the US population. The same Diversity Plan was less effective in supportive Cohort B likely due to health care disparities resulting in limited access to BCMA-directed CAR-T and ADC therapies (Kanapuru et al, 2022).

The FDA's Assessment:

In general, FDA agrees with the Applicant's description of the demographic characteristics of the overall safety population in Study C1071003 presented in the Applicant's Table 26. Overall, there was an underrepresentation of racial and ethnic minority patients. Of the 187 patients in the safety population, only 11 (5.9%) were Black or African American, 17 (9.1%) were Asian, and 18 (9.6%) were Hispanic or Latino. In addition, race was missing or unknown for 43 (23%) patients. FDA's summary of race and ethnicity for patients enrolled in Study C1071003 is provided in Table 28 below. In the overall safety population of patients who have received at least one full dose of elranatamab (76 mg/1000 µg/kg) across six studies in the clinical development program (N=265), 19 (7.2%) were Black or African American, 40 (15.1%) were Asian, and 23 (8.7%) were Hispanic or Latino.

Considering the low percentages of patients who were Black or African American and patients who were ≥75 years of age in Study C1071003, as well as the low percentage of racial and ethnic minorities in the overall elranatamab development program, additional data is needed in underrepresented patient populations to further characterize the safety and efficacy of elranatamab in the U.S. patient population. To this end, the PMR issued to verify the clinical benefit of elranatamab 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 elranatamab in a study population that better reflects the U.S. population of patients with MM. In addition, a separate PMC will be issued to conduct an integrated analysis of data from clinical trials to further characterize the safety, efficacy, pharmacokinetics, and pharmacodynamics of elranatamab among U.S. racial and ethnic minority patients with multiple myeloma.

Table 28: FDA – Analysis of Race and Ethnicity (Study C1071003)

	Cohort A N = 123 n(%)	Cohort B N = 64 n(%)	Total N = 187 n(%)
Race			
White	72 (58.5)	44 (68.8)	116 (62.0)
Asian	16 (13.0)	1 (1.6)	17 (9.1)
Black or African American	9 (7.3)	2 (3.1)	11 (5.9)
Missing	24 (19.5)	16 (25.0)	40 (21.4)
Unknown	2 (1.6)	1 (1.6)	3 (1.6)
Ethnicity			
Not Hispanic or Latino	85 (69.1)	34 (53.1)	119 (63.6)
Hispanic or Latino	11 (8.9)	7 (10.9)	18 (9.6)
Not Reported	26 (21.1)	22 (34.4)	48 (25.7)
Missing	1 (0.8)	1 (1.6)	2 (1.1)

Source: FDA Analysis, ADSL dataset

FDA's analysis of the demographic characteristics in the U.S. safety population is slightly different than the Applicant's. Based on FDA's analysis, there was 1 patient (2.1%) with race unknown (2.1%), and 1 patient (2.1%) whose race was not reported.

In addition to above, FDA analyzed the baseline demographic characteristics for FDA's defined efficacy population, which consisted of 97 patients from Cohort A. Among the 97 efficacy patients in Cohort A, the median age was 69 years (range: 46 to 89 years). There were 32 patients (33.0%) <65 years of age, 47 (48.5%) ≥65 to <75 years of age, and 18 (18.6%) ≥75 years of age. There were 58 male patients (59.8%), and most patients were White (59.8%) or had missing or unknown race (21.6%). Only 5.2% of patients were Black or African American. A summary of the baseline demographic characteristics based on FDA defined efficacy population is provided in Table 29.

Table 29: FDA – Demographic Characteristics Including the FDA's Defined Efficacy Population (Study C1071003)

Participants n (%)	Naïve to BCMA-directed therapy (Cohort A) (N=97)	Received prior BCMA-directed therapy (Cohort B) (N=63)	Total (N=160)
Age (Years)			
Median (range) years	69 (46, 89)	67 (41, 84)	68 (41, 89)
18 - <65 (n (%))	32 (33.0)	28 (44.4)	60 (37.5)
≥65 - <75 (n (%))	47 (48.5)	23 (36.5)	70 (43.8)
≥75 (n (%))	18 (18.6)	12 (19.1)	30 (18.8)
Gender, n (%)			
Male	58 (59.8)	30 (47.6)	88 (55)
Female	39 (40.2)	33 (52.4)	72 (45)
Race, n (%)			
White	58 (59.8)	43 (68.3)	101 (63.1)
Black or African American	5 (5.2)	2 (3.2)	7 (4.4)
Asian	13 (13.4)	1 (1.6)	14 (8.8)
Unknown	2 (2.1)	1 (1.6)	3 (1.9)
Not reported	19 (19.6)	16 (25.4)	35 (21.9)

Source: FDA Analysis; ADSL dataset

Other Baseline Characteristics (eg, disease characteristics, important concomitant drugs)

Data:

Table 30: Applicant – Baseline Characteristics (Safety Analysis Set) (Protocol C1071003)

Participants n (%)	Naïve to BCMA-directed therapy (Cohort A) (N=123)	Received prior BCMA-directed therapy (Cohort B) (n=64)	Total (N=187)
Disease Stage (R-ISS)			
I	28 (22.8)	11 (17.2)	39 (20.9)
II	68 (55.3)	36 (56.3)	104 (55.6)
III	19 (15.4)	15 (23.4)	34 (18.2)
Unknown	8 (6.5)	2 (3.1)	10 (5.3)
ECOG Performance Status			
0	45 (36.6)	20 (31.3)	65 (34.8)
1	71 (57.7)	40 (62.5)	111 (59.4)
2	7 (5.7)	4 (6.3)	11 (5.9)
3	0	0	0
Baseline bone marrow plasma cells			
< 50%	89 (72.4)	44 (68.8)	133 (71.1)
≥50%	26 (21.1)	11 (17.2)	37 (19.8)
Missing	8 (6.5)	9 (14.1)	17 (9.1)
Cytogenetic Risk			
Standard Risk	83 (67.5)	42 (65.6)	125 (66.8)
High-Risk	31 (25.2)	13 (20.3)	44 (23.5)
Missing	9 (7.3)	9 (14.1)	18 (9.6)
Extramedullary Disease by BICR			
Yes	39 (31.7)	37 (57.8)	76 (40.6)
No	84 (68.3)	27 (42.2)	111 (59.4)
Number Prior Lines of			
Median (range) prior lines	5.0 (2, 22)	7.5 (3, 19)	5.0 (2, 22)
Prior BCMA-targeted therapy	0	64 (100.0)	64 (34.2)
ADC	0	46 (71.9)	46 (24.6)
CAR-T	0	21 (32.8)	21 (11.2)
ADC and CAR-T	0	3 (4.7)	3 (1.6)
Anti-BCMA Bispecific	0	1 (1.6)	1 (0.5)
Triple-class exposed	123 (100.00)	64 (100.0)	187 (100.0)
Penta-class exposed	87 (70.7)	54 (84.4)	141 (75.4)
Triple-class refractory	119 (96.7)	62 (96.9)	181 (96.8)
Penta-drug Refractory (refractory to at least 2 PIs, 2 IMiDs and 1 anti-CD38)	52 (42.3)	33 (51.6)	85 (45.5)
Refractory to last line of therapy	118 (95.9)	56 (87.5)	174 (93.0)

The Applicant's Position:

Overall baseline characteristics were consistent with expectation in heavily pretreated advanced RRMM population, including a subset of participants with poor prognostic features: R-ISS Stage III disease (18.2%), ECOG PS of 2 (5.9%), high-risk cytogenetics (23.5%), baseline EMD (39.6%), and penta-drug refractory (45.5%). In supportive Cohort B, the proportion of participants with EMD at baseline (57.8%) was higher than in Cohort A (31.7%) and is with an advanced, heavily pretreated (median: 7.5 prior lines of therapy) population.

The FDA's Assessment:

In general, FDA agrees with the Applicant's presentation of the results of the baseline disease characteristics for the overall safety population. FDA notes that in the overall safety population (N=187), the median number of prior lines of therapy was 5 (range: 2-22), and 27 patients (14.4%) received 1-3 prior lines of therapy. In addition to the data presented by the Applicant, FDA analyzed the baseline demographic characteristics for the FDA's defined efficacy population, which was consistent with the indicated patient population and included patients who received at least 4 prior lines of therapy including a PI, an IMiD, and an anti-CD38 monoclonal antibody who were treated in Cohort A (N=97). The baseline characteristics of FDA's primary efficacy population are displayed in Table 31.

Table 31: FDA – Baseline Characteristics Including the FDA's Defined Efficacy Population (Study C1071003)

Participants n (%)	Naïve to BCMA-directed therapy (Cohort A) (N=97)	Received prior BCMA-directed therapy (Cohort B) (N=63)	Total (N=160)
Disease Stage (R-ISS)			
I	20 (20.6)	11 (17.5)	31 (19.4)
II	52 (53.6)	35 (55.6)	87 (54.4)
III	17 (17.5)	15 (23.8)	32 (20)
Unknown	8 (8.2)	2 (3.17)	10 (6.3)
ECOG Performance Status			
0	30 (30.9)	19 (30.2)	49 (30.6)
1	62 (63.9)	40 (64.5)	102 (63.8)
2	5 (5.2)	4 (6.4)	9 (5.6)
3	0 (0)	0 (0)	0 (0)
Baseline bone marrow plasma cells			
< 50%	70 (72.2)	43 (68.3)	113 (70.6)
≥50%	20 (20.6)	11 (17.5)	31 (19.4)
Missing	7 (7.2)	9 (14.3)	16 (10.0)
Cytogenetic Risk			
Standard Risk	66 (68.0)	**42 (66.7)**	108 (67.5)
High-Risk	22 (22.7)	13 (20.6)	35 (21.9)
Missing	9 (9.3)	8 (12.7)	17 (10.6)
Extramedullary Disease by BICR			
Yes	33 (34.0)	36 (57.1)	69 (43.1)
No	64 (66.0)	27 (42.9)	91 (56.9)
Number Prior Lines of			
Median (range) prior lines	5 (4, 22)	8 (4, 19)	6 (4, 22)
Prior BCMA-targeted therapy	0	63 (100.0)	63 (39.4)
ADC	0	46 (73.0)	46 (28.8)
CAR-T	0	20 (32)	20 (12.5)
ADC and CAR-T	0	3 (4.8)	3 (1.9)
Anti-BCMA Bispecific	0	1 (1.6)	1 (0.6)
Triple-class exposed	97 (100)	63 (100)	160 (100)
Penta-class exposed	75 (77.3)	54 (85.7)	129 (80.6)
Triple-class refractory	94 (96.9)	61 (96.83)	155 (96.9)
Penta-drug Refractory (refractory to at least 2 PIs, 2 IMiDs and 1 anti-CD38)	45 (46.4)	33 (52.4)	78 (48.8)
Refractory to last line of therapy	92 (94.9)	55 (87.3)	147 (91.9)

FDA Analysis; ADSL dataset

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Treatment Compliance:

All doses of elranatamab were administered SC by qualified study personnel at the study site.

Median relative dose: 82.08% overall (range: 13.4, 100.0); 82.08% in participants naïve to BCMA-directed therapy (Cohort A); 82.88% in participants who received prior BCMA-directed therapy (Cohort B).

Overall, 147 participants (78.6%) had ≥1 dose reduction/interruption (Cohort A: 99 [80.5%]; Cohort B: 48 [75.0%]).

Prior and Concomitant Medications:

Overall, 183 participants (97.9%) received prior medications (99.2% and 95.3%, respectively). The most frequently (≥20%) reported prior medications were acyclovir (42.2%), sulfamethoxazole; trimethoprim (27.3%), and acetylsalicylic acid (20.3%). All study participants received ≥1 concomitant medication.

Concomitant medications administered as prophylaxis for infection in the overall population included antiviral (46.5%), anti-pneumocystis jirovecii pneumonia (46.5%), antifungal (8.6%), and antibacterial (5.3%). In addition, 38.5% of participants received IVIG therapy.

All participants (100%) received premedication for CRS prior to the first priming dose; 98.4% and 94.0% of participants received premedication prior to the second priming dose and first full dose, respectively.

Rescue Medication Use: Not applicable.

The Applicant's Position:

The proposed USPI provides guidance in the dosage and administration section for the recommended use of pretreatment medications. The USPI will also recommend appropriate infection prophylaxis.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. However, FDA notes that on January 11, 2023, the Applicant submitted an updated table for the antimicrobial agents administered for prophylaxis of infection. The Applicant states that there was a reporting error in the initial table presented in the Assessment Aid above due to some instances of alternate spelling of medications (i.e., acyclovir/acyclovir). Based on the Applicant's updated table, overall, 108 patients (87.7%) received anti-viral prophylaxis, including 58 (47.2%) who received acyclovir prophylaxis. In general, the concomitant medications administered in Study C1071003 were consistent with commonly prescribed medications for patients with relapsed or refractory multiple myeloma. The USPI will state that prophylactic antimicrobials and anti-viral medications should be administered according to current practice guidelines.

FDA agrees with the Applicant's assessment regarding the number of participants who received pre-medications for CRS. Details regarding the recommended pre-treatment medications

participants should receive prior to the first three doses of elranatamab in the step-up dosing schedule will be included in Section 2.3 of the USPI.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Efficacy Analysis of Primary Endpoint:

Table 32: Applicant – Primary Efficacy Analysis: BOR by BICR per IMWG (Protocol C1071003)

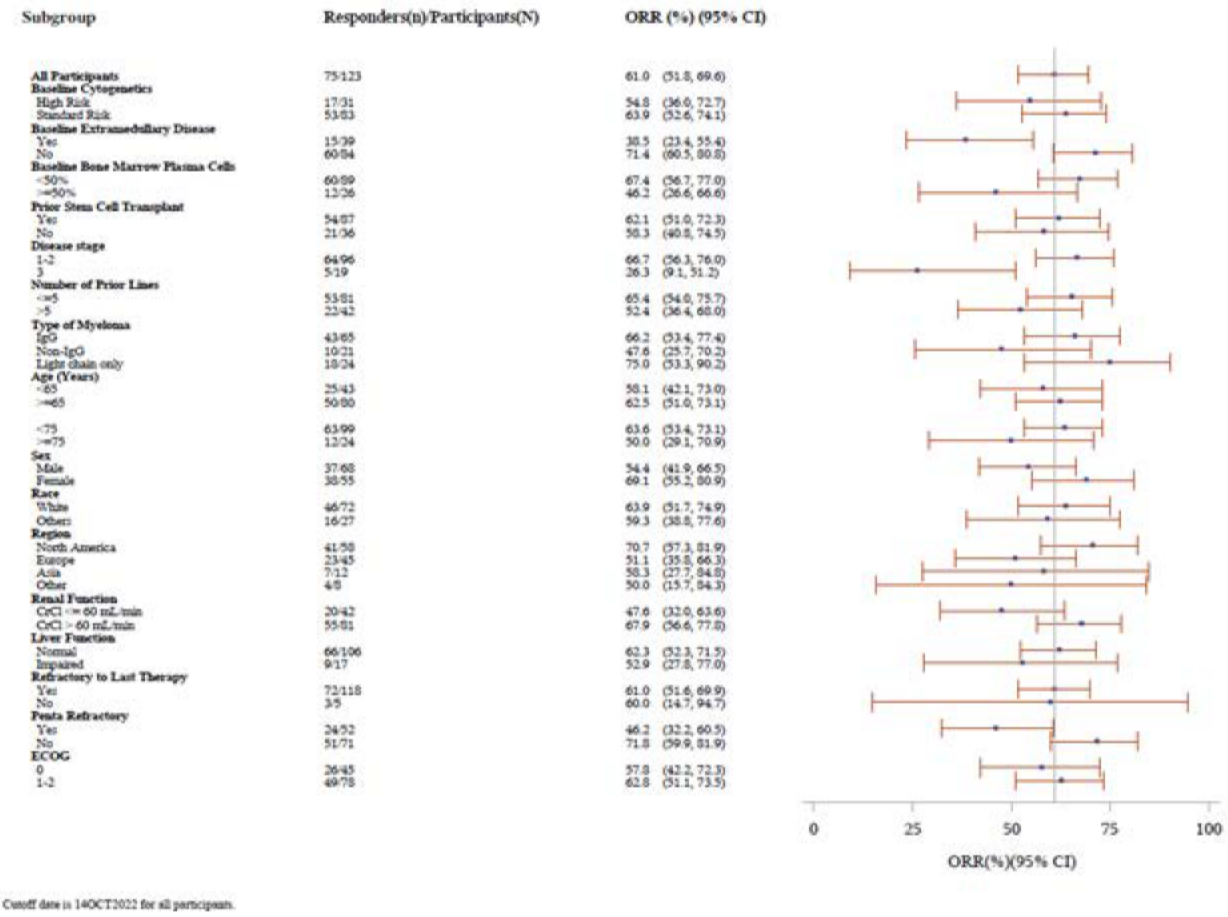
	Naïve to BCMA-directed therapy (Cohort A) (n=123)
ORR (sCR+CR+VGPR+PR); n (%), 95% CI	75 (61.0); 51.8, 69.6
Stringent Complete Response (sCR); n (%)	16 (13.0)
Complete response (CR); n (%)	18 (14.6)
Very Good Partial Response (VGPR); n (%)	34 (27.6)
Partial response (PR); n (%)	7 (5.7)
Stable disease (SD); n (%)	21 (17.1)
Progressive disease (PD); n (%)	22 (17.9)
Not evaluable (NE); n (%)	5 (4.1)

In Cohort B (n=64), confirmed ORR by BICR was 34.4% (95% CI: 22.9, 47.3); 7.8% of patients achieved CR, and 32.8% achieved VGPR or better.

Sensitivity Analyses of Primary Endpoint Analysis: For ORR by BICR, sensitivity analysis including enrolled and untreated participants was not performed as all participants were treated.

Supportive Analysis of Primary Efficacy Endpoint: In the overall population (n=187), ORR by a computerized algorithm using investigator and BICR data, showed a high degree of concordance between (1) programmatically derived ORR by investigator vs ORR by BICR and (2) between programmatically derived ORR by BICR versus ORR by BICR.

Figure 9: Applicant – Forest Plot – Objective Response Rate by BICR in Subgroups in Participants Naïve to BCMA-directed Therapy (Cohort A) (Safety Analyses Set) (Study C1071003)



The Applicant's Position:

In pivotal Cohort A, elranatamab administered at the RP2D (b) (4) met the primary endpoint with an ORR of 61.0% (95% CI: 51.8, 69.6) (Table 38). A consistent ORR benefit as assessed by BICR was observed across prespecified subgroups; however, ORR interpretation in some subgroups was limited by small sample size. Although differences in ORR were observed in participants with poor prognostic features, including EMD at baseline, R-ISS Stage III disease, and penta-refractory disease, the ORR in these subgroups was clinically meaningful (Figure 9).

In Cohort B, a clinically meaningful efficacy was observed in a heavily pretreated population (median of 7.5 prior lines of therapy) and met the primary endpoint with an ORR of 34.4% (95% CI: 22.9, 47.3).

The FDA's Assessment:

FDA does not agree (b) (4) FDA's primary efficacy analysis only included the results from the indicated patient population, which included 97 patients in Cohort A who received at least 4 prior lines of therapy including a PI, IMiD,

and an anti-CD38 monoclonal antibody. The analysis results of response rate in the FDA's primary efficacy population are presented in Table 33.

Table 33: FDA – Summary of Best Overall Response by BICR (Participants with ≥4 Prior Lines of Therapy in Cohort A)

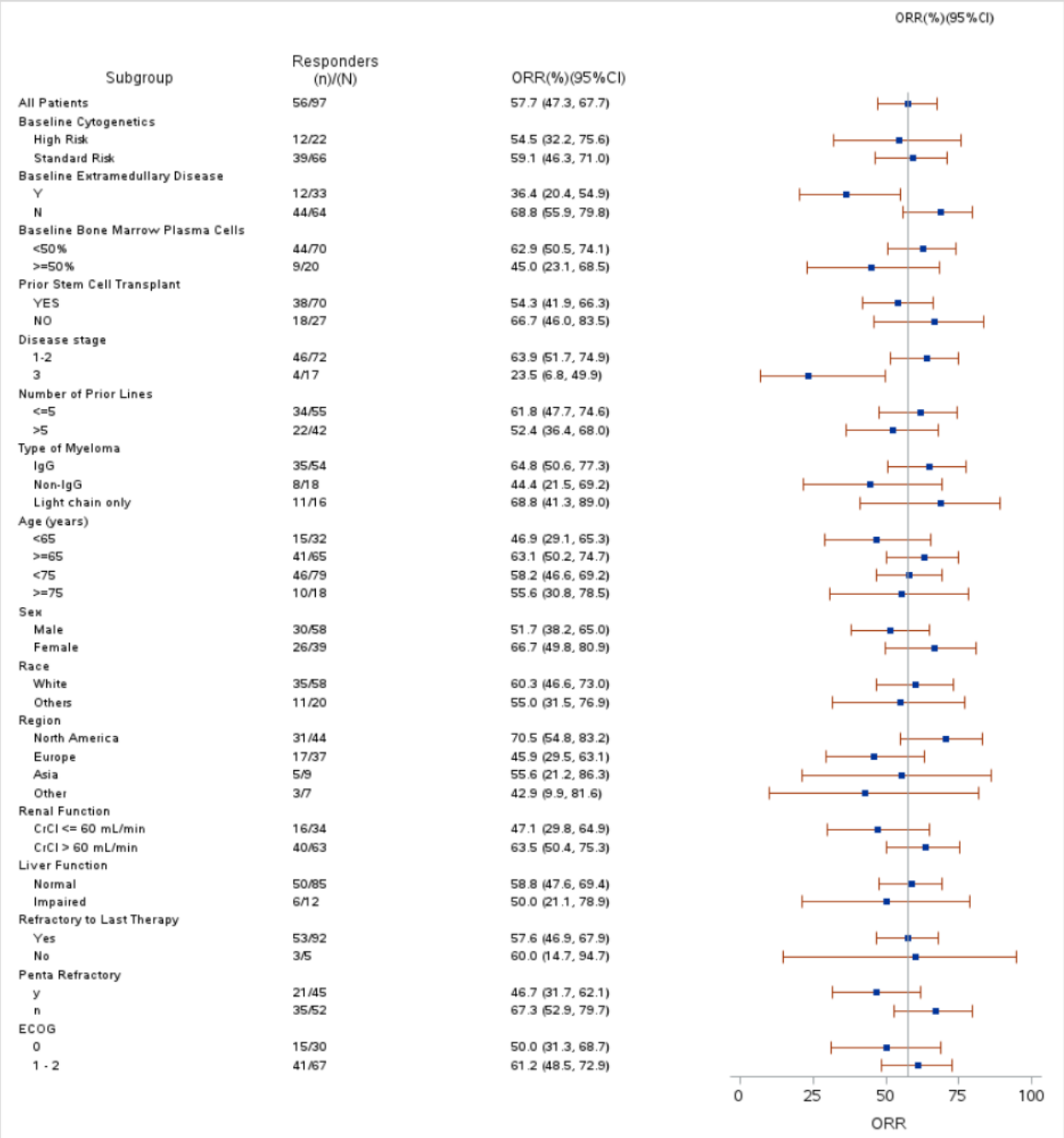
	Cohort A (N=97)
Best Overall Response, n (%)	
Stringent Complete Response (sCR)	12 (12.4)
Complete response (CR)	13 (13.4)
Very Good Partial Response (VGPR)	25 (25.8)
Partial response (PR)	6 (6.2)
Minimal Response (MR)	0 (0)
Stable disease (SD)	18 (18.6)
Progressive disease (PD)	19 (19.6)
Not evaluable (NE)	4 (4.1)
Objective Response (sCR+CR+VGPR+PR) Rate, n (%)	56 (57.7)
95% CI	47.3, 67.7
Complete Response (sCR+CR) Rate, n (%)	25 (25.8)
95% CI	17.4, 35.7
VGPR or Better (sCR+CR+VGPR) Rate, n (%)	50 (51.5)
95% CI	41.2, 61.8
Clinical Benefit (sCR+CR+VGPR+PR+MR) Rate, n (%)	56 (57.7)
95% CI	47.3, 67.7

Source: FDA Reviewer generated from ADRSB dataset

Among participants with ≥4 prior lines of therapy, the confirmed ORR per BICR was 57.7% (95% CI: 47.3, 67.7). There were 51.5% of participants who achieved VGPR or better and 25.8% who achieved CR or better. Among the 64 patients enrolled in Cohort B, 63 patients received at least four prior lines of therapy including a PI, an IMiD, and an anti-CD38 monoclonal antibody. Confirmed ORR by BICR was 33.3% (95% CI: 22.0, 46.3), 6.4% of patients achieved CR, and 31.8% achieved VGPR or better.

The confirmed ORR in Cohort A participants by clinically relevant subgroups is presented in Figure 10. Overall, the results are consistent with the analysis in the primary analysis population. However, the results of some subgroups with small sample sizes were associated with large variability and should be interpreted with caution. For example, the ORR for patients with impaired liver function was 50% (95% CI: 21.1, 78.9), and the ORR for patients who were not refractory to last therapy was 60% (95% CI: 14.7, 94.7). Additionally, FDA also conducted post hoc subgroup analyses including extramedullary disease and geographic region, but no significant results were identified.

Figure 10: FDA – Forest Plot: Objective Response Rate by BICR in Subgroups in Participants with ≥4 prior line therapy (Study C1071003, Cohort A)



Source: FDA Reviewer generated from ADRSB dataset

Data Quality and Integrity

The Applicant's Position:

There were no issues related to data quality and integrity. The sponsor or delegate provided study instruction and monitored the study through routine center visits to ensure the collection of accurate, reliable, and complete data. See Compliance with GCP for Study C1071003.

Impact of COVID-19: Overall, the impact of the COVID-19 pandemic was minimized through the adjustments and mitigations to ensure both participant safety and data integrity. There was minimal impact on conduct of the studies and efficacy analysis measures due to the COVID-19 pandemic.

The FDA's Assessment:

The Agency agrees with the Applicant's position. In general, the data quality of the study appeared acceptable with no data integrity concerns identified for the primary endpoint. The submitted datasets are generally consistent, and variables are clearly labeled and/or explained.

Efficacy Results – Secondary and other relevant endpoints

Data:

Table 34: Applicant – Efficacy Results: Secondary and Other Relevant Endpoints

	Naïve to BCMA-directed therapy (Cohort A)
DOR by BICR (months)	Median not yet reached (95% CI: 12.0, NE); KM probability of maintaining response at 9 months: 84.4% (95% CI: 72.7, 91.4)
TTR by BICR; median (range)	1.22 (0.89, 7.36) months
MRD Negativity Rate[a] in participants achieving CR or sCR and evaluable for MRD (N=22) n (%), 95% CI	20 (90.9) [95% CI: 70.84, 98.88]

a by threshold 10^{-5}, Next Generation Sequencing clonoSEQ assay (Adaptive Biotechnologies).

Figure 11: Applicant – Swimmers Plot – Duration of Response by BICR in Subgroups in Participants Naïve to BCMA-directed Therapy (Cohort A; N=75) (Safety Analyses Set) (Study C1071003)

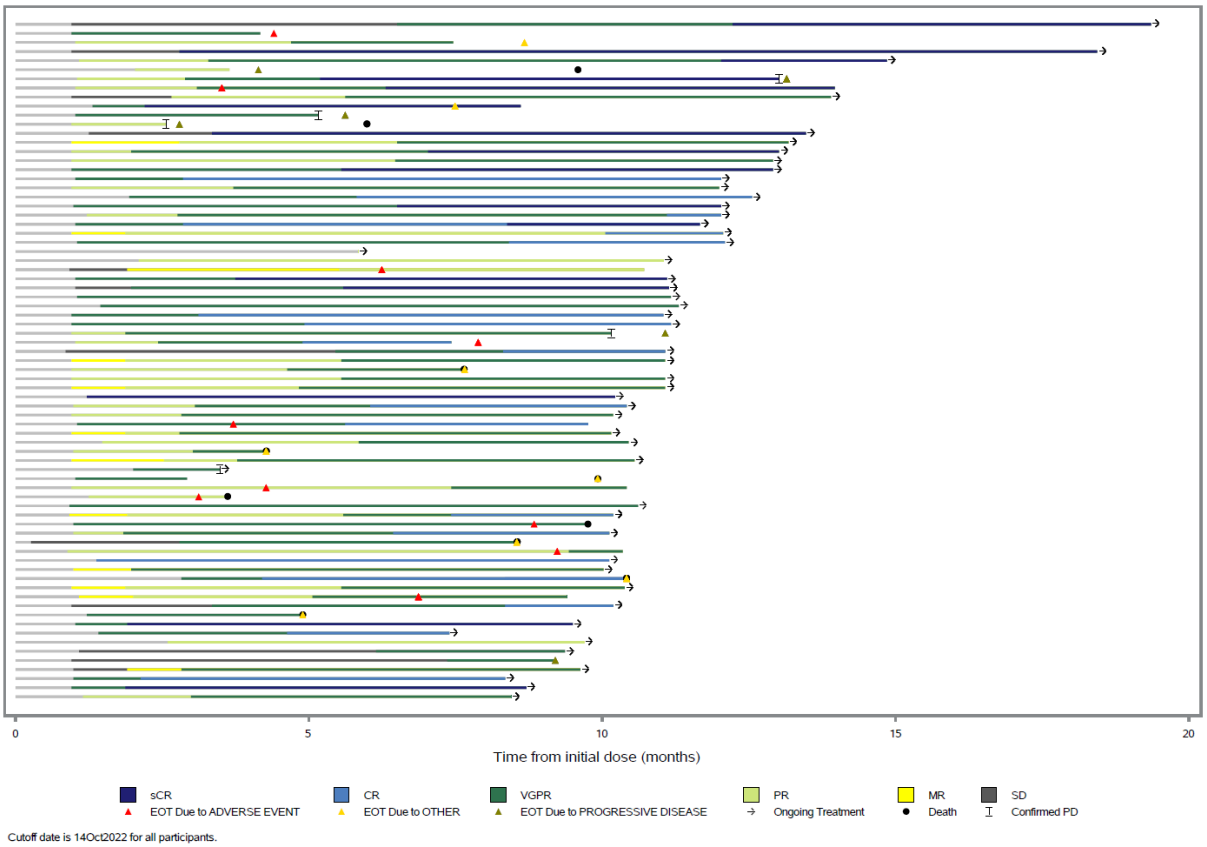
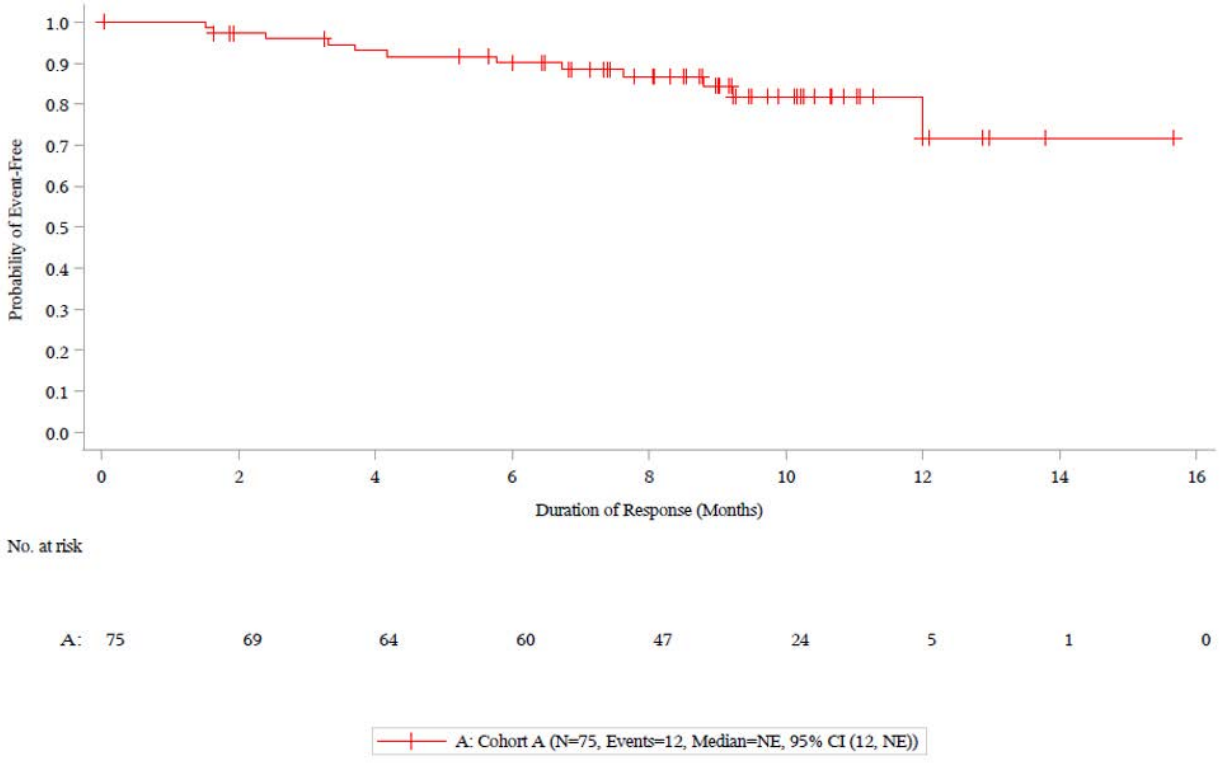


Figure 12: Applicant – Duration of Response by BICR in Participants Naïve to BCMA-directed Therapy (Cohort A) (for Responders Only) – Kaplan Meier Plot (Study C1071003)



Cutoff date is 14OCT2022 for all participants.

In Cohort A, responses deepened over time, the PR, VGPR, CR, sCR over time are shown in Figure 11. At data cutoff, 63/75 responders were still ongoing (Figure 11). After a median (range) follow-up from initial dose of 10.94 (3.61, 20.14) months and from initial response of 9.49 (2.40, 18.53) months for responders, the median DOR (months) by BICR was not yet reached (95% CI: 12.0, NE), and among responders, the Kaplan-Meier probability of maintaining response at 9 months was 84.4% (95% CI: 72.7, 91.4).

In Cohort A, among responders by BICR who switched to Q2W dosing at least 12 weeks prior to the data cutoff (48 participants), 45 (93.8%) maintained/improved their response ≥12 weeks after the switch. One participant (2.1%) lost response (i.e., met PD criteria per IMWG in at least one assessment post-switch) and 2 participants (4.2%) permanently discontinued elranatamab before 12 weeks while in response. Among the 45 participants who maintained/improved response for at least 12 weeks after the switch, 34 (75.6%) maintained their response before and after the switch and 11 (24.4%) improved (deepened) their response after the switch to Q2W dosing.

In Cohort B, after a median (range) follow-up from initial dose of 10.18 (6.41, 12.32) months and from initial response of 8.08 (2.43, 11.10) months for responders, the median DOR (months) by BICR was not yet reached (95% CI: NE, NE), and among responders, the Kaplan-Meier probability of maintaining response at 9 months was 85.1% (95% CI: 60.5, 95.0).

The Applicant's Position:

In Cohort A, elranatamab demonstrated deep and durable responses in participants with an objective response assessed by BICR. The median DOR (months) by BICR was not yet reached (95% CI: 12.0, NE), after a median (range) follow-up from initial response of 9.49 (2.40, 18.53) months. Among responders, the Kaplan-Meier probability of maintaining response at 9 months was 84.4% (95% CI: 72.7, 91.4). The median time to response was 1.22 months. Among participants who achieved CR or better and with a baseline diagnostic clone available, 90.9% achieved MRD-negativity at a sensitivity of 10^{-5}. In participants with PR or better who switched to Q2W, there was a continued benefit after switching to Q2W dosing with the majority of patients maintaining and or deepening their responses after the switch to Q2W dosing.

Similarly, in Cohort B, elranatamab demonstrated deep and durable responses in participants with an objective response assessed by BICR. The median DOR (months) by BICR was not yet reached (95% CI: NE, NE), after a median (range) follow-up from initial response of 8.08 (2.43, 11.10) months. Among responders, the Kaplan-Meier probability of maintaining response at 9 months was 85.1% (95% CI: 60.5, 95.0).

The FDA's Assessment:

FDA was able to reproduce the Applicant's analysis results of secondary endpoints based on the Applicant-defined efficacy population which include 123 participants who were Naïve to BCMA-directed therapy. However, FDA's efficacy assessment population consists of 97 patients based on the indicated population in Cohort A. The results in the efficacy population was generally consistent with the enrolled patient population. Table 35 presents DOR, time to response and MRD negativity rate in participants achieving CR or sCR and evaluable for MRD in Cohort A.

Duration of Response

Among the 56 patients in Cohort A who achieved an BIRC-assessed response, 9 (16.1%) subsequently had disease progression or died. In responders by BICR, after a median (range) follow-up from initial response of 9.22 (3.32, 18.53) months, the median DOR (months) had not been reached (95% CI: 12.0, NE). With a median follow-up of 11.1 months (95% CI: 10.6, 12.0) among responders, the DOR rate at 6 months was 90.4% (95% CI: 78.4%, 95.9%), at 9 months was 82.3% (95% CI: 67.1%, 90.9%), and at 12 months was 68.6% (35.2, 87.3).

For the 21 patients in Cohort B who achieved an BIRC-assessed response, 3 (14.3%) subsequently had disease progression or died. After a median (95% CI) follow-up of 10.2 (9.9, 11.0) months among responders, median DOR was not reached (95% CI: NE, NE) and the DOR rate at 6 and 9 months were both 84.3% (95% CI: 58.7, 94.7). Figure 13 presents Kaplan-Meier plot of BIRC-assessed DOR.

For responders, the Agency has required a minimum follow-up of 9 months. However, among the indicated population, 19 patients in Cohort A were censored with less than 9 months of follow-up due to insufficient follow-up among a total of 47 censored patients, 9 patients in Cohort B were censored with less than 9 months of follow-up due to insufficient follow-up, among a total of 18 censored patients. The early censoring may impact the reliability of the estimate from the DOR analysis.

Time to Response
Among the 56 patients in Cohort A who achieved an BIRC-assessed response, the median (range) time to first response (TTR) was 1.22 (0.89 to 6.51) months.

MRD negativity rate
MRD negative status was a secondary endpoint. MRD results were obtained by Next Generation Sequencing ClonoSEQ assay (Adaptive Biotechnologies). Out of 34 patients with CR/sCR in Cohort A, only 29 had samples that were available. Therefore, there was a high rate of missing data. Of the 29 with samples available, 7 (24%) had calibration failure. As a result, only 22 patients were evaluable for MRD status. The FDA's analysis of MRD negativity rate was based on the indicated efficacy population (N=97). Of these 97 patients, 17 patients with CR/sCR had an evaluable sample, and of these, 16 (94.1%) were MRD negative at a sensitivity of 10^{-5}.

(b) (4)

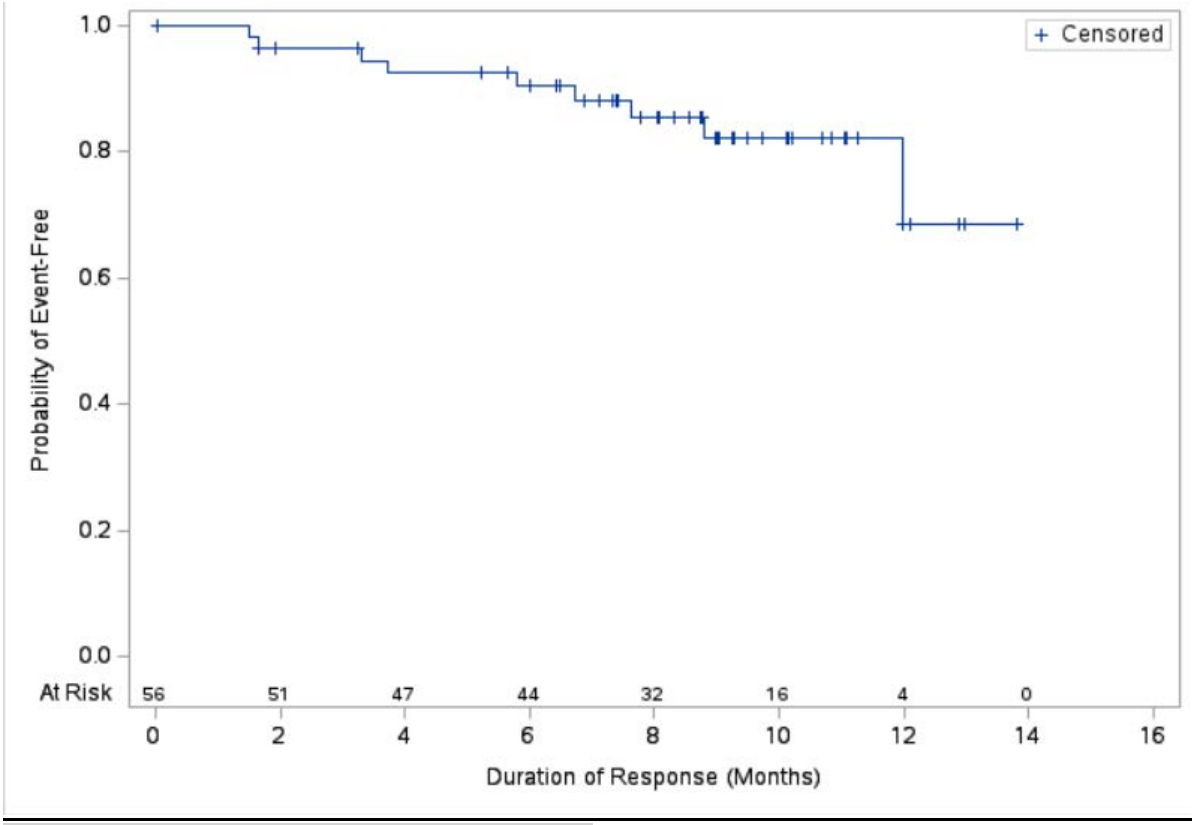
Reference
1. Costa, L. J., Derman, B. A., Bal, S., Sidana, S., Chhabra, S., Silbermann, R., ... & Paiva, B. (2021).International harmonization in performing and reporting minimal residual disease assessment in multiple myeloma trials. *Leukemia*, *35*(1), 18-30.

Table 35: FDA – Efficacy Results: Secondary and Other Relevant Endpoints (Cohort A, Efficacy Population)

Efficacy Parameter	Cohort A (N=97)
Duration of response in all responders	
Patients with response, n (%)	56 (57.7)
Participants with event, n (%)	9 (16.1)
Censored, n (%)	47 (83.9)
Kaplan-Meier estimates of time to event (months)	
Median (95% CI)	NE (12.0, NE)
Duration of Follow-up from Initial Response (months)	
Median (range)	9.22 (3.32, 18.53)
Duration of Follow-up (months)	
Median (95% CI)	11.1 (10.6, 12.0)
K-M event-free proportion, % at: (95% CI)	
at 6 months	90.4 (78.4, 95.9)
at 9 months	82.3 (67.1, 90.9)
at 12 months	68.6 (35.2, 87.3)
Time to Response (TTR) (Months)	
Median (range)	1.22 (0.89, 6.51)
MRD Negativity Rate in participants achieving CR or sCR and evaluable for MRD(N=17)	
n (%)	16 (94.1)
95% CI	71.31, 99.85

Source: FDA Reviewer generated from ADTTEB and ADMRD datasets

Figure 13: FDA – Duration of Response by BICR for Responders Only – Kaplan Meier Plot (Study C1071003, Cohort A, Efficacy Population)



Source: FDA Reviewer generated from ADTTEB dataset

Dose/Dose Response

Data: See Clinical Pharmacology Section 6.2.2 and efficacy and safety data tables in Sections 8.1 and 8.2, respectively.

The Applicant's Position:

Overall, the efficacy, safety, and PD data support the proposed elranatamab dosing regimen for the proposed indication. The recommended dosing regimen for elranatamab is proposed as follows in the USPI: 76 mg QW administered as a SC injection with a 2 step-up priming dose regimen (12 mg on Day 1 and 32 mg on Day 4) administered during the first week of treatment. The dosing interval should be switched to 76 mg Q2W from QW to Q2W for responding patients after 24 weeks.

The FDA's Assessment:

FDA agrees with Applicant's position that proposed dose and schedule of 12/32/76 mg of elranatamab is appropriate for the general patient population for which the indication is being sought. See detailed discussion in section 6.2.2.1.

Durability of Response

Data:

Results are presented in the Study C1071003 Key Secondary Efficacy Endpoint Analysis data table and in Figure 11 and Figure 12.

The Applicant's Position:

See Key Secondary Efficacy Endpoint Analysis Applicant's Position.

The FDA's Assessment:

Refer to FDA's Assessment for Efficacy Results – Secondary and other relevant endpoints.

Persistence of Effect

Data:

Results are presented in the Study C1071003 Key Secondary Efficacy Endpoint Analysis data table.

The Applicant's Position:

See Key Secondary Efficacy Endpoint Analysis Applicant's Position.

The FDA's Assessment:

Refer to FDA's Assessment for Efficacy Results – Secondary and other relevant endpoints

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:

PROs data were collected for assessment of exploratory endpoints with validated questionnaires commonly used to assess quality of life in oncology patients. Cancer-specific global health status and quality of life, functioning, and symptoms data were collected using the EORTC QLQ-C30 and MY20 questionnaires and general health-related quality of life was assessed using the EQ-5D health questionnaire. The EORTC QLQ CIPN20 was used to assess chemotherapy-induced peripheral neuropathy.

Based on the results from Study 1003 Cohort A, treatment with elranatamab was typically associated with a maintenance of health-related quality of life with some dimensions worsening briefly before being restored to baseline levels (eg, global QOL, physical functioning, role functioning, and social functioning from the EORTC QLQ-C30). For other dimensions (eg, pain and insomnia from the EORTC QLQ-C30) a brief period of maintenance was followed by a consistent (particularly in the case of pain) improvement over time.

The Applicant's Position:

PROs demonstrated a maintenance of QOL. In most instances, elranatamab was associated with a maintenance in health-related QOL in Cohort A. For certain domains, there was a transient worsening (eg, global QOL, physical functioning, and fatigue from the QLQ-C30) followed by a restoration to baseline levels. In other domains, there was improvement over time which was maintained (eg, disease symptoms, future perspectives from the QLQ-MY20).

The FDA's Assessment:

The FDA acknowledges the descriptive summary of the PRO outcomes evaluated in Study C1071003 Cohort A. However, to support adequate interpretation, a comparator arm along with a prespecified PRO endpoint and analysis plan are necessary. Additionally, the single-arm, open-label trial design limits the PRO data interpretation since the patient's knowledge of the treatment

regimen may lead to systematic overestimation or underestimation of the treatment effect. Therefore, all PRO results are considered to be exploratory and hypothesis generating.

Additional Analyses Conducted on the Individual Trial

Data: Not applicable

The Applicant's Position: Not applicable

The FDA's Assessment:

FDA conducted additional analyses based on FDA's defined efficacy population, which included the 97 patients in Cohort A who had received at least 4 prior lines of therapy including a PI, IMiD, and an anti-CD38 monoclonal antibody, see section 8.1 Review of Relevant Individual Trials Used to Support Efficacy.

8.1.3 Integrated Review of Effectiveness

The FDA's Assessment:

Refer to the Integrated Assessment of Effectiveness in Section 8.1.5.

8.1.4 Assessment of Efficacy Across Trials

The Applicant's Position:

The overview of efficacy for this submission focuses on the statistically significant and clinically meaningful results from pivotal Study C1071003 Cohort A and supportive Study C1071003 Cohort B that were conducted by the applicant/designee and were sufficient to demonstrate the efficacy of elranatamab in patients with RRMM. Individual studies included in this submission are presented in the Table of Clinical Studies (Table 19).

The FDA's Assessment:

Not applicable.

8.1.5 Integrated Assessment of Effectiveness

The Applicant's Position:

Clinical evidence for elranatamab for the proposed indication is based on efficacy data from Study C1071003 in 123 participants in pivotal Cohort A (naive to BCMA-targeted therapies) and 64 participants in supportive Cohort B (exposed to prior BCMA-targeted therapies), ≥9 months after the last enrolled participant. Efficacy data from this study and accompanying Applicant Positions to support efficacy of elranatamab are provided in the Study C1071003 Efficacy Analyses section. In Study C1071003 Cohort A, elranatamab demonstrated clinically meaningful efficacy, with deep and durable responses.

The FDA's Assessment:

In general, FDA agrees with the Applicant's statement. FDA's efficacy assessment was based on the 97 patients in Cohort A who had received at least 4 prior lines of therapy including a PI, IMiD, and anti-CD38 antibody. The results based on Cohort B were supportive. The FDA did not conduct an integrated assessment across multiple cohorts or studies.

8.2 Review of Safety

The Applicant's Position:

The safety profile of elranatamab was primarily determined from the pooled datasets from 4 ongoing clinical studies (C1071003 [pivotal study], C1071001, C1071002, and C1071009) that enrolled participants with RRMM and specifically evaluated elranatamab monotherapy (see Table 19). Appropriate pooling of safety data across studies provides a more precise estimate of the overall safety profile, safety events that occur infrequently, and the safety profile across subpopulations. The pivotal population for safety came from clinical Study C1071003, that enrolled 2 independent, parallel cohorts: participants who are naïve to BCMA-directed therapy (Cohort A) and participants who have received previous treatment with BCMA-directed therapy (CAR-Ts and/or ADC) (Cohort B). The safety findings were generally consistent between Cohort A and Cohort B and data from both cohorts is included in the pooled safety data.

The safety analyses specifically included: Pool 1 - all participants in ongoing open-label Phase 2 Study C1071003 as of the cutoff date assigned to receive elranatamab monotherapy at the recommended dosing regimen of 12 mg (step-up priming dose 1), 32 mg (step-up priming dose 2) and 76 mg (full dose) (N=183); Pool 2 - all other participants assigned to receive a 76 mg elranatamab monotherapy full dose or equivalent dose calculated on a body weight basis (1000 µg/kg) regardless of step-up priming dose(s) (excluding participants who were to receive the 12 mg/32 mg step-up priming regimen) from ongoing open-label Studies C1071001, C1071002, C1071003, and Part 1 of C1071009 as of the data cutoff dates (N=82); Pool 3 - all participants in Pool 1 + Pool 2 (N=265). This safety population was considered appropriate for the detection and characterization of AEs and other safety endpoints and to provide guidance on toxicity management.

The FDA's Assessment:

The FDA's analysis of safety focused on the entire safety population from Study C1071003 who received the recommended dosing regimen of 12 mg (step-up priming dose one), 32 mg (step-up priming dose two), and 76 mg (full dose) (N=183). This included patients in Cohort A (no prior BCMA-directed therapy) (N=119) and Cohort B (prior BCMA-directed therapy) (N=64). These cohorts were analyzed separately and were also pooled. In addition, the FDA notes that four patients in Cohort A received a different step-up dosing regimen that included a single step-up priming dose of 44 mg, followed by the target dose of 76 mg. These four patients were analyzed both separately and pooled with the overall safety population (N=187).

The FDA's safety analyses were conducted based on the complete datasets provided by the Applicant for Study C1071003 with a data cutoff of October 14, 2022. Safety data from studies C1071001, C1071002, and C1071009 were reviewed and considered supportive for the proposed indication.

8.2.1 Safety Review Approach

The Applicant's Position:

Safety evaluation included review of treatment emergent AEs, SAEs, deaths, permanent treatment discontinuations, dosing interruptions, dose reductions, AESIs (including CRS, ICANS, and peripheral neuropathy [PN]), oAECIs (including infections, cytopenias, hypogammaglobulinemia,

hypersensitivity, injection site reactions, and secondary primary malignancies), clinical laboratory evaluations, QT prolongation, and subgroup analyses. AESIs and oAECIs were identified from key effects in nonclinical and clinical studies with elranatamab and from published data on other members of the therapeutic class (Section 2.2).

The pooled safety population from Studies C1071003, C1071001, C1071002, and C1071009 (Pool 3) was used to characterize the safety profile of elranatamab. Safety data from participants that received the recommended dosing regimen (Pool 1) were used to determine the incidence of adverse reactions, including CRS, neurologic toxicity including ICANS, infections, neutropenia, and hypogammaglobulinemia which are included in the Warnings and Precautions section and which formed the basis for ADR information in the Adverse Reactions Clinical Trials Experience section of the proposed USPI.

Clinical Studies

Studies C1071003, C1071001, C1071002, and C1071009 provided the pooled data used to define the clinical safety profile of elranatamab. Details on Study C1071003 are provided in Section 8.1.1. Further details on Studies C1071001, C1071002, and C1071009 are provided in Section 7.1.

All but 4 of the participants in pivotal Study C1071003 received the recommended dosing regimen of 12 mg (step-up priming dose 1), 32 mg (step-up priming dose 2) and 76 mg (full dose) and comprise Pool 1 (N=183). Pool 2 included participants from Studies C1071003, C1071001, C1071002, and C1071009 who were treated with 1000 µg/kg or 76 mg full dose (N=82) but received no step-up or different step-up priming dosing regimens. Pool 3 includes all participants in Pool 1 and Pool 2 (N=265).

The FDA's Assessment:

See **Section 8.2 Review of Safety** for a description of the FDA's safety review approach. In general, the FDA's approach for the analysis of safety was consistent with the Applicant's and included review of treatment emergent AEs, SAEs, deaths, permanent treatment discontinuations, dosing interruptions, dose reductions/modifications, and adverse events of special interest (AESIs). In addition to the AESIs identified by the Applicant, the FDA also identified hepatotoxicity as an AESI and included this in the Warnings and Precautions section of the USPI. The additional pooled safety analyses listed by the Applicant were considered supportive.

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** Error! Reference source not found. for the full listing of FDA grouped terms).

8.2.2 Review of the Safety Database

Overall Exposure

Data:

Table 36: Applicant – Exposure to Treatment (All Participants as Treated)

	Pool 1 (N=183)[a] (C1071003)	Pool 3 (N=265)[b] (C1071003, C1071001, C1071002, C1071009)
Treatment Duration (months) [1]		
Mean (SD)	5.581 (4.6203)	6.007 (5.2490)
Median (Range: min, max)	4.107 (0.03, 14.85)	4.665 (0.03, 24.41)

Table 36: Applicant – Exposure to Treatment (All Participants as Treated)

	Pool 1 (N=183)[a] (C1071003)	Pool 3 (N=265)[b] (C1071003, C1071001, C1071002, C1071009)
Participants treated for>6 months (n (%))	77 (42.1%)	112 (42.3%)
Participants treated for >12 months (n (%))	17 (9.3%)	34 (12.8%)
Total Cumulative Dose (mg) [2]		
Mean (SD)	1244.4 (961.96)	1290.2 (1060.03)
Median (range)	988.0 (12.0, 4528.0)	1024.0 (12.0, 6863.1)
Overall Relative Dose (%) [3]		
Mean (SD)	77.2 (21.24)	79.2 (20.93)
Median (range)	82.1 (13.4, 100.0)	84.8 (13.4, 107.4)
Overall Relative Dose Intensity (%) [4]		
Mean (SD)	76.0 (21.07)	77.4 (20.66)
Median (range)	81.5 (13.4, 103.7)	83.3 (13.4, 106.0)

a Received recommended dosing regimen of 12 mg (priming dose 1), 32 mg (priming dose 2) and 76 mg (full dose) as of cutoff date.
b All participants treated with 1000 µg/kg or 76 mg full dose regardless of step-up dose(s).
Data cut-off date: C1071001 = 22JUN2022, C1071002 = 27MAY2022, C1071003 = 14OCT2022, C1071009 = 29JUN2022
[1] Treatment duration (months) = (last dose date – first dose date + 1)/30.4375
[2] Total cumulative dose = sum of actual dose levels (mg) of study drug across all cycles.
[3] Overall RD (%) = Total cumulative dose (mg) / Total planned dose (mg) × 100.
[4] Overall RDI (%) = [Overall DI (mg/week) / Overall Planned DI (mg/week)] × 100.
The descriptive summary statistics are calculated based on n, the number of participants who have received at least one dose of study drug.

The Applicant's Position:

The size of the pooled safety database (N=265), which included 183 participants that were assigned to the recommended dosing regimen, and the duration of treatment allowed a reliable safety assessment of the use of elranatamab in participants with RRMM. As anticipated in this patient population, the median treatment duration (4.7 months) was impacted by the early loss of participants due to disease progression, although treatment duration was ≥6 months in 42.3% of participants and ≥12 months in 12.8% of participants.

The FDA's Assessment:

FDA's assessment of treatment exposure was based on the 183 participants from Study C1071003 who were treated in Cohort A (N=119) or Cohort B (N=64) and received the recommended dosing regimen of elranatamab. In general, FDA concurs with the exposure data presented by the Applicant. However, based on FDA's analysis, the median treatment duration for participants in Study C1071003 was 3.9 months (range: 0.03-19.8 months) likely reflecting the refractory nature of the patient population and poor outcomes. The median number of treatment cycles received was 6 (range: 1-22). FDA reviewed but did not independently confirm the exposure or safety results for the Applicant's Pool 3. Additional details of the FDA's analysis of exposure are provided in Table 37.

Table 37: FDA – Summary of Exposure (Study C1071003)

	Cohort A (N=119)	Cohort B (N=64)	Total (N=183)
Treatment Duration (Months)			
Mean (SD)	6.2 (5.05)	4.5 (4.05)	5.6 (4.79)
Median (Min, Max)	4.8 (0.03, 19.8)	2.8 (0.03, 12.1)	3.9 (0.03, 19.8)
Number of Actual Cycles			
Mean (SD)	7.8 (5.48)	5.8 (4.54)	7.1 (5.24)
Median (Min, Max)	8.0 (1, 22)	4.0 (1, 14)	6.0 (1, 22)
Treatment Discontinued			
Yes	70 (58.8)	46 (71.9)	116 (63.4)
Dose Reduction, n (%)			
Yes	36 (30.3)	11 (17.2)	47 (25.7)
Dose Delay, n (%)			
Yes	84 (70.6)	41 (64.1)	125 (68.3)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics Filter: SAFFL = 'Y' COHORT = 'Cohort A' or 'Cohort B'.
Treatment Duration (Months) - Dataset: Exposure Filter: PARAM = 'Treatment Duration (Months)'.
Number of Actual Cycles - Dataset: Exposure; Filter: PARAM = 'Number of Actual Cycles'.
Treatment Discontinued - Dataset: Exposure; Filter: SAFFL = 'Y', PARAM = 'Treatment Discontinued'.
Dose Reduction, n(%) - Dataset: Exposure; Filter: SAFFL = 'Y', PARAM = 'Any Dose Reductions'.
Dose Delay, n(%) - Dataset: Exposure; Filter: SAFFL = 'Y', PARAM = 'Any Dose Delays'.
SD = Standard Deviation.

Source: FDA Analysis

Relevant characteristics of the safety population:

Data:

Table 38: Applicant – Demographic and Baseline Characteristics (All Participants as Treated)

	Pool 1 (N=183) (C1071003)	Pool 3 (N=265) (C1071003, C1071001, C1071002, C1071009)
Age (Years), n (%)		
18-<65	70 (38.3)	110 (41.5)
≥65	113 (61.7)	155 (58.5)
≥75	35 (19.1)	43 (16.2)
Mean (SD)	66.5 (9.36)	65.5 (9.79)
Median (Range)	68.0 (36, 88)	66.0 (36, 89)
Gender, n (%)		
Male	95 (51.9)	136 (51.3)
Female	88 (48.1)	129 (48.7)
Race, n (%)		
White	112 (61.2)	160 (60.4)
Black or African American	11 (6.0)	19 (7.2)
Asian	17 (9.3)	40 (15.1)
Unknown	3 (1.6)	3 (1.1)
Not reported	40 (21.9)	43 (16.2)
ECOG Performance Status, n (%)		
0	64 (35.0)	96 (36.2)
1	109 (59.6)	154 (58.1)
2	10 (5.5)	14 (5.3)
3	0	1 (0.4)

The Applicant's Position:

(b) (4) MM is more common in the African American/Black population than in the white American population. African American/Black participants were underrepresented in the overall safety population (7.2%). However, because of targeted diversity enrollment activities within the US, 12% of participants overall in Study C1071003 enrolled in the US were Black/African American.

The FDA's Assessment:

FDA disagrees (b) (4) FDA notes that, in the overall safety population for Study C1071003 (N=187), there were only 11 (5.9%) Black or African American participants, and only 18 (9.6%) Hispanic or Latino patients. This is lower than the percentage of patients with MM in the U.S. who are Black or African American. While the FDA agrees with the Applicant's statement that 12% of participants enrolled in the US were Black or African American, there were only 9 Black or African American participants enrolled in the United States. Additionally, there were only 7 Hispanic or Latino patients enrolled in the United States. Additional data is needed regarding the clinical benefit of elranatamab in underrepresented patient populations. See **Section 8.1.2** for additional discussion of the baseline demographic characteristics for Study C1071003, including discussion of the related PMR and PMC that will be issued.

Adequacy of the safety database:

Data:

Table 39: Applicant – Duration of Follow-up (All Participants as Treated)

Duration of Follow-up (months)[a]	Pool 1 (N=183) (C1071003)	Pool 3 (N=265) (C1071003, C1071001, C1071002, C1071009)
Median (range)	10.0 (0.2, 15.1)	9.7 (0.2, 24.4)

a Duration (months) = (Date of last contact/alive date – first dose date + 1)/30.4375

The Applicant's Position:

The safety database of 183 participants that received the recommended dosing regimen from pivotal Study C1071003 (Pool 1) with a median follow-up of 10.0 months was considered adequate to characterize common adverse events, support a benefit-risk assessment of elranatamab, and most accurately represents the safety prolife of elranatamab in the target population, especially for adverse reactions such as CRS and ICANS. The overall pooled safety database of 265 participants was used to further characterize and confirm safety findings and to identify adverse reactions that might have occurred at a lower incidence.

The FDA's Assessment:

FDA agrees with the Applicant's presentation of the median duration of follow-up for Study C1071003. The size of the safety database of 183 patients from Study C1071003 who received the recommended dosing regimen of elranatamab with a median follow-up of 10 months (range 0.2, 15.1 months), and the extended safety database, which included a total of 265 patients who received elranatamab monotherapy, is considered adequate based on elranatamab being a product that is intended to treat a life-threatening disease. However, the overall assessment of safety is limited by the single-arm trial design, and there is currently no randomized data available comparing elranatamab to either placebo or standard of care therapy.

8.2.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

No issues were identified regarding data integrity or submission quality that had an effect on the clinical safety review.

The FDA's Assessment:

The quality of the safety data submitted was adequate for substantive primary review. The Applicant provided the full datasets for patients enrolled in Study C1071003.

Categorization of Adverse Event

The Applicant's Position:

All AEs (except CRS and ICANS) were graded by the investigator according to NCI CTCAE and coded using MedDRA. Study C1071001 was graded according to NCI CTCAE version 4.03 and all other studies were graded according to NCI CTCAE version 5.0. The severity of CRS and ICANS was graded according to ASTCT criteria (Lee et al, 2019), except for CRS events in Study C1071001 IV cohorts, which were graded using (Lee et al, 2014), and coded using MedDRA. Adverse events were treatment-emergent unless otherwise specified, and throughout the document the terms AEs and TEAEs may be presented interchangeably. TEAEs were considered treatment-emergent relative to study intervention if the AE start date was during the on-treatment period (including on

the date of first dose) through a minimum of 90 days after the last dose in Studies C1071002, C1071003, and C1071009 and also for Study C1071001 after PA 8 (the period was 28 days after the last dose prior to this amendment) or start of new anti-cancer therapy (whichever occurred first). AEs were collected as specified in the study protocols and regardless of whether or not the AE was considered drug related.

The safety of study treatment was evaluated on the basis of the AEs, SAEs, Deaths, and other clinically significant AEs (including AEs leading to discontinuation and AEs requiring dose interruption and/or reduction), and the frequency and type of AEs by demographic subgroups (age, sex, body weight, race, geographic region) and by baseline disease characteristics (hepatic and renal function).

The following AESIs (including CRS, ICANS, and PN) and oAECIs (including infections, cytopenias, hypogammaglobulinemia, hypersensitivity, injection site reactions, and secondary primary malignancies) were summarized.

The FDA's Assessment:
FDA's evaluation of safety was based on Study C1071003. Adverse events were categorized with the same methods for both Cohorts A and B. All adverse events, with the exception of CRS and ICANS, were graded according to NCI CTCAE version 5.0. CRS and ICANS were graded according to ASTCT criteria (Lee at all, 2019). In addition to the AESIs listed by the Applicant, the FDA also identified hepatotoxicity as an AESI. FDA considers all TEAEs regardless of investigator attribution. 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).

Routine Clinical Tests

The Applicant's Position:
Standard clinical laboratory parameters were assessed at baseline and throughout the studies as per protocol. Hematology and clinical chemistry data were from local laboratories, and laboratory data were classified into severity grades according to CTCAE v5.0 (as applicable).

For hematology and clinical chemistry parameters, changes from baseline, the worst on-treatment toxicity grade, and shifts from baseline to worst value on study (from treatment start to 90 days after last dose or the start of subsequent anti-cancer therapy, whichever was earlier) were analyzed. Quantitative immunoglobulin data were also analyzed in Study C1071003.

Other safety parameters included physical examination, vital signs, ECG, and immunogenicity.

The assessment methods and time points for collection and analysis of safety measures other than AEs were appropriate for the disease and indication investigated.

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:

Table 40: Applicant – Summary of Death (All Participants as Treated)

Number (%) of Participants	Pool 1 (N=183) (C1071003)	Pool 3 (N=265) (C1071003, C1071001, C1071002, C1071009)
Death	73 (39.9)	96 (36.2)
Cause of Death		
Disease Under Study	53 (29.0)	65 (24.5)
Study Treatment Toxicity	3 (1.6)	4 (1.5)
Other	11 (6.0)	17 (6.4)
Unknown	6 (3.3)	10 (3.8)
Death Within 90 Days After Last Dose of Study Drug	47 (25.7)	65 (24.5)
Cause of Death		
Disease Under Study	32 (17.5)	43 (16.2)
Study Treatment Toxicity	3 (1.6)	4 (1.5)
Other	10 (5.5)	14 (5.3)
Unknown	2 (1.1)	4 (1.5)
Death Within 28 Days After First Dose of Study Drug	10 (5.5)	10 (3.8)
Cause of Death		
Disease Under Study	9 (4.9)	9 (3.4)
Other	1 (0.5)	1 (0.4)

Table 41: Applicant – Summary of TEAEs Leading to Death by MedDRA System Organ Class and Preferred Term (All Causalities) (All Participants as Treated)

Number (%) of Participants	Pool 1 (N=183) (C1071003)	Pool 3 (N=265) (C1071003, C1071001, C1071002, C1071009)
With Any Adverse Event	37 (20.2)	50 (18.9)
CARDIAC DISORDERS	3 (1.6)	3 (1.1)
Cardio-respiratory arrest	1 (0.5)	1 (0.4)
Cardiogenic shock	1 (0.5)	1 (0.4)
Cardiopulmonary failure	1 (0.5)	1 (0.4)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	10 (5.5)	18 (6.8)
Disease progression	10 (5.5)	16 (6.0)
Death	0	1 (0.4)
Sudden death	0	1 (0.4)
INFECTIONS AND INFESTATIONS	12 (6.6)	15 (5.7)
COVID-19 pneumonia	4 (2.2)	4 (1.5)
Septic shock	4 (2.2)	4 (1.5)
Adenovirus infection	1 (0.5)	2 (0.8)
COVID-19	1 (0.5)	2 (0.8)
Sepsis	1 (0.5)	2 (0.8)
Pneumonia adenoviral	1 (0.5)	1 (0.4)
Pneumonia pseudomonal	1 (0.5)	1 (0.4)

Table 41: Applicant – Summary of TEAEs Leading to Death by MedDRA System Organ Class and Preferred Term (All Causalities) (All Participants as Treated)

Number (%) of Participants	Pool 1 (N=183) (C1071003)	Pool 3 (N=265) (C1071003, C1071001, C1071002, C1071009)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	1 (0.4)
Fall	0	1 (0.4)
METABOLISM AND NUTRITION DISORDERS		
Failure to thrive	1 (0.5)	1 (0.4)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	9 (4.9)	10 (3.8)
Plasma cell myeloma	6 (3.3)	7 (2.6)
Metastases to meninges	1 (0.5)	1 (0.4)
Neoplasm progression	1 (0.5)	1 (0.4)
Plasma cell myeloma refractory	1 (0.5)	1 (0.4)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (1.1)	2 (0.8)
Acute respiratory distress syndrome	1 (0.5)	1 (0.4)
Pulmonary embolism	1 (0.5)	1 (0.4)

Participants are only counted once per event.
Summaries are ordered by alphabetical order for SOC and by descending order for PT in Pool 3 column.

The Applicant's Position:

The most common cause of death in study participants was the disease under study, which is not unanticipated for this patient population. The most common Grade 5 AEs were also related to disease progression (disease progression, plasma cell myeloma, metastases to meninges, neoplasm progression, plasma cell myeloma refractory) and the majority of non-disease progression Grade 5 AEs were due to infections. All other AEs leading to death were reported in one participant each across multiple SOCs. Infection has been identified as an AE of clinical interest and is discussed further in Section 8.2.5.

The FDA's Assessment:

FDA verified the data above based on datasets submitted by the Applicant and concurs that as of the October 14, 2022, data cutoff, a total of 73 deaths (39.9%) occurred within the primary safety population, including 32 deaths (17.5%) within 30 days of the last dose of elranatamab. Overall, a higher percentage of patients who had received prior BCMA-directed therapy (Cohort B) died (Cohort B: 46.9%; Cohort A: 36.1%), with the majority of deaths due to progressive disease in both cohorts.

FDA does not agree with the cause of death presented by the Applicant for all cases. FDA adjudication of deaths within 30 days identified 7 additional deaths due to TEAEs, for a total of 22 deaths (12.0%) due to progressive disease and 9 deaths (4.9%) due to adverse events (Table 42). Specifically, FDA does not agree with the categorization of the deaths as "Other" in patients (b) (6), because all deaths due to TEAEs that occur within

30 days of the last dose of study treatment should be considered. Based on review of the patient narratives, the deaths due to progressive disease in patients (b) (6) were adjudicated as deaths due to adverse events.

Table 42: FDA – Adjudication of Deaths within 30 Days (Study C1071003 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
	PROGRESSIVE DISEASE	Y	PROGRESSIVE DISEASE
	ADVERSE EVENT	Y	ADVERSE EVENT (Pneumonia)
	UNKNOWN	Y	UNKNOWN
	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	N	ADVERSE EVENT (Septic Shock)
	PROGRESSIVE DISEASE	N	ADVERSE EVENT (Sepsis)
	PROGRESSIVE DISEASE	Y	PROGRESSIVE DISEASE
	PROGRESSIVE DISEASE	Y	PROGRESSIVE DISEASE
	PROGRESSIVE DISEASE	Y	PROGRESSIVE DISEASE
	OTHER	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
	OTHER	N	ADVERSE EVENT (Pulmonary embolism)
	OTHER	N	ADVERSE EVENT (Septic shock)
	UNKNOWN	Y	PROGRESSIVE DISEASE
	PROGRESSIVE DISEASE	N	ADVERSE EVENT (fungal pneumonia)
	OTHER	N	ADVERSE EVENT (Adenovirus infection)
	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	N	ADVERSE EVENT (Cardiogenic shock)

Source: FDA Reviewer's analysis [ADAE and ADSL datasets and C1071003 patient narratives]

FDA's analysis of fatal TEAEs included all patients included in the overall safety population for Study C1071003 (N=183) and utilized FDA's Grouped Terms (**Appendix 19.6**) Overall, 37 patients (20.2%) died due to fatal adverse events. Of these, 19 (10.4%) died from disease progression, which was coded as an adverse event. Based on FDA's analysis, fatal adverse reactions (excluding

disease progression) occurred in 18 patients (9.8%). Fatal adverse reactions reported in the USPI (based on events that occurred within 30 days of last dose of elranatamab) will include pneumonia (3.3%), sepsis (2.7%), acute respiratory distress syndrome (0.5%), cardio-respiratory arrest (0.5%), cardiogenic shock (0.5%), cardiopulmonary failure (0.5%), COVID-19 (0.5%), failure to thrive (0.5%), and pulmonary embolism (0.5%). FDA's summary of fatal TEAEs in the overall safety population is provided in Table 43.

Table 43: FDA – Fatal Treatment Emergent Adverse Events (Study C1071003, Safety Population)

	Cohort A N = 119 n(%)	Cohort B N = 64 n(%)	Total N = 183 n(%)
Death due to AE	21 (17.6)	16 (25.0)	37 (20.2)
Disease Progression	6 (5.0)	4 (6.3)	10 (5.5)
Neoplasms Benign, Malignant, and Unspecified SOC*	5 (4.2)	4 (6.3)	9 (4.9)
Pneumonia (GT)	3 (2.5)	3 (4.7)	6 (3.3)
Sepsis (GT)	2 (1.7)	3 (4.7)	5 (2.7)
Cardio-respiratory arrest	1 (0.8)	0 (0)	1 (0.5)
Cardiopulmonary failure	1 (0.8)	0 (0)	1 (0.5)
Adenovirus infection	1 (0.8)	0 (0)	1 (0.5)
Failure to thrive	1 (0.8)	0 (0)	1 (0.5)
Acute Respiratory Distress Syndrome	1 (0.8)	0 (0)	1 (0.5)
COVID-19	1 (0.8)	0 (0)	1 (0.5)
Pulmonary embolism	0 (0)	1 (1.6)	1 (0.5)

** Includes PTs: Plasma cell myeloma, metastases to meninges, neoplasm progression, plasma cell refractory*
Source: FDA Analysis; ADAE dataset

Serious Adverse Events

Data:

Table 44: Applicant – Summary of Most Common Treatment-Emergent SAEs (≥5% in any group) by MedDRA Preferred Term (All Causalities) (All Participants as Treated)

Number (%) of Participants	Pool 1 (N=183) (C1071003)	Pool 3 (N=265) (C1071003, C1071001, C1071002, C1071009)
With Any SAE	125 (68.3)	183 (69.1)
Cytokine release syndrome	23 (12.6)	42 (15.8)
COVID-19 pneumonia	22 (12.0)	22 (8.3)
Pneumonia	12 (6.6)	20 (7.5)
Disease progression	10 (5.5)	16 (6.0)

Participants are only counted once per event. Includes data from the first dose of study intervention through the minimum of [90 days after last dose, or (start day of new anticancer therapy – 1 day)].
Summaries are ordered by descending order for PT in Pool 3 column.

The Applicant's Position:

In general, the most common SAEs were associated with identified risks for elranatamab including CRS and infections or were due to disease progression. Other SAEs occurred across multiple SOCs with no obvious pattern. SAEs related to disease progression were reported in 10.2% of participants (Disease progression, Plasma cell myeloma, Metastases to meninges, Neoplasm

progression, Plasma cell myeloma refractory, and Plasmacytoma) and are not unexpected in this patient population.

The FDA's Assessment:

FDA analysis of SAEs was based on FDA's grouped terms (See **Appendix 19.6**) and included analysis of SAEs that occurred in Cohorts A and B independently, as well as in the entire safety population. Overall, 68% of patients experienced a SAE, and there was no significant difference in the incidence of SAEs that occurred in Cohort A (68%) and Cohort B (69%). Based on FDA's analysis, the most frequent SAEs included pneumonia (25%), sepsis (13%), and cytokine release syndrome (13%). Serious TEAEs that occurred in >2% of patients are shown in Table 45. This information will be included in Section 6.1 of the USPI. FDA agrees with the Applicant's statement that, in general, the most common SAEs were associated with identified risks for elranatamab.

Table 45: FDA – Serious Adverse Events in >2% (Study C1071003, Safety Population)

SOC/Preferred/Grouped Terms	Cohort A N = 119 n(%)	Cohort B N = 64 n(%)	Total N = 183 n(%)
Any SAE	81 (68)	44 (69)	125 (68)
Infections and Infestations			
Pneumonia (GT)	33 (28)	12 (19)	45 (25)
Sepsis (GT)	18 (15)	6 (9.4)	24 (13)
Upper Respiratory Tract Infection (GT)	6 (5.0)	2 (3.1)	8 (4.4)
Urinary Tract Infection (GT)	4 (3.4)	2 (3.1)	6 (3.3)
Immune System Disorders			
Cytokine Release Syndrome	16 (13)	7 (11)	23 (13)
Nervous System Disorders			
Encephalopathy (GT)	3 (2.5)	3 (4.7)	6 (3.3)
Renal and Urinary Disorders			
Acute Kidney Injury (GT)	5 (4.2)	2 (3.1)	7 (3.8)
General Disorders and Administration Site Conditions			
Pyrexia	3 (2.5)	1 (1.6)	4 (2.2)

Source: FDA Analysis

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

Table 46: Applicant – Disposition Events Summary – Treatment (All Participants as Treated)

Number (%) of Participants	Pool 1 (N=183) (C1071003)	Pool 3 (N=265) (C1071003, C1071001, C1071002, C1071009)
Participants Entered Treatment:	183 (100.0)	265 (100.0)
Discontinued	115 (62.8)	165 (62.3)
Adverse event	17 (9.3)	24 (9.1)
Death	16 (8.7)	20 (7.5)
Lack of efficacy	4 (2.2)	5 (1.9)
Physician's decision	0	2 (0.8)
Progressive disease	70 (38.3)	98 (37.0)

Table 46: Applicant – Disposition Events Summary – Treatment (All Participants as Treated)

Number (%) of Participants	Pool 1 (N=183) (C1071003)	Pool 3 (N=265) (C1071003, C1071001, C1071002, C1071009)
Refused further treatment	0	2 (0.8)
Refused further study procedures	1 (0.5)	1 (0.4)
Withdrawal by subject	7 (3.8)	13 (4.9)
Ongoing	68 (37.2)	100 (37.7)

Table 47: Applicant – Summary of TEAEs Leading to Permanent Discontinuation of Study Drug (>1% in any group) by MedDRA Preferred Term (All Causalities) (All Participants as Treated)

Number (%) of Participants	Pool 1 (N=183) (C1071003)	Pool 3 (N=265) (C1071003, C1071001, C1071002, C1071009)
With Any Adverse Event	31 (16.9)	41 (15.5)
COVID-19	3 (1.6)	4 (1.5)
Septic shock	4 (2.2)	4 (1.5)
Disease progression	2 (1.1)	3 (1.1)
Neutropenia	2 (1.1)	3 (1.1)
Sepsis	2 (1.1)	3 (1.1)
Immune effector cell-associated neurotoxicity syndrome	2 (1.1)	2 (0.8)

Participants are only counted once per event. Includes data from the first dose of study intervention through the minimum of [90 days after last dose, or (start day of new anticancer therapy – 1 day)]. Summaries are ordered by descending order for PT in Pool 3 column and then by alphabetical order for same percentages.

The Applicant's Position:

The most common AEs leading to discontinuation of study drug were Infections. Other less frequent causes were Neutropenia and Disease progression. Otherwise, there was no consistent trend in AEs leading to permanent discontinuation of study drug, with the majority of AEs occurring in 1 participant each.

The FDA's Assessment:

FDA agrees with the Applicant's presentation of the patient disposition for the safety population in Study C1071003. Based on the data cutoff date of October 14, 2022, in the overall safety population, 115 patients (63%) discontinued treatment while 68 (37%) remained on treatment. FDA's analysis of TEAEs leading to treatment discontinuation was based on the ADAE dataset utilizing the AEACN variable of "drug withdrawn", as well as the FDA's Grouped Terms (**Appendix 19.6**). Of note, events of "COVID-19 Pneumonia" were grouped under "Pneumonia". Based on FDA analysis, a total of 32 patients (27%) in the safety population had treatment withdrawn due to an adverse event. The most common TEAEs leading to treatment discontinuation were sepsis (3.8%) and pneumonia (3.3%). FDA agrees with the Applicant's statement that there was no consistent trend in AEs leading to permanent discontinuation of study drug. FDA's analysis of TEAEs leading to treatment discontinuation in >1% of patients is presented in Table 48 below.

Table 48: FDA – TEAEs Leading to Treatment Discontinuation in >1% (Study C1071003, Safety Population)

	Cohort A N = 119 n(%)	Cohort B N = 64 n(%)	Total N = 183 n(%)
TEAE Leading to Treatment Discontinuation	19 (16)	13 (20)	32 (27)
Sepsis (GT)	5 (4.2)	2 (3.1)	7 (3.8)
Pneumonia (GT)	4 (3.4)	2 (3.1)	6 (3.3)
Disease Progression	0 (0)	2 (3.1)	2 (1.1)
Immune effector cell-associated neurotoxicity syndrome	0 (0)	2 (3.1)	2 (1.1)
Neutropenia	2 (1.7)	0 (0)	2 (1.1)
Pulmonary embolism	0 (0)	1 (1.6)	1 (0.5)

Source: FDA Analysis

Dose Interruption/Reduction Due to Adverse Effects

Data:

Table 49: Applicant – Summary of TEAEs Leading to Dose Interruption (>2% in any group) by MedDRA PT (All Causalities) (All Participants as Treated)

Number (%) of Participants by PT	Pool 1 (N=183) (C1071003)	Pool 3 (N=265) (C1071003, C1071001, C1071002, C1071009)
With Any Adverse Event	134 (73.2)	194 (73.2)
Neutropenia	53 (29.0)	86 (32.5)
COVID-19	37 (20.2)	40 (15.1)
Anaemia	11 (6.0)	19 (7.2)
Pneumonia	11 (6.0)	19 (7.2)
Thrombocytopenia	12 (6.6)	18 (6.8)
Sinusitis	9 (4.9)	16 (6.0)
Upper respiratory tract infection	14 (7.7)	16 (6.0)
Cytokine release syndrome	6 (3.3)	11 (4.2)
Pyrexia	7 (3.8)	11 (4.2)
Diarrhoea	4 (2.2)	10 (3.8)
Fatigue	5 (2.7)	10 (3.8)
Sinusitis	9 (4.9)	10 (3.8)
Leukopenia	7 (3.8)	9 (3.4)
Pneumocystis jirovecii pneumonia	7 (3.8)	9 (3.4)
Decreased appetite	6 (3.3)	8 (3.0)
Febrile neutropenia	3 (1.6)	8 (3.0)
Asthenia	6 (3.3)	7 (2.6)
Cough	4 (2.2)	6 (2.3)
Urinary tract infection	5 (2.7)	6 (2.3)
Bronchitis	5 (2.7)	5 (1.9)
Aspartate aminotransferase increased	4 (2.2)	4 (1.5)

Table 49: Applicant – Summary of TEAEs Leading to Dose Interruption (>2% in any group) by MedDRA PT (All Causalities) (All Participants as Treated)

Number (%) of Participants by PT	Pool 1 (N=183) (C1071003)	Pool 3 (N=265) (C1071003, C1071001, C1071002, C1071009)
Peripheral sensory neuropathy	4 (2.2)	4 (1.5)
Pneumonia bacterial	4 (2.2)	4 (1.5)

Participants are only counted once per event. Includes data from the first dose of study intervention through the minimum of [90 days after last dose, or (start day of new anticancer therapy – 1 day)]. Summaries are ordered by descending order for PT in Pool 3 column and then by alphabetical order for same percentages.

Table 50: Applicant – Summary of TEAEs Leading to Dose Reduction (>2% in any group) by MedDRA PT (All Causalities) (All Participants as Treated)

Number (%) of Participants by PT	Pool 1 (N=183) (C1071003)	Pool 3 (N=265) (C1071003, C1071001, C1071002, C1071009)
With Any Adverse Event	39 (21.3)	67 (25.3)
Neutropenia	19 (10.4)	37 (14.0)
Cytokine release syndrome	4 (2.2)	5 (1.9)
Asthenia	4 (2.2)	4 (1.5)

Participants are only counted once per event. Summaries are ordered by descending order for PT in Pool 3 column.

The Applicant's Position:

The most common AEs leading to dose interruptions were infections and cytopenias. Therefore, additional analyses were conducted to further characterized these events. In participants with interruption of elranatamab due to an infection, 82.9% of participants received a subsequent dose and 93.7% of these were able to continue receiving elranatamab. In participants with interruption of elranatamab due to a cytopenia, 87.3% of participants received a subsequent dose and 98.2% of these were able to continue receiving elranatamab treatment. The majority of participants that did not receive a subsequent dose of elranatamab following interruption due to an infection or a cytopenia discontinued study drug due to disease progression or death; some had a status of study drug still interrupted at the time of the data cut-off.

Neutropenia was the most frequent AE leading to temporary or permanent dose reduction of elranatamab, accounting for ~50% (19/39) of participants with reductions. Other AEs infrequently led to dose reduction. Following dose reduction, 38.5% of participants resumed dosing at 76 mg elranatamab. In addition, the median overall relative dose was 84.8%.

The FDA's Assessment:

FDA's analysis of TEAEs leading to dose interruption was based on the AEACN variable in the ADAE dataset as well as FDA's Grouped Terms (**Appendix 19.6**). FDA agrees that dose interruptions due to a TEAE occurred in 73% of patients in the safety population. Adverse reactions which resulted in dose interruptions of elranatamab in >5% of patients included neutropenia (29%), pneumonia (21%), COVID-19 (18%), upper respiratory tract infection (16%), thrombocytopenia (5%), and anemia (5%). The list of adverse reactions which resulted in dose interruptions in >5% of patients will be included in Section 6.1 of the USPI.

A total of 35 patients (19%) had dose reductions due to a TEAE. The most common TEAE leading to dose reduction was neutropenia (9.8%).

Significant Adverse Events

Data: Not applicable.

The Applicant's Position: Adverse events leading to discontinuation and dose interruptions/reductions are presented in Table 49, Table 50, and Table 52.

The FDA's Assessment:

FDA does not agree that this section is not applicable. Overall, 71% of participants treated with the recommended dosing regimen experienced at least one Grade 3-4 adverse event. The most common Grade 3-4 adverse events were pneumonia (20%) and sepsis (11%). Cytopenias were also common adverse events. However, laboratory abnormalities will be based on the laboratory dataset, as laboratory abnormalities may be underreported as TEAEs. See **Laboratory Findings** below for additional information. An overview of the Grade 3-4 adverse events that occurred in >2% of patients in the safety population for Study C1071003 is provided in Table 51. (b) (4)

Additionally, FDA notes that the Table numbers referenced in the Applicant's section above are incorrect.

Table 51: FDA – Grade 3-4 Adverse Events in >2% (Safety Population, Study C1071003)

Preferred Term	Cohort A N = 119 n(%)	Cohort B N = 64 n(%)	Total N = 183 n(%)
Any Grade 3-4 TEAE	88 (74)	42 (66)	130 (71)
Pneumonia (GT)	25 (21)	12 (19)	37 (20)
Sepsis (GT)	15 (13)	6 (9.4)	21 (11)
Hypertension	7 (5.9)	5 (7.8)	12 (6.6)
Fatigue (GT)	8 (6.7)	1 (1.6)	9 (4.9)
Upper respiratory tract infection (GT)	5 (4.2)	3 (4.7)	8 (4.4)
Urinary tract infection (GT)	6 (5.0)	2 (3.1)	8 (4.4)
Dyspnea (GT)	2 (1.7)	4 (6.2)	6 (3.3)
Pyrexia	4 (3.4)	1 (1.6)	5 (2.7)
Musculoskeletal pain (GT)	4 (3.4)	1 (1.6)	5 (2.7)
Encephalopathy (GT)	3 (2.5)	2 (3.1)	5 (2.7)
Motor dysfunction (GT)	1 (0.8)	4 (6.2)	5 (2.7)
Cardiac arrhythmia (GT)	2 (1.7)	2 (3.1)	4 (2.2)

Source: FDA Analysis, ADAE dataset

Treatment Emergent Adverse Events and Adverse Reactions

Data: All study participants had a least 1 AE.

Table 52: Applicant – Overview of Treatment-Emergent Adverse Events (All Causalities) (All the Participants as Treated)

	Pool 1 (N=183) (C1071003)	Pool 3 (N=265) (C1071003, C1071001, C1071002, C1071009)
Participants Evaluable for AEs	183	265
Number of AEs	2710	4149
Participants with AEs	183 (100.0)	265 (100.0)
Participants with SAEs	125 (68.3)	183 (69.1)

Table 52: Applicant – Overview of Treatment-Emergent Adverse Events (All Causalities) (All the Participants as Treated)

	Pool 1 (N=183) (C1071003)	Pool 3 (N=265) (C1071003, C1071001, C1071002, C1071009)
Participants with Maximum Grade 3 or 4 AEs	130 (71.0)	191 (72.1)
Participants with Maximum Grade 5 AEs	37 (20.2)	50 (18.9)
Participants with AESI CRS	106 (57.9)	170 (64.2)
Participants with AESI ICANS	6 (3.3)	16 (6.0)
Participants with AESI PN	35 (19.1)	53 (20.0)

Includes data from first dose of study intervention through minimum of [90 days after last dose, or (start day of new anticancer therapy – 1 day)]. Except for Number of Adverse Events Participants are counted only once in each row. Serious Adverse Events - according to investigator's assessment.

Table 53: Applicant – Summary of Most Common (≥10%) Adverse Reactions by MedDRA SOC and Preferred Term (All Causalities) (All Participants as Treated)

System Organ Class Preferred Term	Pool 1 (N=183)	
	All Grades (%)	Grade 3 or 4 (%)
Immune system disorders		
Cytokine release syndrome	106 (57.9)	1 (0.5)
Hypogammaglobulinemia[1]	24 (13.1)	4 (2.2)
General disorders and site administration conditions		
Fatigue[2]	78 (42.6)	10 (5.5)
Injection site reaction[3]	68 (37.2)	0
Pyrexia	39 (21.3)	5 (2.7)
Peripheral edema[4]	22 (12.0)	2 (1.1)
Gastrointestinal disorders		
Diarrhea	65 (35.5)	2 (1.1)
Nausea	39 (21.3)	0
Constipation	26 (14.2)	0
Vomiting	26 (14.2)	0
Infections		
Upper respiratory tract infection[5]	63 (34.4)	9 (4.9)
Pneumonia[6]	58 (31.7)	35 (19.1)
Sepsis[7]	28 (15.3)	20 (10.9)
Urinary tract infection[8]	22 (12.0)	8 (4.4)
Metabolism and nutrition disorders		
Decreased appetite	48 (26.2)	2 (1.1)
Respiratory, thoracic and mediastinal disorders		
Cough[9]	44 (24.0)	0
Dyspnea[10]	29 (15.8)	7 (3.8)
Musculoskeletal and connective tissue disorders		
Arthralgia[11]	40 (21.9)	2 (1.1)
Skin and Subcutaneous Tissue disorders		
Rash[12]	47 (25.7)	0
Dry Skin[13]	38 (20.8)	0
Nervous system disorders		
Headache	33 (18.0)	0

Table 53: Applicant – Summary of Most Common (≥10%) Adverse Reactions by MedDRA SOC and Preferred Term (All Causalities) (All Participants as Treated)

System Organ Class Preferred Term	Pool 1 (N=183)	
	All Grades (%)	Grade 3 or 4 (%)
Peripheral neuropathy[14]	25 (13.7)	2 (1.1)
Encephalopathy[15]	24 (13.1)	3 (1.6)
Motor dysfunction[16]	23 (12.6)	0
Psychiatric disorders		
Insomnia	24 (13.1)	0
Injury, poisoning and procedural complications		
Fall	19 (10.4)	1 (0.5)

* Excludes 4 patients that did not receive the recommended initial two step-up doses.

1. Hypogammaglobulinemia includes blood immunoglobulin G decreased, hypogammaglobulinaemia, and immunoglobulins decreased.
2. Fatigue includes asthenia, fatigue, malaise.
3. Injection site reaction includes injection site reaction, injection site erythema, injection site inflammation, injection site pruritus, injection site rash, injection site induration, injection site pain, injection site urticaria, injection site dryness, injection site haemorrhage.
4. Peripheral edema includes oedema peripheral, peripheral swelling.
5. Upper respiratory tract infection includes upper respiratory tract infection, sinusitis, acute sinusitis, pharyngitis, rhinitis, rhinovirus infection, viral upper respiratory tract infection, bronchitis viral, chronic sinusitis, nasopharyngitis, sinusitis bacterial, bronchitis, respiratory tract infection viral.
6. Pneumonia includes pneumonia, COVID-19 pneumonia, bronchopulmonary aspergillosis, lower respiratory tract infection, pneumocystis jirovecii pneumonia, pneumonia adenoviral, pneumonia bacterial, pneumonia cytomegaloviral, pneumonia fungal, pneumonia viral, pneumonia influenzal, pneumonia pseudomonal.
7. Sepsis includes sepsis, bacteraemia, device related bacteraemia, device related sepsis, escherichia bacteraemia, escherichia sepsis, klebsiella sepsis, pseudomonal sepsis, septic shock, staphylococcal bacteraemia, staphylococcal sepsis, streptococcal sepsis, urosepsis
8. Urinary tract infection includes urinary tract infection, cystitis, urinary tract infection bacterial, escherichia urinary tract infection, urinary tract infection enterococcal.
9. Cough includes cough, productive cough, upper-airway cough syndrome.
10. Dyspnea includes dyspnoea, dyspnoea exertional, respiratory distress.
11. Arthralgia includes arthralgia, pain in extremity.
12 Rash incudes rash, rash maculo-papular, rash macular, rash erythematous, rash pustular, erythema, dermatitis exfoliative, dermatitis exfoliative generalized, palmar-plantar erythrodysaesthesia syndrome, symmetrical drug-related intertriginous and flexural exanthema.
13. Dry skin includes dry skin, skin exfoliation.
14. Peripheral neuropathy includes peripheral sensory neuropathy, paraesthesia, peripheral sensorimotor neuropathy, dysaesthesia, neuropathy peripheral, peripheral motor neuropathy, Guillain-Barre syndrome, hypoaesthesia, neuralgia, polyneuropathy.
15. Encephalopathy includes agitation, confusional state, delirium, depressed level of consciousness, disorientation, hallucination, lethargy, memory impairment, somnolence.
16. Motor dysfunction includes, dysphonia, gait disturbance, motor dysfunction, muscle spasms, muscular weakness, peroneal nerve palsy, tremor.

All AEs underwent internal clinical and safety review to apply medical judgment in determining ADRs likely associated with elranatamab and are described in the ISS. Event terms representing the same medical concept or condition were grouped together and an overall pooled incidence was reported. The AEs that were reported in ≥10% of participants (either as single PTs or pooled event terms) in Pool 1 (b) (4) as ADRs are presented in Table 53.

The Applicant's Position:

The observed AE profile was generally consistent across studies and safety pools and was anticipated based on the mechanism of action of elranatamab, published data in the class and the disease under study.

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. In general, the FDA agrees that overall, 100% of patients experienced at least one TEAE. The incidences of several 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 the most common adverse reactions of any grade and grade 3 or 4 based on the FDA recommended grouped terms (**Appendix** Error! Reference source not found.). The most common laboratory abnormalities (based on worsening from baseline using the laboratory dataset) will be presented separately. See Section Error! Reference source not found. below for discussion of neurologic toxicity based on FDA recommended grouped terms.

While FDA agrees that overall, the adverse reactions were consistent with the mechanism of action of elranatamab, 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** Error! Reference source not found., Error! Reference source not found., and **Section 12** for further discussion).

Laboratory Findings

Data:

Table 54: Applicant – Select Laboratory Abnormalities (≥30%) That Worsened from Baseline[a]

Laboratory Abnormality	Pool 1 (N=183)	
	All Grades (%)	Grade 3 or 4 (%)
Hematology		
Lymphocyte count decreased	166 (90.7)	153 (83.6)
White blood cell decreased	126 (68.9)	74 (40.4)
Hemoglobin decreased	124 (68.1)	79 (43.4)
Neutrophil count decreased	113 (61.7)	93 (50.8)
Platelet count decreased	112 (61.2)	58 (31.7)
Chemistry		
Albumin decreased	101 (55.2)	10 (5.5)
AST increase	72 (39.8)	10 (5.5)
Creatinine increased	69 (37.9)	6 (3.3)
Potassium decreased	66 (36.3)	15 (8.2)
ALT increase	65 (35.5)	7 (3.8)
Alkaline phosphatase increased	63 (34.4)	2 (1.1)
Creatinine clearance decreased	58 (32.2)	18 (9.9)

a Laboratory tests were graded according to NCI CTCAE Version 4.03.

The Applicant's Position:

Overall, laboratory test abnormalities were consistent with the mechanism of action of elranatamab and the disease under study. The majority of abnormalities occurred in hematologic evaluations, with less abnormalities observed in chemistry evaluations, a pattern that was

consistent with the AE profile of elranatamab, where cytopenias were frequently reported. (b) (4)

The FDA's Assessment:
FDA agrees with the Applicant's statement that overall, laboratory test abnormalities were consistent with the mechanism of action of elranatamab and the disease under study. Cytopenias were common in patients who received elranatamab. A Warning and Precaution for neutropenia will be included in the USPI based on the overall incidence of neutropenia (62%) and Grade 3 or 4 neutropenia (51%). FDA also notes that 29% of patients had at least one dose interruption of elranatamab due to a TEAE of neutropenia and febrile neutropenia occurred in 2% of patients.

The FDA disagrees (b) (4) FDA notes that there were relatively high rates of AST (40%)/ALT (36%) and total bilirubin elevation (4.8%) in Study C1071003. In addition, the Applicant reported three potential Hy's Law cases. While it is known that CRS is associated with hepatic enzyme elevations, due to the cases of Hy's Law, the Division of Hepatology and Nutrition was consulted for evaluation of potential drug-induced liver injury (DILI), as well as the overall risk of hepatotoxicity with elranatamab. After review, the DHN team concluded that two of the three cases were not DILI cases. The third case was deemed a possible DILI because ALT and AST improved while elranatamab was held. However, this case was confounded because the patient had a hepatic plasmacytoma, and patient's Lambda FLC also improved during this time, potentially indicating a therapeutic response in the liver. FDA notes that based on the chronology of events and clinical and laboratory findings, a strong signal for drug-induced liver injury is lacking. However, a definitive contribution of elranatamab to the events also cannot be ruled out. Based on the totality of evidence, the FDA determined that an additional Warning and Precaution for hepatotoxicity would be added to the USPI to adequately convey the potential risk of hepatotoxicity with elranatamab.

Vital Signs

Data:
In the clinical trials with elranatamab, clinically significant changes in vital sign data were to be reported as AEs. In Pool 3, AEs related to vital sign abnormalities, with the exception of pyrexia, included:

- Sinus tachycardia and tachycardia were reported in 6.4% and 4.9% of participants, respectively. Bradycardia was reported in 1.1% of participants.
- Hypertension and hypotension were reported in 7.2% and 8.3% of participants, respectively.

The Applicant's Position:
There were no data to suggest an adverse effect of elranatamab on cardiac function or vital signs, with the exception of pyrexia and hypotension that were associated with events of CRS. Pyrexia was also frequently reported outside of the context of CRS and is included as an ADR in the proposed USPI.

The FDA's Assessment:
FDA notes that changes in vital signs that occur are clinically relevant in the context of patients experiencing CRS following elranatamab administration. Pyrexia, hypotension, and hypoxia were noted as symptoms of CRS (based on AE reporting) in 21%, 9%, and 4% of patients, respectively.

Electrocardiograms (ECGs)
Data: See QT subsection.
The Applicant's Position: See QT subsection.

The FDA's Assessment:
Using grouped terms and the adverse event dataset, a total of 6.0% of the safety population had cardiac events that could be associated with ECG changes. The preferred terms include atrial fibrillation, bundle branch block right, cardio-respiratory arrest, electrocardiogram QT prolonged, and ventricular tachycardia.

QT
Data:

Table 55: Applicant – Overview of QT Results (All Participants as Treated)

	Pool 1 (C1071003)		Pool 3 (C1071003, C1071001, C1071002, C1071009)	
Number (%) of Participants	N	n (%)	N	n (%)
Participants with maximum on-treatment QTcF of <450 msec	174	145 (83.3)	254	194 (76.4)
Participants with maximum on-treatment QTcF of ≥450 to ≤480 msec	174	26 (14.9)	254	47 (18.5)
Participants with maximum on-treatment QTcF of >500 msec	174	2 (1.1)	254	8 (3.1)
Participants with QTcF interval change from baseline of >60 msec	174	5 (2.9)	254	10 (3.9)

Table 56. Applicant – Overview of Adverse Event of ECG QT Prolonged (All Causality)

	Pool 1 (C1071003)		Pool 3 (C1071003, C1071001, C1071002, C1071009)	
Number (%) of Participants	N	n (%)	N	n (%)
Participants with all-causality AEs of Electrocardiogram QT prolonged	183	2 (1.1) Grade 1 (n=1). Grade 3 (n=1)	265	4 (1.5) Grade 1 (n=2). Grade 3 (n=2)

Participants are only counted once per event. Includes data from first dose of study intervention through minimum of [90 days after last dose, or (start day of new anticancer therapy – 1 day)].

The Applicant's Position: There were no clinically meaningful changes in QTcF in participants treated with elranatamab. The majority of participants (7/8) with clinically significant values for QTcF (>500 msec) had elevated QTcF at baseline or had QT prolongation in their medical history. There were few participants that reported ECG abnormalities as AEs.

The FDA's Assessment:
FDA agrees that based on the AE dataset, 2 patients (1.1%) experienced an adverse event of electrocardiogram QT prolonged. Per the FDA Clinical Pharmacology team, a dedicated QT

assessment was not required and was not conducted as per ICH E14 Q&A (R3). Elranatamab is a large, targeted protein and bispecific antibody that has a low likelihood of direct ion channel interactions, and therefore is not expected to cause concentration dependent prolongation of the QT interval. See section 19.4.4.4 for additional E-R Safety Analysis for QTc Prolongation.

Immunogenicity

Data:

Overall, the ADA response was characterized to be of low incidence, low titer with a relatively early onset, and transient.

- The incidence of participants producing ADA to elranatamab at the recommended full treatment dose (IG Pool 3) was low (20/240, 8.3%).
- Majority of ADA positive participants exhibited treatment-induced ADA response (16/20; 80.0%).
- The incidence of treatment-boosted ADA was low (4/240, 1.7%).

The Applicant's Position:

There was no identified clinically significant effect of ADA on the pharmacokinetics, safety, or effectiveness of elranatamab.

The FDA's Assessment:

Refer to FDA's assessment of immunogenicity performed by the Clinical Pharmacology review team. Because low occurrence (8.9%) of anti-drug antibodies, effect of these antibodies on PK, safety, and effectiveness of elranatamab cannot be evaluated.

8.2.5 Analysis of Submission-Specific Safety Issues

Targeted reviews were completed for AESIs including CRS, ICANS and other neurologic AEs, and peripheral neuropathy (PN); and oAECIs including infections, cytopenias, hypogammaglobulinemia, hypersensitivity, injection site reactions, and secondary primary malignancies.

8.2.5.1 Cytokine Release Syndrome

Data:

Table 57: Applicant – Overview of AESI - CRS (All Causalities) (All Participants as Treated)

Number (%) of Participants	Pool 1 (N=183) (C1071003)
Participants with AE CRS	106 (57.9)
Participants with SAE CRS	23 (12.6)
Participants with Maximum Grade 1 AE CRS	80 (43.7)
Participants with Maximum Grade 2 AE CRS	25 (13.7)
Participants with Maximum Grade 3 AE CRS	1 (0.5)
Participants with Maximum Grade 4 or 5 AE CRS	0
Participants with >1 AE CRS	24 (13.1)
Participants with Adverse Events Outcome as Resolved	106 (57.9)
Participants with Permanent Discontinuation of Study Drug due to AE CRS	1 (0.5)
Participants with Dose Reduction or Interruption due to AE CRS	9 (4.9)
Participants with Dose Reduction due to AE CRS	4 (2.2)
Participants with Dose Interruption due to AE CRS	6 (3.3)
Time to First Onset of CRS (days)	
Number of Participants	106
Number of Events	130
Median (range)	2.0 (1.0, 9.0)
Mean (SD)	2.4 (1.10)
Time to Resolution of CRS (days)	
Number of Participants	106
Number of Events	130
Median (range)	2.0 (1.0, 19.0)
Mean (SD)	2.6 (2.07)

Includes data from the first dose of study intervention through the minimum of [90 days after last dose, or (start day of new anticancer therapy - 1 day)]. Except for the Number of Adverse Events Participants are counted only once in each row.

The Applicant's Position:

As a CD3-targeting bispecific antibody, elranatamab stimulates cytokine release and CRS has been identified as an ADR. (b) (4) The 12/32 priming dose regimen led to a predictable CRS profile, with most events occurring after the first or second dose of elranatamab. CRS was fully reversible and was managed with standard supportive care and in some cases with tocilizumab and/or corticosteroids.

To mitigate risk of CRS, the proposed USPI will include a boxed warning and will provide guidance on the appropriate use of elranatamab, and on monitoring and treatment of CRS. The Sponsor is also proposing a REMS with ETASU to mitigate the risk of CRS and neurologic toxicity including ICANS.

The FDA's Assessment:

FDA concurs with the data presented by the Applicant regarding CRS. However, FDA disagrees (b) (4) Despite the implementation of a two-dose step up dosing

regimen, CRS was still prevalent occurring in 58% of patients who received the recommended dosing regimen.

CRS Incidence and Severity

CRS was frequent in patients treated at the RP2D, occurring in 58% of patients (Grade 1: 44%; Grade 2: 14%). Grade 3 CRS occurred in one patient (0.5%), and there were no Grade 4 or 5 events. However, 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 of CRS was high despite consistent use of pre-medications, including diphenhydramine 25 mg PO (or equivalent), acetaminophen 650 mg PO (or equivalent) and dexamethasone 20 mg PO or IV (or equivalent), prior to each of the step-up doses as well as the first target dose. 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 3 patients (1.6%) had a first occurrence of CRS after completion of the step-up dosing schedule. The median time to onset of CRS was 2 (range: 1 to 9) days after the most recent dose, with a median duration of 2 (range: 1 to 19) days. Serious CRS events were reported in 23 patients (12.6%), and recurrent CRS occurred in 13.1% of patients.

Hospitalization Requirements

Patients were monitored closely in Study C1071003. For all patients treated at the RP2D, hospitalization was required for at least 48 hours after the start of the injection for step-up dose one (C1D1), and for 24 hours after the start of the injection for step-up dose two (C1D4). FDA did not agree (b) (4) . Based on the extent of the risk, FDA determined it would be most appropriate for the USPI to be consistent with what was done in Study C1071003, and state that, "Patients should be hospitalized for 48 hours after administration of the first step-up dose, and for 24 hours after administration of the second step-up dose". In addition, the USPI will also state that patients should be hospitalized for 48 hours following the next dose after the first occurrence of Grade 3 CRS with the previous dose.

Management of CRS

FDA notes that 39% of patients treated at the recommended dosing schedule received supportive therapy for management of CRS including tocilizumab or siltuximab in 36%, and steroids in 8.7%. A total of 14 patients (7.6%) required supplemental oxygen. However, no patients required supportive care with a vasopressor or mechanical ventilation. While management of CRS, including the 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 Study C1071003 submitted in response to the FDA March 29, 2023, Clinical Information Requests, FDA determined that the (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 elranatamab 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. 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 14% of patients and Grade 3 CRS in 0.5%, despite all patients receiving pre-medications, and the occurrence of recurrent events, 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 elranatamab outweigh the risks in the post-marketing setting. Refer to **Section 12** for further details regarding the REMS with ETASU.

8.2.5.2 ICANS and Other Neurologic Toxicities

Data:

ICANS:

For participants in Pool 1 (received pre-medications and the recommended step-up priming dose regimen), the overall incidence of ICANS was 3.3%. Of the 6 participants with ICANS, 1 (0.5%) had a Grade 1 event, 3 (1.6%) had Grade 2 events and 2 (1.1%) had Grade 3 events (both participants had prior BCMA-directed therapy). No ICANS were Grade 4 or Grade 5. The majority of participants had ICANS after the first step-up dose (5 [2.7%]); 1 (0.5%) of these participants also experienced ICANS after the second step-up dose and 1 participant initially experienced ICANS after the third (first full dose) dose and had events after the fourth and sixth doses. CRS occurred concurrently with ICANS in the 4 participants that had a single ICANS event and occurred concurrently with the first ICANS event in the 2 participants that experienced more than 1 ICANS event.

Table 58: Applicant – Overview of AESI - ICANS (All Causalities) (All Participants as Treated)

Number (%) of Participants	Pool 1 (N=183) (C1071003)
Participants with AE ICANS	6 (3.3)
Participants with SAE ICANS	2 (1.1)
Participants with Maximum Grade 1 AE ICANS	1 (0.5)
Participants with Maximum Grade 2 AE ICANS	3 (1.6)
Participants with Maximum Grade 3 AE ICANS	2 (1.1)
Participants with Maximum Grade 4 or 5 AE ICANS	0
Participants with >1 AE ICANS	2 (1.1)
Participants with AEs Outcome as Resolved	6 (3.3)
Participants with ICANS concurrent with CRS	6 (3.3)
Participants with Permanent Discontinuation of Study Drug due to AE ICANS	2 (1.1)
Participants with Dose Reduction or Interruption due to AE ICANS	1 (0.5)
Participants with Dose Reduction due to AE ICANS	0
Participants with Dose Interruption due to AE ICANS	1 (0.5)
Time to First Onset of ICANS (days)	
Number of Participants	6
Number of Events	9
Median (range)	3.0 (1.0, 4.0)
Mean (SD)	2.6 (0.88)
Time to Resolution of ICANS (days)	
Number of Participants	6
Number of Events	9
Median (range)	2.0 (1.0, 18.0)
Mean (SD)	4.3 (5.34)

Includes data from the first dose of study intervention through the minimum of [90 days after last dose, or (start day of new anticancer therapy - 1 day)]. Except for the Number of Adverse Events Participants are counted only once in each row.

Other Neurologic Adverse Events:

Table 59: Applicant – Overview of AESI – Neurotoxicity (All Causalities) (All Participants as Treated)

Number (%) of Participants	Pool 1 (N=183) (C1071003)	Pool 3 (N=265) (C1071003, C1071001, C1071002, C1071009)
Participants with Neurotoxicity Events	53 (29.0)	77 (29.1)
Participants with SAE Neurotoxicity Events	3 (1.6)	10 (3.8)
Participants with Maximum Grade 1 Neurotoxicity Events	29 (15.8)	41 (15.5)
Participants with Maximum Grade 2 Neurotoxicity Events	20 (10.9)	26 (9.8)
Participants with Maximum Grade 3 Neurotoxicity Events	4 (2.2)	10 (3.8)
Participants with Maximum Grade 4 or 5 Neurotoxicity Events	0	0
Participants with AEs Outcome as Resolved	24 (13.1)	37 (14.0)
Participants with Permanent Discontinuation of Study Drug due to Neurotoxicity Events	2 (1.1)	3 (1.1)
Participants with Dose Reduction or Interruption due to Neurotoxicity Events	11 (6.0)	15 (5.7)
Participants with Dose Reduction due to Neurotoxicity Events	3 (1.6)	3 (1.1)
Participants with Dose Interruption due to Neurotoxicity Events	11 (6.0)	15 (5.7)
Neurotoxicity AEs by Clustered Term		
Encephalopathy	24 (13.1)	36 (13.6)
Motor dysfunction	23 (12.6)	33 (12.5)
Sensory neuropathy	12 (6.6)	17 (6.4)
Time to Resolution of Neurotoxicity (days)		
Number of Participants	30	45
Number of Events	40	63
Median (range)	4.5 (1.0, 80.0)	5.0 (1.0, 80.0)
Mean (SD)	10.8 (14.96)	10.0 (12.98)

Except for the Number of Adverse Events Participants are counted only once in each row. Serious Adverse Events - according to the investigator's assessment.

Peripheral Neuropathy:

Table 60: Applicant – Overview of AESI - PN (All Causalities) (All Participants as Treated)

Number (%) of Participants	Pool 1 (N=183) (C1071003)	Pool 3 (N=265) (C1071003, C1071001, C1071002, C1071009)
Participants with PN Events	35 (19.1)	53 (20.0)
Participants with Serious PN Events	2 (1.1)	6 (2.3)
Participants with Maximum Grade 1 PN Events	17 (9.3)	30 (11.3)
Participants with Maximum Grade 2 PN Events	16 (8.7)	19 (7.2)
Participants with Maximum Grade 3 PN Events	2 (1.1)	4 (1.5)
Participants with Maximum Grade 4 or 5 PN Events	0	0
Participants with AEs Outcome as Resolved	9 (4.9)	21 (7.9)
Participants with Permanent Discontinuation of Study Drug due to PN Events	4 (2.2)	5 (1.9)
Participants with Dose Reduction or Interruption due to PN Events	10 (5.5)	12 (4.5)
Participants with Dose Reduction due to PN Events	3 (1.6)	3 (1.1)
Participants with Dose Interruption due to PN Events	10 (5.5)	12 (4.5)

Includes data from the first dose of study intervention through the minimum of [90 days after last dose, or (start day of new anticancer therapy – 1 day)]. Except for the Number of Adverse Events Participants are counted only once in each row. Serious Adverse Events - according to the investigator's assessment.

The Applicant's Position:

ICANS and Other Neurologic Adverse Events: The incidence of ICANS (b) (4) was 3.3% in the 183 participants that received this regimen. Most events were of short duration and none were associated with seizures, motor findings or elevated ICP/cerebral edema. All ICANS events resolved and were managed with standard supportive care and in some cases with the use of corticosteroids, tocilizumab (or siltuximab), and anakinra. The majority of participants with other neurotoxicity events had Grade 1 or Grade 2 events and serious events were infrequent.

To mitigate the risk of ICANS and other neurologic toxicities, the proposed USPI will include a boxed warning and will provide guidance on the appropriate use of elranatamab, and on monitoring and treatment of ICANS. The Sponsor is also proposing a REMS with ETASU to mitigate the risk of CRS and neurologic toxicity including ICANS.

PN: The majority of participants had Grade 1 or Grade 2 events; serious events were infrequent. Of the participants who had potential PN events, 51.8% had a medical history of PN; similarly, of participants who did not have PN events, 47.4% had a medical history of PN. These findings suggest that participants with a history of PN are not at increased risk for PN when receiving elranatamab.

The FDA's Assessment:

ICANS

FDA agrees with the Applicant's description of the occurrence of ICANS in Study C1071003. FDA does not agree (b) (4) FDA agrees that four patients (3.3%) who received the recommended dosing regimen experienced ICANS. FDA also notes that in the overall safety population (N=187), which includes the initial four patients treated with a single step-up dose, two additional patients experienced ICANS. Therefore, the overall incidence of ICANS in Study C1071003 was 4.3%. An overview of FDA's analysis of ICANS is provided in Table 61. A Boxed Warning will be utilized in the USPI so practitioners are aware of the risk of ICANS. A REMS with ETASU will also be issued to help mitigate the risk of ICANS and ensure the benefits of elranatamab outweigh the risks in the post-marketing setting. Refer to **Section 12** for further details regarding the REMS with ETASU.

Table 61: FDA – Overview of ICANS (Study C1071003, Safety Population)

Preferred Term	Cohort A Single Step-up N=4 n(%)	Cohort A Two-dose step-up N = 119 n(%)	Cohort B N = 64 n(%)	Total Two-dose Step-up N = 183 n(%)	Total Safety Population N = 187 n(%)
Patients with ICANS	2 (50)	4 (3.4)	2 (3.1)	6 (3.3)	8 (4.3)
Maximum Toxicity Grade					
Grade 1	1 (25)	1 (0.8)	0 (0)	1 (0.5)	2 (1.1)
Grade 2	1(25)	3 (2.5)	0 (0)	3 (1.6)	4 (2.1)
Grade 3	0 (0)	0 (0)	2 (3.1)	2 (1.1)	2 (1.1)
Grade 4-5	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ICANS SAE	0 (0)	0 (0)	2 (3.1)	2 (1.1)	2 (1.1)
ICANS Concurrent with CRS	2 (50)	4 (3.4)	2 (3.1)	6 (3.3)	8 (4.3)
Treatment Discontinued due to ICANS	0 (0)	0 (0)	2 (3.1)	2 (1.1)	2 (1.1)
Dose Reduction due to ICANS	0 (0)	3 (2.5)	0 (0)	3 (1.6)	3 (1.6)

Source: FDA Analysis; ADAE dataset

Neurologic Toxicity

Definition of Neurologic Toxicity

FDA does not agree with the Applicant's analysis and assessment of neurologic toxicity. In addition to peripheral neuropathy, the Applicant's analysis of neurologic toxicity focused on three categories of adverse events: encephalopathy, motor dysfunction, and sensory neuropathy, which were assessed using pooling of preferred terms. Based on the Applicant's analysis, (b) (4) . FDA does not agree with this approach, as it underestimates the true occurrence of neurologic toxicity with elranatamab. The FDA analysis of neurologic toxicity includes all TEAEs within the Nervous System Disorders and Psychiatric Disorders SOCs, as well as several related preferred terms that mapped

to other SOCs, with grouping of related terms for encephalopathy, motor dysfunction, and sensory neuropathy, as follows:

- Encephalopathy: agitation, altered state of consciousness, cognitive disorder, confusional state, delirium, depressed level of consciousness, disorientation, hallucination, lethargy, memory impairment, mental status changes, metabolic encephalopathy, somnolence, toxic encephalopathy
- Motor dysfunction: ataxia, balance disorder, gait disturbance, motor dysfunction, muscle contracture, muscle spasms, muscular weakness, peripheral motor neuropathy, peroneal nerve palsy, tremor
- Sensory neuropathy: burning sensation, dysaesthesia, hypoaesthesia, neuropathy peripheral, paraesthesia, parosmia, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, polyneuropathy, sensory loss.

Incidence and Severity of Neurologic Toxicity

Using the above methodology, FDA analysis of neurologic toxicity showed that neurologic TEAEs occurred in 59% of patients who received the recommended dosing regimen, with Grade 3-4 neurologic AEs occurring in 7.1%. FDA also notes that one patient treated with the recommended dosing regimen experienced Grade 3 Guillain-Barre Syndrome. FDA's analysis of neurologic toxicity is provided in Table 62 below.

Table 62: FDA – Analysis of Neurologic Toxicity (Study C1071003, Safety Population)

	Cohort A N = 119 n(%)		Cohort B N = 64 n(%)		Total N=183 n(%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4	All Grades	Grade 3-4
Any TEAE in Nervous System or Psychiatric Disorder SOC	72 (61)	7 (5.9)	36 (53)	6 (9.4)	108 (59)	13 (7.1)
Nervous System Disorders SOC	68 (55)	7 (5.7)	29 (45)	6 (9.4)	93 (51)	11 (6.0)
Psychiatric Disorder SOC	35 (29)	2 (1.6)	13 (20)	0 (0)	48 (26)	2 (1.1)
Headache (GT)	26 (22)	1 (0.8)	7 (11)	0 (0)	33 (18)	1 (0.5)
Motor Dysfunction (GT)	16 (13)	1 (0.8)	8 (13)	4 (6.2)	24 (13)	5 (2.7)
Encephalopathy (GT)	16 (13)	3 (2.4)	11 (17)	2 (3.1)	27 (15)	5 (2.7)
Sensory Neuropathy (GT)	16 (13)	0 (0)	7 (11)	1 (1.6)	23 (13)	1 (0.5)

Source: FDA Analysis; ADAE dataset

Guidance for USPI:

FDA determined that a boxed warning for neurologic toxicity including ICANS, and a REMS with ETASU are necessary to ensure prescribers are trained how to recognize and manage these risks in the post-market setting to ensure the benefit of elranatamab outweighs the risks. Refer to **Section 12** for further details regarding the REMS with ETASU.

8.2.5.3 Infections

Data:

Table 63: Applicant – Overview of AESI - Infections (All Causalities) (All Participants as Treated)

Number (%) of Participants	Pool 1 (N=183) (C1071003)	Pool 3 (N=265) (C1071003, C1071001, C1071002, C1071009)
Participants with Infections	122 (66.7)	183 (69.1)
Participants with Serious Infections	76 (41.5)	104 (39.2)
Participants with Maximum Grade 3 or 4 Infections	57 (31.1)	82 (30.9)
Participants with Maximum Grade 5 Infections	12 (6.6)	15 (5.7)
COVID-19 pneumonia	4 (2.2)	4 (1.5)
COVID-19	1 (0.5)	2 (0.8)
Sepsis	1 (0.5)	2 (0.8)
Septic shock	4 (2.2)	4 (1.5)
Adenovirus infection	1 (0.5)	2 (0.8)
Pneumonia adenoviral	1 (0.5)	1 (0.4)
Pneumonia pseudomonal	1 (0.5)	1 (0.4)
Participants with Opportunistic Infections	16 (8.7)	25 (9.4)
Participants with Serious Opportunistic Infections	11 (6.0)	13 (4.9)
Participants with Maximum Grade 3/4 Opportunistic Infections	10 (5.5)	12 (4.5)
Participants with Maximum Grade 5 Opportunistic Infections	1 (0.5)	2 (0.8)
Participants with Infections Adverse Events Outcome as Resolved	72 (39.3)	105 (39.6)
Participants with Permanent Discontinuation of Study Drug due to Infections	12 (6.6)	14 (5.3)
Participants with Dose Reduction or Interruption due to Infections	76 (41.5)	110 (41.5)
Participants with Dose Reduction due to Infections	1 (0.5)	7 (2.6)
Participants with Dose Interruption due to Infections	76 (41.5)	109 (41.1)

Includes data from the first dose of study intervention through the minimum of [90 days after last dose, or (start day of new anticancer therapy – 1 day)]. Except for the Number of Adverse Events, Participants are counted only once in each row.
Serious Adverse Events - according to the investigator's assessment.

The Applicant's Position:

Infections are common in patients with RRMM due to underlying immunosuppression. As elranatamab causes plasma cell depletion and may contribute to worsening hypogammaglobulinemia and neutropenia (also common in this patient population), elranatamab treatment increases the risk of infections. The most common infections were of the respiratory tract, including pneumonia and upper respiratory tract infection. Serious and Grade 5 infections were also generally respiratory or related to sepsis. The risk for infections can be decreased with appropriate use of prophylactic antimicrobial and/or antiviral agents and through monitoring and treatment of cytopenias and hypogammaglobulinemia. The proposed USPI will provide guidance on monitoring for infections and recommendations on appropriate prophylaxis and treatment.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of the overall incidence of infection in patients treated with elranatamab (67%), as well as the incidence of serious infections (42%) and fatal infections (7%). However, the FDA's analysis of the incidence of specific infections was based on FDA's grouped terms (**Appendix 19.6**), and therefore differs from the Applicant's analysis. FDA's summary of infections that occurred in >10% of patients treated with the recommended dosing regimen of elranatamab is shown in Table 64 below. The USPI will have a Warning and Precaution to communicate the risk of infection with elranatamab. This will include instructions to administer prophylactic antimicrobial and anti-viral medications according to current practice guidelines, and to consider treatment with subcutaneous or intravenous immunoglobulin (IVIG) as appropriate. The USPI will also include dosage modifications for Grade 3 and 4 infections.

Table 64: FDA – Infections that Occurred in >10% of Patients (Study C1071003; Safety Population)

	Cohort A N = 119 n(%)		Cohort B N = 64 n(%)		Total N=183 n(%)	
Grouped Term	**All Grades**	**Grade 3-4**	**All Grades**	**Grade 3-4**	**All Grades**	**Grade 3-4**
Upper Respiratory Tract Infection (GT)	43 (36)	5 (4.2)	20 (31)	3 (4.7)	63 (34)	8 (4.3)
Pneumonia (GT)	42 (35)	25 (21)	17 (27)	12 (19)	59 (32)	37 (20)
Sepsis (GT)	20 (17)	15 (13)	8 (13)	6 (9.4)	28 (15)	21 (11)
Urinary Tract Infection (GT)	14 (12)	6 (3.4	8 (13)	2 (3.1)	22 (12)	8 (4.4)

Source: FDA Analysis

8.2.5.4 Neutropenia

Data:

Table 65: Applicant – Overview of AESI - Neutropenia (All Causalities) (All Participants as Treated)

Number (%) of Participants	Pool 1 (N=183) (C1071003)	Pool 3 (N=265) (C1071003, C1071001, C1071002, C1071009)
Participants with Neutropenia	81 (44.3)	136 (51.3)
Participants with Serious Neutropenia	2 (1.1)	3 (1.1)
Participants with Maximum Grade 3 Neutropenia	37 (20.2)	57 (21.5)
Participants with Maximum Grade 4 Neutropenia	41 (22.4)	74 (27.9)
Participants with Maximum Grade 5 Neutropenia	0	0
Participants with Adverse Events Outcome as Resolved	71 (38.8)	121 (45.7)
Participants with Permanent Discontinuation of Study Drug due to Neutropenia	2 (1.1)	3 (1.1)
Participants with Dose Reduction or Interruption due to Neutropenia	54 (29.5)	89 (33.6)
Participants with Dose Reduction due to Neutropenia	19 (10.4)	37 (14.0)
Participants with Dose Interruption due to Neutropenia	53 (29.0)	86 (32.5)

Includes data from the first dose of study intervention through the minimum of [90 days after last dose, or (start day of new anticancer therapy – 1 day)]. Except for the Number of Adverse Events Participants are counted only once in each row. Serious Adverse Events - according to the investigator's assessment.

The Applicant's Position:

Cytopenias are common AEs associated with the expected pharmacological activity of bispecific T-cell engager therapy and with the underlying multiple myeloma. Neutropenia was the most frequently reported Grade 3/4 cytopenia in participants treated with elranatamab. The risk for neutropenia and associated infection will be communicated in the USPI.

The FDA's Assessment:

FDA agrees that cytopenias, including neutropenia, are common AEs associated with bispecific T-cell engager therapy, and with underlying multiple myeloma. FDA concurs with the data presented by the Applicant regarding the incidence of neutropenia based on AE reporting. However, FDA notes that this is likely an underrepresentation of the actual occurrence of neutropenia. FDA notes that the incidence of all Grade decreased neutrophil count (62%), and Grade 3-4 decreased neutrophil count (51%) was substantially higher based on the laboratory dataset compared to AE reporting of neutropenia. The USPI will include the incidence of neutropenia based on the laboratory dataset. FDA also agrees with the Inclusion of a Warning and Precaution for neutropenia in the USPI.

8.2.5.5 Hypogammaglobulinemia

Data:

Quantitative immunoglobulin laboratory values were only available in Study C1071003 (N=39 participants with quantitative IgG among participants with non-IgG myeloma and who had baseline and ≥1 on-treatment IgG assessment); no pooled data are available. For Study C1071003:

- A total of 92.3% of participants with baseline IgG values available had IgG levels <400 mg/dL at some point during elranatamab treatment. Overall, 82.1% of participants already had a value <400 mg/dL at baseline.
- A total of 84.6% of participants with baseline IgG values available had IgG levels <200 mg/dL at some point during elranatamab treatment. Overall, 33.3% of participants already had a value <200 mg/dL at baseline.
- No participant had a shift in IgG from ≥LLN at baseline to a worst post-baseline on treatment assessment of <400 mg/dL or <200 mg/dL. Only 5.1% of participants had an IgG ≥LLN at baseline.

The Applicant's Position:

A large proportion of participants had lower than normal IgG at baseline due to their underlying multiple myeloma, and elranatamab may contribute to worsening of hypogammaglobulinemia during treatment. (b) (4)

The FDA's Assessment:

FDA agrees with the Applicant's assessment. Based on adverse event reporting a total of 8.7% of the safety population experienced hypogammaglobulinemia. (b) (4) . Nearly 80% of the patients had baseline IgG levels <400 mg/dL prior to treatment. Routine pharmacovigilance will be used to monitor for hypogammaglobulinemia in the post marketing setting.

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

Data: Not Applicable.

The Applicant's Position: See Efficacy Results – Secondary or exploratory COA (PRO) endpoints.

The FDA's Assessment:

FDA notes that patient-reported outcomes (PROs) were collected in Study C1071003 and consisted of evaluation of health-related quality of life (HRQoL) using the EORTC QLQ-C30 and EQ5D-5L. 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 Error! Reference source not found..

8.2.7 Safety Analyses by Demographic Subgroups

Data:

Table 66: Applicant – Summary of Elranatamab General Safety in Patient Subgroups (Intrinsic Factors)

Patient Subgroup Category	Overall Conclusions (Pool 3; N=265)
Age *<65 and ≥65 years*	• There were no clinically relevant differences in the safety of elranatamab in adults ≥65 years of age (n=155) compared to younger adults (n=110).
Age *<75 and ≥75 years*	• There were no clinically relevant differences in the safety of elranatamab in adults ≥75 years of age (n=43) compared to younger adults (n=222).
Sex *Males and Females*	• There were no clinically relevant differences in the safety of elranatamab in male participants (n=136) compared to female participants (n=129).
Body Weight *<72 kg, ≥72 kg*	• There were no clinically relevant differences in the safety of elranatamab in participants with body weight <72 kg (n=141) compared to participants with body weight ≥72 kg (n=124).
Race *White, Black/African American, Asian*	• Although the majority of participants were White (n=160), there were no clinically relevant differences in the safety of elranatamab compared to participants that were Black (n=19), although the overall incidence of SAEs was notably lower in Black participants. • There were no clinically relevant differences in the safety of elranatamab for White participants (n=160) compared to participants that were Asian (n=40).
Hepatic Function at Baseline[a] *Normal, Impaired*	• There were no clinically relevant differences in the safety of elranatamab in participants with hepatic impairment (n=41) compared with those with normal hepatic function (n=224). • The overall incidence of AEs, Grade 3/4 AEs, SAEs, and discontinuations due to AEs was similar between participants with normal hepatic function and those with hepatic impairment. Although the incidence of Grade 5 events appeared to be higher in participants with hepatic impairment (29.3% vs 17.0%), the majority of Grade 5 events (7/12 participants) were due to disease progression.
Renal Function at Baseline CrCl ≤60 mL/min, CrCl >60, mL/min	• There were no clinically relevant differences in the safety of elranatamab in participants with CrCl >60 mL/min (n=177) compared with participants with renal function ≤60 mL/min (n=88).

a Normal: AST and total bilirubin ≤ULN, Impaired: AST or total bilirubin >ULN.

The Applicant's Position:

The impact of demographic subgroups of age, sex, race, baseline weight, and hepatic and renal function on the safety of elranatamab was evaluated in the pooled safety population and no clinically relevant differences between sub-groups were identified.

The FDA's Assessment:

FDA sent an Information Request (June 8, 2023) requesting additional data from the Applicant, including analyses of efficacy and safety by age, race, and ethnicity. Several factors including the lack of a control arm and the small sample sizes in several subgroups, makes interpretation of the data challenging. However, in general, there were no significant differences in safety based on age, race, or ethnicity. A summary of safety findings by age is provided in Table 67 below.

Table 67: FDA – Overview of Safety by Age (Study C1071003; Safety Population)

Safety Population (N=183)	<65 (N=70)	≥65-<75 (N=78)	≥75 (N=35)
Any TEAE	**70 (100)**	**78 (100)**	**35 (100)**
Grade 3-4	**49 (70)**	**58 (74)**	**23 (66)**
Grade 5 TEAE	**16 (23)**	**12 (15)**	**9 (26)**
Neurotoxicity SOC All	**18 (26)**	**33 (42)**	**11 (31)**
Neurotoxicity – Grade 3-4	1 (1.4)	3 (3.8)	2 (5.7)
Encephalopathy	9 (13)	11 (14)	6 (17)
Motor Dysfunction	9 (13)	13 (17)	4 (11)
Sensory Neuropathy	5 (7.1)	14 (18)	4 (11)
ICANS	2 (2.9)	3 (3.8)	1 (2.9)
Immune System Disorders	**45 (64)**	**49 (63)**	**17 (49)**
CRS	43 (61)	47 (60)	16 (46)
CRS (Grade 3-4)	1 (1.4)	1 (1.3)	0
Blood and Lymphatic System Disorders	**59 (84)**	**61 (78)**	**29 (83)**
Anemia	39 (56)	37 (47)	22 (63)
Neutropenia	33 (47)	38 (49)	10 (29)
Thrombocytopenia	29 (41)	23 (30)	12 (34)
Lymphopenia	15 (21)	21 (27)	18 (51)
Leukopenia	9 (13)	13 (17)	7 (20)
Gastrointestinal Disorders	**48 (69)**	**53 (68)**	**23 (66)**
Diarrhea	23 (33)	27 (35)	15 (43)
Nausea	15 (21)	17 (22)	7 (20)
General Disorders and Administration Site Conditions	**56 (80)**	**58 (74)**	**28 (80)**
Fatigue	16 (23)	19 (24)	14 (40)
Injection site reaction	17 (24)	16 (21)	6 (17)
Pyrexia	17 (24)	17 (22)	5 (14)
Infections and Infestations	**51 (73)**	**52 (67)**	**19 (54)**
Upper Respiratory Tract Infection	16 (23)	11 (14)	2 (5.7)
Respiratory, Thoracic and Mediastinal Disorders	**31 (44)**	**35 (45)**	**15 (43)**
Cough	17 (24)	15 (19)	4 (11)

Source: FDA's Analysis; adapted from Applicant's response to Clinical IR sent June 8, 2023.

8.2.8 Specific Safety Studies/Clinical Trials

Data: No applicable.

The Applicant's Position: Safety summaries were included as part of pivotal Study C1071003 and the pooled safety population; no specific safety studies were performed.

The FDA's Assessment:

FDA agrees that no specific safety studies were performed, and that this is not applicable.

8.2.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Data: Not applicable.

The Applicant's Position: No studies have been performed to evaluate the effects of elranatamab.

The FDA's Assessment:

FDA agrees that no carcinogenicity studies have been conducted.

Human Reproduction and Pregnancy

Data: Not applicable.

The Applicant's Position: No studies have been performed to evaluate the effects of elranatamab.

The FDA's Assessment:

The FDA agrees with the Applicant's statement that no studies have been performed to evaluate the effects of elranatamab on human reproduction and pregnancy. However, the USPI will include a Warning and Precaution for embryo-fetal toxicity, consistent with other products in this drug class.

Pediatrics and Assessment of Effects on Growth

Data: Not applicable to this submission.

The Applicant's Position: The safety and effectiveness of elranatamab has not been established in pediatric patients.

The FDA's Assessment:

FDA agrees with the Applicant's statement that the safety and effectiveness of elranatamab has not been established in pediatric patients. FDA notes that no studies were conducted in pediatric patients, and the development of elranatamab is focused on adult patients with MM.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data: Not applicable.

The 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: Elranatamab is not yet marketed in any region.

The Applicant's Position: No postmarketing experience.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

Safety in the postmarket setting is expected to be generally similar to that observed in the clinical trials reviewed in this application, but use will likely be in a broader population of prescribers and patients. Therefore, it will be important for healthcare professionals and patients to understand the risks for CRS and neurologic toxicity including ICANS and how to minimize them, as these

events have the potential to be life-threatening if not properly managed. Therefore, a REMS with ETASU is proposed with the goal of mitigating the risk of CRS and neurologic toxicity including ICANS. In addition, patients administered elranatamab should be monitored and treated promptly for infections and other adverse drug reactions associated with the use of elranatamab.

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 elranatamab can be adequately managed in the post-market setting. FDA notes that teclistamab is another bispecific CD3 T-cell engager recently approved for the treatment of patients with RRMM that also has risks of CRS and neurologic toxicity, including ICANS, and has a REMS with ETASU in place. 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

The Applicant's Position:
Based on the totality of the safety data, the Applicant has determined that elranatamab at the recommended dosing regimen of 76 mg SC QW with pre-medications and a 2 step-up priming dose regimen, reduced to 76 mg SC Q2W after Week 24 for patients who have achieved a response, has a manageable safety profile that supports a positive benefit/risk assessment for use in patients with RRMM.

The FDA's Assessment:
FDA agrees that based on the totality of the safety data, elranatamab at the recommended dosing regimen has a favorable benefit/risk profile for use in patients with RRMM who have received at least 4 prior lines of therapy including a PI, an IMiD, and an anti-CD38 mAb.

FDA reviewed the Applicant's Summary of Clinical Safety, which included safety data from 372 participants across 6 studies who received at least one dose of elranatamab. FDA notes that the safety profile of elranatamab 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 90-day Safety Update submitted by the Applicant on March 13, 2023 (January 12, 2023, data cut-off) with a focus on the primary safety population from Study C1071003 (N=183). FDA notes that there were six additional deaths due to TEAEs. The majority of deaths not related to disease progression were due to AEs of infection (15 in the initial BLA submission, 17 in the 90-DSU, PTs of sepsis and septic shock). All other AEs leading to death in the 90-DSU were reported in one participant each, with the exception of acute respiratory distress syndrome, which was reported in 2 participants. Of the most frequently reported AEs leading to treatment discontinuation in both datasets, only neutropenia increased in incidence (1.5% in 90-DSU compared to 1.1% in the initial dataset). There were no new cases of CRS or ICANS.

Overall, CRS and neurologic toxicity, including ICANS, are the key safety concerns for elranatamab. Additional concerns include the risks of hepatoxicity, infections, and neutropenia. A Warning and Precaution for each of these safety issues will be included in the USPI.

The incidence of CRS (58%) was high, including Grade 2 CRS in 14% of patients and Grade 3 CRS in 0.5%, despite consistent use of pre-medications and hospitalization of patients for at least 48 hours after administration of the first step-up dose and for at least 24 hours after the second step-up dose. 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 the first step-up dose and for 24 hours after the second step-up dose, 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 (59%), including ICANS in 3.3% of patients, motor dysfunction in 13%, sensory neuropathy in 13%, encephalopathy in 14%, and GBS in 0.5%. Grade 3 or 4 neurologic toxicity occurred in 7.1% of patients. Based on the overall incidence of neurologic toxicity, and the occurrence of serious neurologic TEAEs, FDA determined that additional risk management strategies were needed 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, when interpreting the results, it is important to note that the efficacy of the treatment was based on objective response rate, which is an intermediate endpoint evaluated in a single-arm trial.
- While the study also assessed other endpoints such as time-to response, PFS and PRO, their interpretability is limited in a single-arm trial setting. Therefore, they are considered exploratory (b) (4). Furthermore, the subgroup analyses, conducted with a limited sample size, were regarded as sensitivity analyses for the primary endpoint. As a result, these analyses should be considered exploratory, and the results should be interpreted with caution and considered hypothesis generating only.
- In general, a minimum of 9-12 months follow-up from the onset of first response ensures a robust assessment for durability of response. However, at the time of the data cutoff date 14 October 2022, 23 patients in Cohort A were censored with less than 9 months of follow-up due to insufficient follow-up among a total of 63 censored patients, and 10 patients in Cohort B were censored with less than 9 months of follow-up due to insufficient follow-up among a total of 19 censored patients. The early censoring may impact the reliability of the estimate from the DOR analysis.

- African American/Black participants population and those of Hispanic/Latino ethnicity are underrepresented in the overall Study C1071003. Additional data post approval will be requested.
- For the MRD negativity rate, the FDA's results are slightly different than the Applicant's. However, this difference does not impact the overall summary of the study. Among 123 patients in Cohort A, the MRD negativity rate at a threshold of 10^{-5} was 20.3% (95% CI=13.6, 28.5). Among the 97 patients with ≥4 prior lines of therapy in Cohort A, the MRD negativity rate at a threshold 10^{-5} was 18.6 (95% CI=11.4, 27.7). However, there were high rates of missing data and calibration failure (b) (4)

8.4 Conclusions and Recommendations

The FDA's Assessment:

Among the 97 patients in Cohort A in the efficacy population, the median age was 69 (range: 46 to 89) years with 18.6% of patients ≥75 years of age. Forty percent were female; 59.8% were White, 13.4% were Asian, 7.2% were Hispanic/Latino, 5.2% were Black or African American. Disease stage (R-ISS) at study entry was 20.6% in Stage I, 53.6% in Stage II, and 17.5% in Stage III. The median time since initial diagnosis of multiple myeloma to enrollment was 79.6 (range: 16 to 228) months. A total of 96.9% were triple-class refractory, 94.8% were refractory to their last line of therapy, 69.1% received prior autologous stem cell transplantation, and 7.2% received prior allogenic stem cell transplantation. High-risk cytogenetics [t(4;14), t(14;16), or del(17p)] were present in 22.7% of patients and 34.0% of patients had extramedullary disease at baseline by BICR.

Efficacy was based on response rate and duration of response, as assessed by BICR based on IMWG criteria. Among the 97 participants with ≥4 prior lines of therapy in Cohort A, the confirmed ORR per BICR was 57.7% (95% CI: 47.3, 67.7). There were 51.5% of participants who achieved VGPR or better and 25.8% who achieved CR or better. The median (range) time to first response (TTR) was 1.22 (0.9 to 6.5) months. With a median follow-up of 11.1 months (95% CI: 10.6, 12.0) among responders, median DOR was not reached. The DOR rate at 6 months was 90.4% (95% CI: 78.4%, 95.9%) and at 9 months was 82.3% (95% CI: 67.1%, 90.9%).

Among the 64 patients enrolled in Cohort B who previously received a PI, an IMiD, an anti-CD38 monoclonal antibody, and a BCMA-directed therapy, 63 patients received at least four prior lines of therapy. Patients had received a median of 8 prior lines of therapy (range: 4 to 19); 73% and 32% received prior BCMA-directed ADC and CAR T cell therapy, respectively. Confirmed ORR by BICR was 33.3% (95% CI: 22.0, 46.3). After a median (95% CI) follow-up of 10.2 (9.9, 11.0) months among responders, median DOR was not reached (95% CI: NE, NE) and the DOR rate at 9 months was 84.3% (95% CI: 58.7, 94.7). The efficacy data in this cohort is supportive of the primary efficacy data.

Based on the observed benefit of elranatamab, combined with the REMS with ETASU to help mitigate the risks of CRS and neurologic toxicity, including ICANS, the FDA clinical and statistical review teams recommend accelerated approval of elranatamab for the indication: "ELREXFIO 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, no external consults were requested.

10 Pediatrics

The Applicant's Position:
The safety and effectiveness of elranatamab has not been established in pediatric patients.

The FDA's Assessment:
The FDA agrees with the Applicant's statement. BCMA has been determined to be a non-relevant molecular target to the growth and development of pediatric cancer. Therefore, this application is not subject to PREA as amended by FDARA.

11 Labeling Recommendations

Data: The table below includes a high-level summary of the changes to the USPI made by the FDA during the review of the BLA.

(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.

4 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

A REMS will be issued to ensure the risks of elranatamab 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 elranatamab will include a Communication Plan, ETASU A (certification of prescribers) and ETASU B (certification of pharmacies and healthcare settings that dispense elranatamab). 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 elranatamab.

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 elranatamab 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 Commitment

The FDA's Assessment:

The following accelerated approval PMR will be issued:

Complete a randomized clinical trial in patients with relapsed or refractory multiple myeloma. Patients should be randomized to receive an elranatamab-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 and overall response rate. The trial should enroll sufficient numbers of older patients (ages 65-74 years and 75 years and above) to enable an evaluation of elranatamab in a study population that reflects the age of the U.S. population of patients with multiple myeloma.

Final Protocol Submission:	10/2023
Trial Completion:	03/2026
Final Report Submission:	09/2026

The following PMC will be issued:

Conduct an integrated analysis of data from clinical trials to further characterize the efficacy, pharmacokinetics, pharmacodynamics, and safety of elranatamab among U.S. racial and ethnic minority patients with multiple myeloma. The population should be representative of the U.S. population of patients with multiple myeloma, including racial and ethnic diversity, and allow for interpretation of the results in these populations.

Draft Protocol Submission (Analysis Plan):	01/2024
Final Protocol Submission (Analysis Plan):	04/2024
Study Completion:	08/2026
Final Report Submission:	12/2026

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:

American Cancer Society. Key Statistics About Multiple Myeloma. 2022. Available from: https://www.cancer.org/cancer/multiple-myeloma/about/key-statistics.htm.

Berdeja JG, Madduri D, Usmani SZ, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. Lancet. 2021;398(10297):314-24.

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Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014;15(12):e538-48.

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Vugmeyster Y, Xu X, Theil FP, et al. Pharmacokinetics and toxicology of therapeutic proteins: Advances and challenges. World J Biol Chem. 2012;3(4):73-92.

Waxman AJ, Mink PJ, Devesa SS, et al. Racial disparities in incidence and outcome in multiple myeloma: a population-based study. Blood, The Journal of the American Society of Hematology. 2010;116(25):5501-06.

The FDA's References:

1. Girgis S, Wang Lin SX, Pillarisetti K, Verona R, Vieyra D, Casneuf T, Fink D, Miao X, Chen Y, Stephenson T, Banerjee A, Hilder BW, Russell J, Infante J, Elsayed Y, Smit J, Goldberg JD. Effects of teclistamab and talquetamab on soluble BCMA levels in patients with relapsed/refractory multiple myeloma. Blood Adv. 2023 Feb 28;7(4):644-648. Doi: 10.1182/bloodadvances.2022007625. PMID: 36006441; PMCID: PMC9979748.

19.2 Financial Disclosure

The FDA's Assessment:

FDA reviewed the submitted financial disclosure forms 3454 agrees with the Applicant's position.

The Applicant's Position:

Covered Clinical Study (Name and/or Number):* C1071001

Was a list of clinical investigators provided:			Yes ☒	No ☐ (Request list from Applicant)
	Total number of investigators identified: 295			
	Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0			
	Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1			
	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: _____ Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: _____			

	Significant equity interest held by investigator in study: _____ Sponsor of covered study: _____			
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)

Covered Clinical Study (Name and/or Number):* C1071002

Was a list of clinical investigators provided:			Yes ☒	No ☐ (Request list from Applicant)
	Total number of investigators identified: 24			
	Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0			
	Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 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: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in study: _____ Sponsor of covered study: _____			
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)

Covered Clinical Study (Name and/or Number):* C1071003

Was a list of clinical investigators provided:			Yes ☒	No ☐ (Request list from Applicant)
	Total number of investigators identified: 505			
	Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0			
	Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 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: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in study: _____ Sponsor of covered study: _____			
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)

Covered Clinical Study (Name and/or Number):* C1071009

Was a list of clinical investigators provided:			Yes ☒	No ☐ (Request list from Applicant)
	Total number of investigators identified: 150			
	Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0			
	Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 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: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in study: _____ Sponsor of covered study: _____			
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: Not applicable.

The Applicant's Position: See Section 5.

The FDA's Assessment:

The Pharmacology/Toxicology review is in Section 5.

19.4 OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1 Pharmacokinetics

Population predictions of C_{max}, dose-normalized C_{max}, AUC, dose-normalized AUC of elranatamab following intravenous and SC dose in the first week are presented in Figure 14. Excluding data with 3 evaluable measurements, dose normalized AUC_{tau} and C_{max} were generally consistent across the dosing groups for SQ administration, which suggests that elranatamab exposure is approximately dose proportional (Table 68).

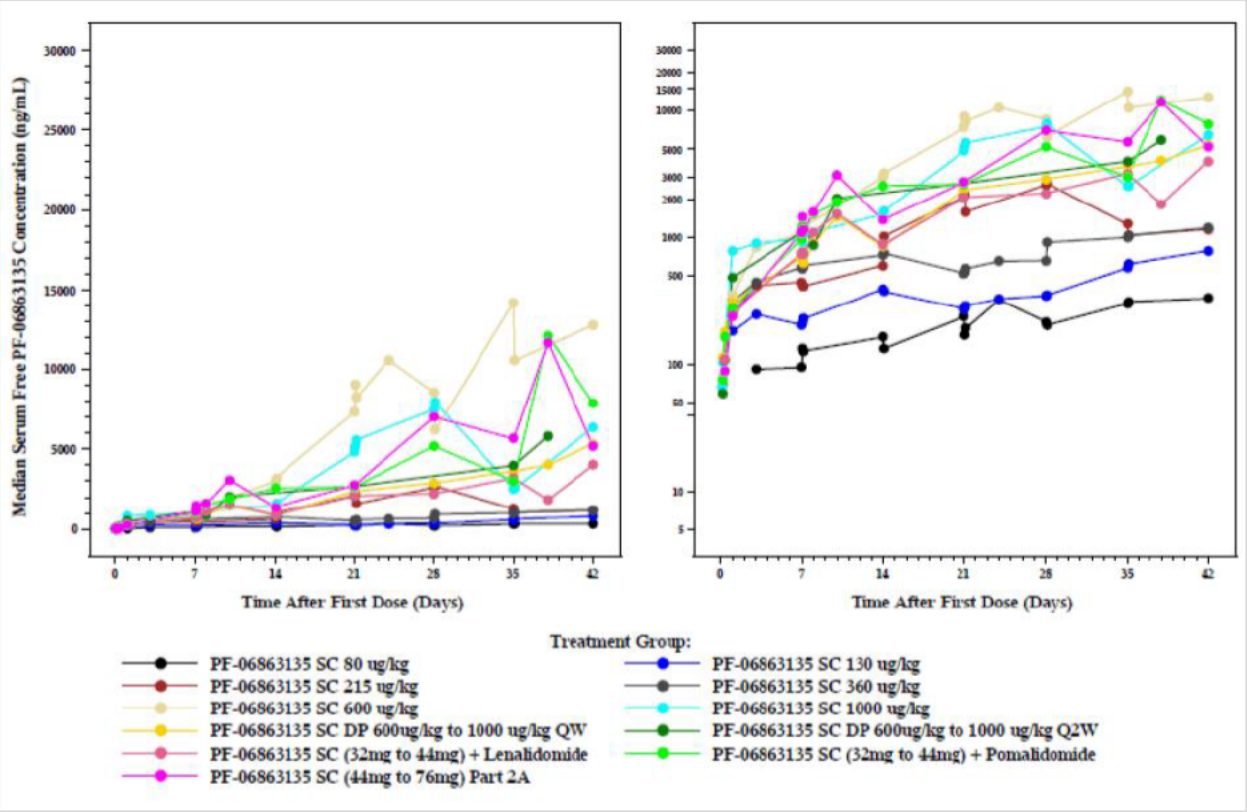
Table 68: FDA – Summary of free elranatamab pharmacokinetic following single IV or SQ administration in the first week from study 1001 part 1.

Cohort	N	Cmax (µg/mL)	AUCtau (µg·day/mL)	AUCtau/ Dose (µg·day/mL)	Cmax/Dose (µg/mL/mg)
Single IV administration in first week [a]					
3.0 µg/kg IV	3	0.0688 [b]	0.0847 [b]	0.303 [b]	0.246 [b]
10 µg/kg IV	2	0.153 [b]	0.261, 0.618 [b]	0.522, 0.951 [b]	0.152, 0.235 [b]
30 µg/kg IV	5	0.185 (40)	0.780 (24)	0.299 (24)	0.0709 (34)
50 µg/kg IV	6	0.302 (75)	0.121 (62)	0.344 (58)	0.0891 (71)
Single SQ administration in the first week					
80 µg/kg SQ	1	0.0692[b]	0.183 [b]	0.044 [b]	0.0165 [b]
130 µg/kg SQ	3	0.2632 (31)	1.478 (23)	0.1314 (58)	0.0234 (68)
215 µg/kg SQ	2	0.445, 1.10	2.67, 3.29	0.225, 0.261 [b]	0.0436, 0.0753 [b]
360 µg/kg SQ	4	0.8304 (131)	4.362 (103)	0.1490 (84)	0.0283 (106)
600 µg/kg SQ	5	0.960 (59)	4.87 (48)	0.088 (39)	0.017 (52)
1000 µg/kg SQ	4	1.15 (38)	6.57 (33)	0.10 (50)	0.019 (56)

a. PK parameters cannot be derived for first three intravenous dose cohorts 0.1, 0.3 and 1 µg/kg due to concentrations were lower limit of quantification (50 ng/ml)
b. Individual values are listed when there are less than 3 evaluable measurements.
c. Geometric mean (geometric %CV) is presented for C_{max}

Source: Applicant CRS C1071001, Table 47

Figure 14: FDA – Serum Free elranatamab free concentration-time profile following subcutaneous dose by treatment (Left panel:linear scale; right panel, semilogarithmic scale) in study 1001

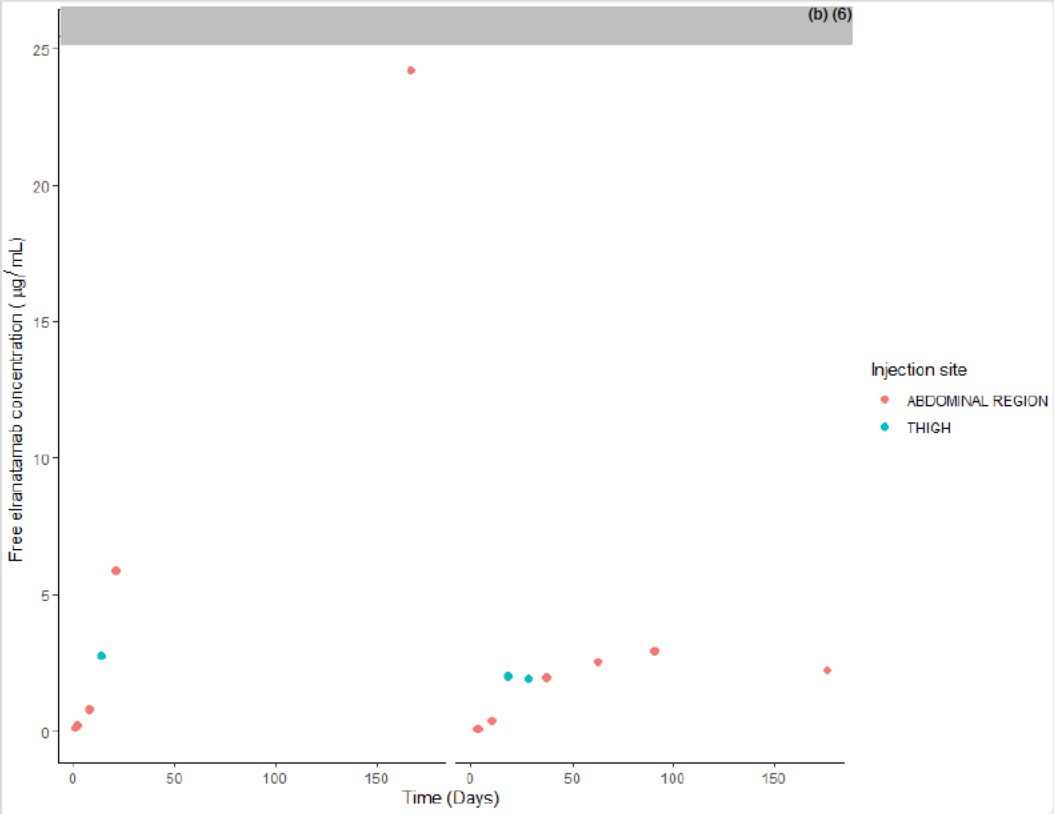


Source: Applicant CRS C1071001 study Report, Figure 9.

Injection site

According to Study C1071003 Protocol, injections to the abdomen are preferred. If SC injections in the abdominal location are not possible, then SC injection can be administered in the thighs. In agreement with the protocol instructions, 183 participants received all their doses in the abdominal region. There were 4 participants received dosing in thigh with at least 1 dose (range: 1 to 15), and no injections were reported in the upper extremities. Limited PK data were available after SC thigh dosing from 2 participants for free PK elranatamab (Figure 15). The conclusion of PK comparability cannot be made due to limitation of sample size.

Figure 15: FDA – Free elranatamab concentration vs time by injection site in two participants who had both abdominal and thigh injection.

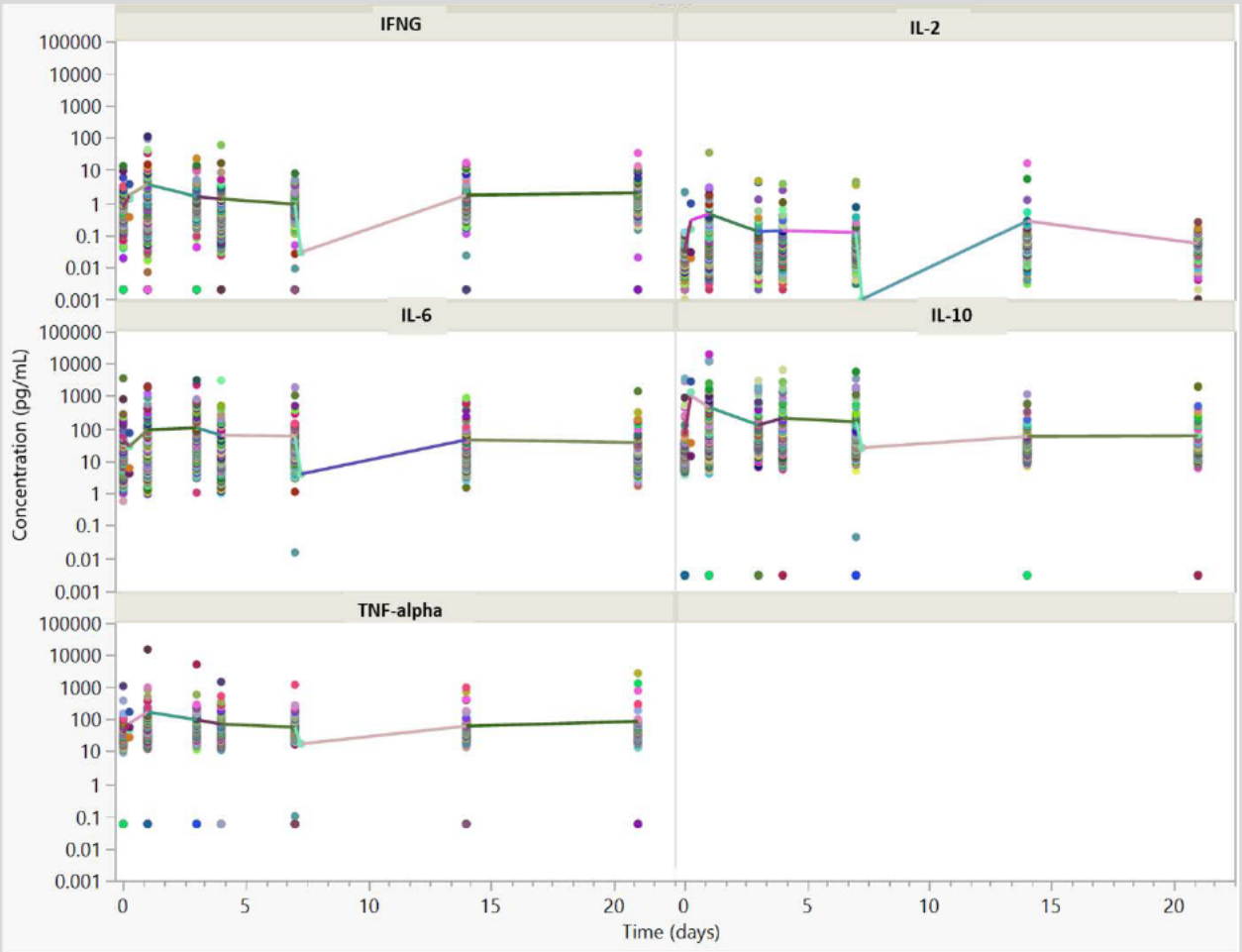


Red and blue colours mark 'dosing' in the abdomen and thigh, respectively. Elranatamab trough concentration associated with SC thigh administration is the one following the dosing time marked with the blue color.
Source: Applicant's response to IR on 6/09/2023, Figure 12

19.4.2 Pharmacodynamics

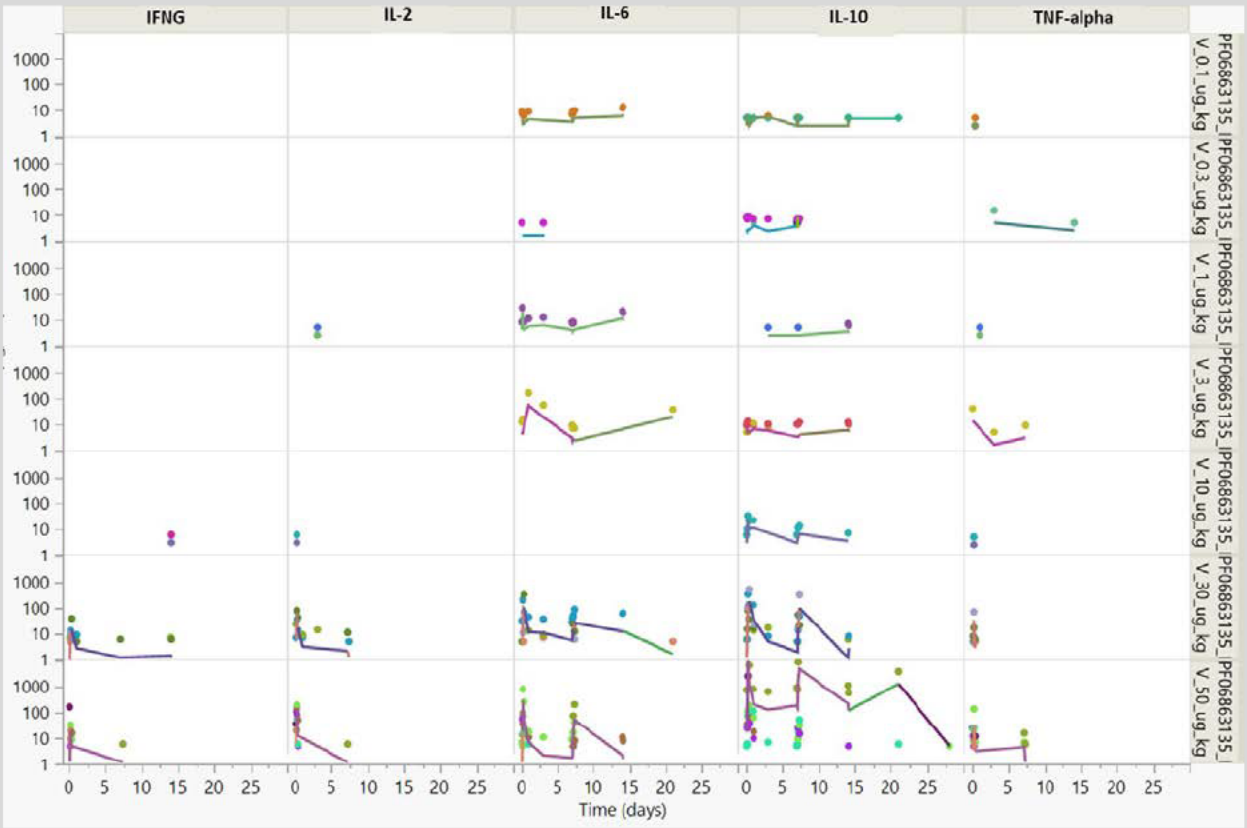
Cytokine elevation is observed following RP2D (12/32/76 mg) of the patients without tocilizumab use in study 1003 (Figure 16). Transient elevation of circulating cytokines was observed at 30 ug/kg (flat dose 2.3 mg) and above in study 1001 dose escalation (Figure 17, Figure 18, and Figure 19).

Figure 16: FDA – Observed cytokine levels over time following RP2D (12/32/76 mg) of the patients without tocilizumab use in study 1003



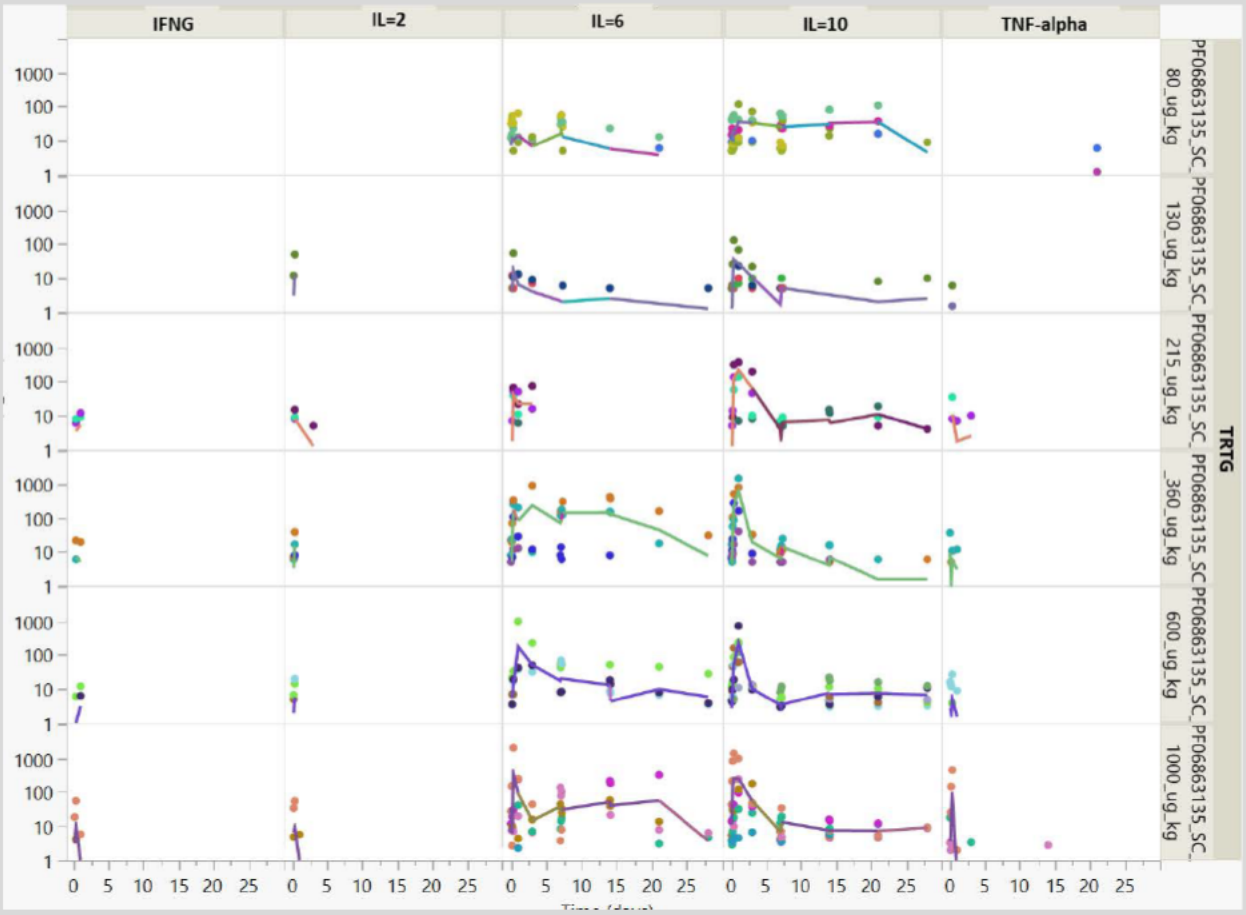
Each point represents a patient. Lines represent arithmetic mean value. Lines represent arithmetic mean value. IFNG represents interferon gamma (IFN-γ); IL-2 represents interleukin 2; IL-6 represents interleukin 6; IL-10 represents interleukin 10; TNF represents tumor necrosis factor-alpha (TNFα).
Source: FDA analysis created from poppk1 dataset

Figure 17: FDA – Cytokine concentration-time profiles following single intravenous dose of elranatamab of total population in study 1001 dose escalation



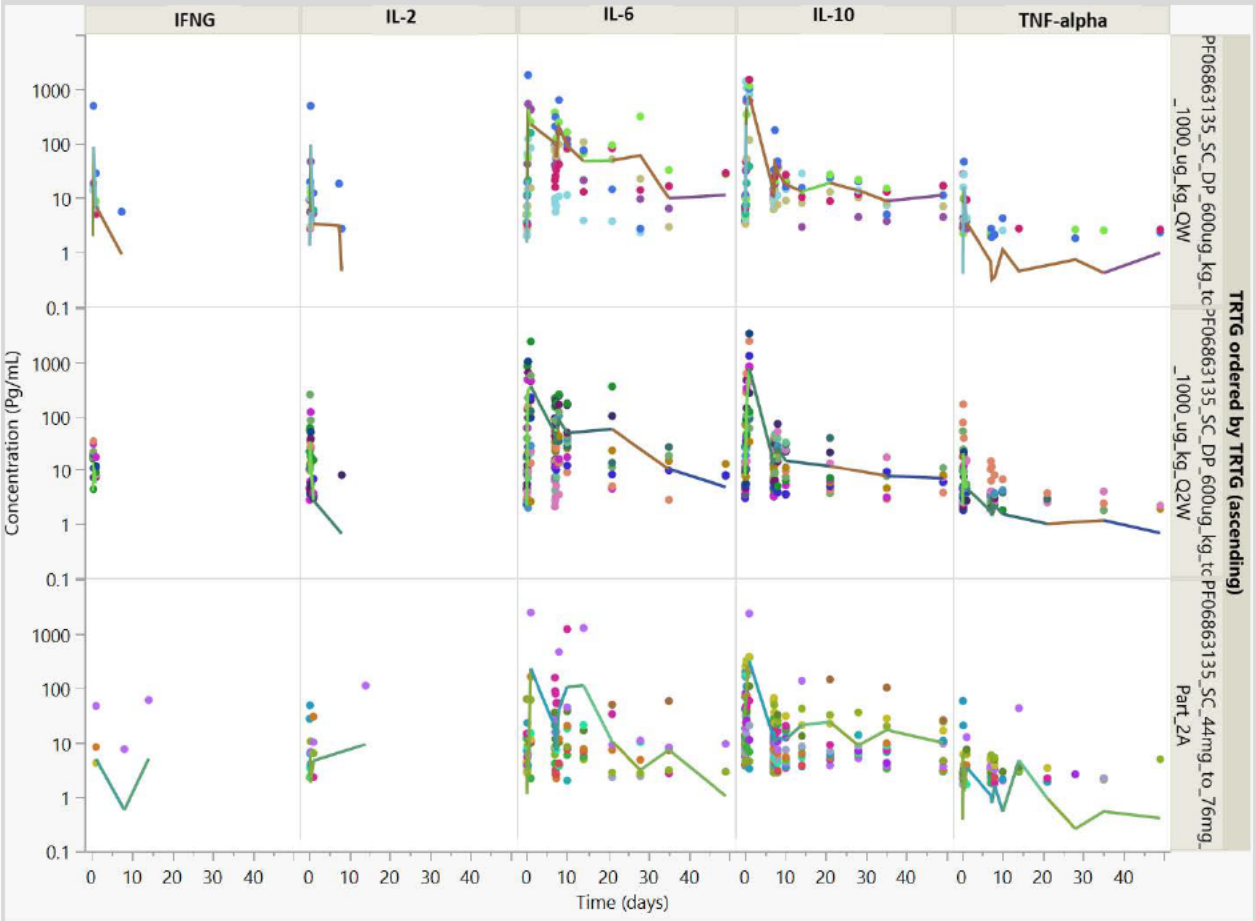
Each point represents a patient. Lines represent arithmetic mean value. Lines represent arithmetic mean value. IFNG represents interferon gamma (IFN-γ); IL-2 represents interleukin 2; IL-6 represents interleukin 6; IL-10 represents interleukin 10; TNF represents tumor necrosis factor-alpha (TNFα).
Source: FDA analysis created from poppk1 dataset.

Figure 18: FDA – Cytokine Concentration-Time Profiles following Single Subcutaneous Dose of Elranatamab in Study 1001 Dose Escalation



Each point represents a patient. Lines represent arithmetic mean value. Lines represent arithmetic mean value. IFNG represents interferon gamma (IFN-γ); IL-2 represents interleukin 2; IL-6 represents interleukin 6; IL-10 represents interleukin 10; TNF represents tumor necrosis factor-alpha (TNFα).
Source: FDA analysis created from poppk1 dataset.

Figure 19: FDA – Cytokine Concentration-Time Profiles of Priming Cohorts (600 µg/kg to 1000 µg/kg full dose either QW or Q2W and 44 mg to 76 mg QW) of Elranatamab in Study 1001 Dose Escalation.



Each point represents a patient. Lines represent arithmetic mean value. Lines represent arithmetic mean value. IFNG represents interferon gamma (IFN-γ); IL-2 represents interleukin 2; IL-6 represents interleukin 6; IL-10 represents interleukin 10; TNF represents tumor necrosis factor-alpha (TNFα).
Source: FDA analysis created from poppk1 dataset.

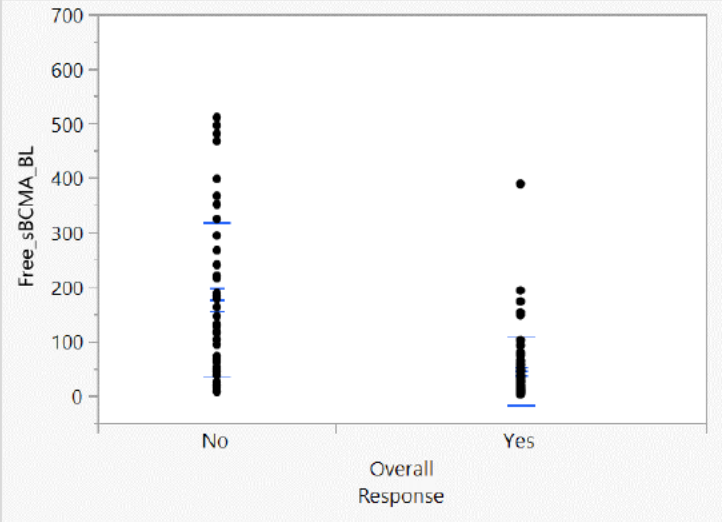
sBCMA

FDA's analysis of study 1003 further showed that free sBCMA levels at both baseline and Cycle 2 Day 1 (C2D1) are significantly ($p<0.001$) associated with the level of response to elranatamab. FDA's analysis showed that free sBCMA levels were significantly ($p<0.001$) associated with the level of response at baseline regardless of prior BCMA treatment. In study 1003 cohort A, the responder group (n=70) had significantly ($p<0.001$) lower mean (±SD) free sBCMA levels (45 ± 62.5 ng/dL) compared with free sBCMA levels (176 ± 141.7 ng/dL) in the non-responder group (n=45) as shown in Figure 20. A similar pattern was also observed in cohort B where patients in the responder group (n=26) had a significantly ($p<0.001$) lower mean (±SD) free sBCMA levels (39.1 ± 51.0ng/dL) compared with free sBCMA levels (128.1 ± 127.0ng/dL) in the non-responder group (n=33) as shown in Figure 21.

Overall, the non-responder group had higher free sBCMA levels at baseline and C2D1 than the responder group. Notably, the mean free sBCMA levels at C2D1 (153.7 ng/mL) did not significantly change from baseline (155.7 ng/mL) in the non-responder group. However, the mean free sBCMA levels at C2D1 (6.5 ng/mL) significantly ($p<0.001$) changed from baseline (43.4 ng/mL) in the responder group (Figure 22). Similar observations have been reported in other bispecific drugs such as teclistamab and talquetamab (Girgis S, et al. Blood Adv. 2023 Feb 28;7(4):644-648). Most patients who responded to the forementioned drugs had significant reductions in sBCMA from baseline following treatment. Like elranatamab (Figure 24), the degree of sBCMA reduction corresponded to the depth of response, with the greatest reduction from baseline observed for patients who achieved a stringent complete response, complete response, and very good partial response (Girgis S, et al. Blood Adv. 2023 Feb 28;7(4):644-648). Collectively, our data further suggest that both baseline free sBCMA and changes in free sBCMA levels at C2D1 may serve as a potential biomarker for the response to elranatamab therapy in RRMM patients.

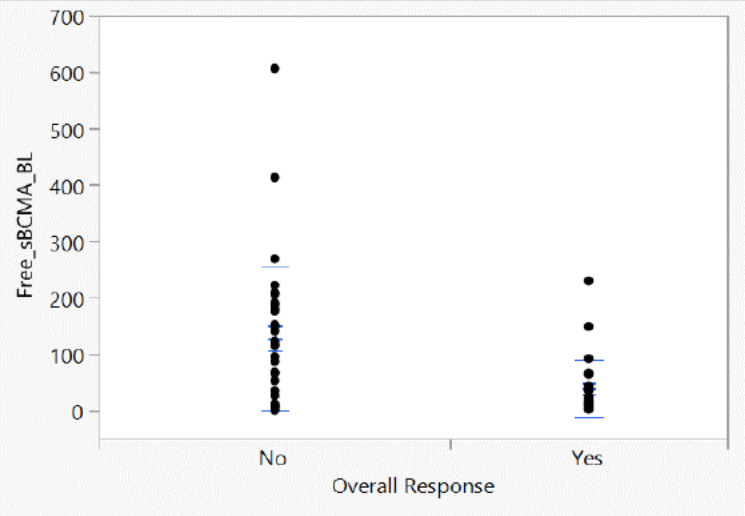
Of note, association between sBCMA and response may be also confounded by the association of sBCMA with severity of disease. Baseline sBCMA was significantly higher in participants with disease stage 3. Baseline sBCMA was also significantly higher in participants with high tumor burden (high tumor burden defined as plasma cell infiltrate in the bone marrow ≥ 80% or serum M-spike ≥ 5 g/dL or FLC ≥ 5000 mg/L). Additionally, sBCMA was also associated free elranatamab concentration. Due to the complex interplay effects of disease on biomarkers, disease on response and biomarker on PK, it is needed to excise careful interpretation of the current result.

Figure 20: FDA – Association between baseline sBCMA and overall response in Study 1003, Cohort A



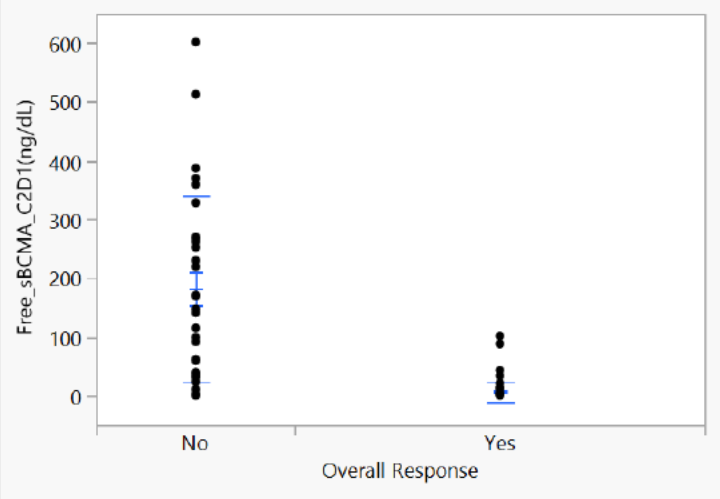
Source: FDA analysis created from Applicant's response to IR 4/27/2023, dataset titled 'C107_COMBINED_EFFICACY_IR_21MAR2023.csv'

Figure 21: FDA – Association between baseline sBCMA and overall response in Study 1003, Cohort B



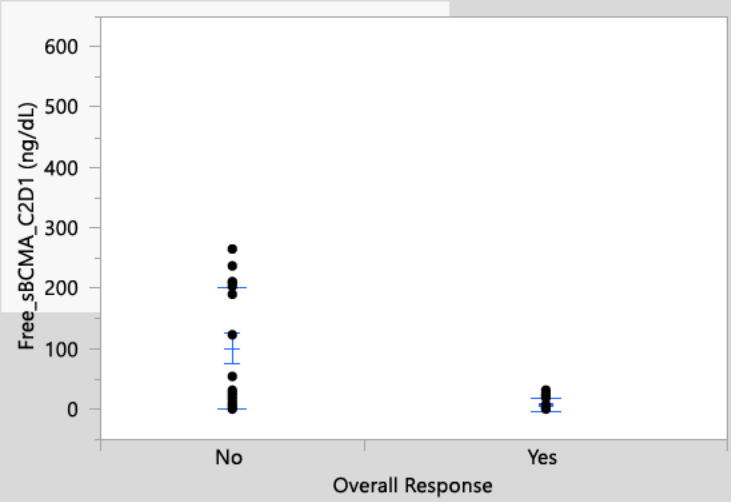
Source: FDA analysis created from Applicant's response to IR 4/27/2023, dataset titled 'C107_COMBINED_EFFICACY_IR_21MAR2023.csv'

Figure 22: FDA – sBCMA level at Cycle 2 Day 1 comparison by response Study 1003, Cohort A



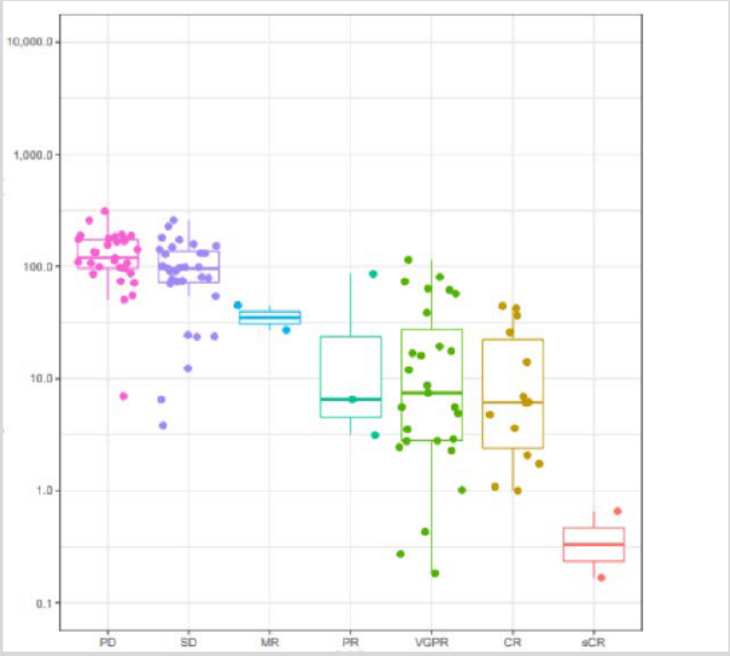
Source: FDA analysis created from Applicant's response to IR 4/27/2023, dataset titled 'C107_COMBINED_EFFICACY_IR_21MAR2023.csv'

Figure 23: FDA – sBCMA level at Cycle 2 Day 1 comparison by response Study 1003 Cohort B



Source: FDA analysis created from Applicant's response to IR 4/27/2023, dataset titled 'C107_COMBINED_EFFICACY_IR_21MAR2023.csv'

Figure 24: FDA – Percent change from baseline free sBCMA at cycle 2 day 1 vs. best overall response, study 1003



Abbreviations: PD=Progressive disease; SD=Stable disease; MR=Minimal response; PR=Partial response; VGPR=Very good partial response; CR=Complete response; sCR=Stringent Complete Response
Source: PMAR-1354 Study Report, Figure 11

19.4.3 Population PK Analysis

19.4.3.1 Executive Summary

The FDA's Assessment:

Target (sBCMA) mediated drug (elranatamab) disposition (TMDD) model was utilized to capture the time course of both elranatamab and sBCMA simultaneously. The model can be used to conduct simulation of both kinetics of elranatamab and sBCMA for a variety circumstance such as dose reduction, interruption, and discontinuation. The elranatamab exposure generated from this TMDD model was used to conduct exposure-response analysis for both efficacy and safety. The TMDD model is acceptable in general; however, it does not capture the drug concentration as well as ADVAN4 TRANS4 at high levels which usually represent the steady-state conditions, and this may have caused bias in the exposure-response analysis, particularly, the exposure-safety analysis.

19.4.3.2 PPK Assessment Summary

The Applicant's Position:

General Information		
Objectives of PPK Analysis		• *To characterize the population PK of free and total elranatamab* • *To identify potential covariates that may be important predictors of variability in free* and total elranatamab PK • *Predict individual exposure for E-R analysis*
Study Included		*C1071001, C1071002, C1071003, C1071009*
Dose(s) Included		*IV: 0.1, 0.3, 1, 3, 10, 30, and 50 mg/kg QW* *SC: 80, 130, 215, 360, 600, and 1000 mg/kg QW* *SC: 600 mg/kg for the first week, then 1000 mg/kg QW or Q2W* *SC: 44 mg for the first week, then 76 mg QW* *SC: 12/32/76 mg C1D1/C1D4/C1D8 then 76 mg QW* *SC: 4/20/76 mg C1D1/C1D4/C1D8 then 76 mg QW starting on C1D15*
Population Included		*Participants with RRMM.*
Population Characteristics (Table 69, Table 70)	General	*Age median (range) 66.00 (36.00-89.00) years* *Weight median (range) 74.46 (36.58-107.47) kg* *167 (52%) male* *29 (9%) Black, 49 (15%) Asian, 193 (60%) White, 50 (16%) missing*
	Organ Impairment	*Hepatic (NCI ODWGC): 278 (60 %) Normal, 33(10%) Mild Group 1, 12 (4%) Mild Group 2, 1 (<1%) severe category* *Renal (NKF KDOQI): 128 (40%) Normal, 123 (38%) Mild, 70 (22%) Moderate, 3 (1%) severe category*
	Pediatrics (if any)	*Not applicable*

No. of Patients, PK Samples, and BLQ		*13233 observations; 3739 total elranatamab (<1% post-dose BLQ) observations, 2947 free elranatamab (13% post-dose BLQ) observations, 3812 total sBCMA (3% post-dose BLQ) observations, and 2735 free sBCMA (22% post-dose BLQ) observations*
Sampling Schedule	Rich Sampling	*Timepoints of sampling (hour)* *Study C1071001 Part 1: C1D1: 0, 2, 4, 24, 72; C2D1: 0, 2, 4, 72.* *Study C1071001 Part 1.1 and 2A: C0D0: 0, 2, 4, 8, 24; C1D1: 0, 2, 4, 24.* *Study C1071002: C0D0: 0, 2, 4, 8, 24, 72; C1D1: 0, 2, 4, 8, 24.* *Sparse sampling (mostly predose) for other cycles and studies.*
	In ITT Population	*Not applicable*
Covariates Evaluated	Static	*Age, sex, body weight, eGFR, sBCMA, formulation strength, hepatic function (albumin, bilirubin, AST), baseline ADA, ADA status (positive/negative) (*Table 73, Table 74*)*
	Time-varying	*Time-varying ADA.*

Final Model	**Summary**	**Acceptability [FDA's comments]**
Software and Version	NONMEM version 7.5.0, PsN version 5.2.6, R version 3.6.1	Acceptable
Model Structure	*A semi-mechanistic target-binding model structure with first-order absorption*	Acceptable
Model Parameter Estimates	Table 71	Acceptable
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	*All main model parameters were estimated with good precision (relative standard error (RSE) <30%), were within the 95% CIs, and are in agreement with published values for monoclonal antibodies.*	Acceptable
BLQ for Parameter Accuracy	*M1 method – BLQ were ignored*	Acceptable
GOF, VPC	Figure 31 *for total elranatamab and* Figure 32 *for free elranatamab*	Acceptable
Significant Covariates and Clinical Relevance	Figure 33 *exposure by sex,* Figure 34 *exposure by body weight,* Figure 35 *exposure by Age.*	Acceptable

Analysis Based on Simulation (optional)	Figure 36 *and* Figure 37*: Dose-proportionality* *On average, total and free elranatamab exhibited approximately linear PK over the dose range evaluated via SC route (fixed doses of 6 to 76 mg QW).* Figure 38 *and* Figure 39*: Dose-proportionality across different baseline sBCMA levels, total PK is expected to increase in an approximately dose proportional manner over the clinical dose range (slope = 0.98 to 1.1). Free PK is linear over the clinical dose range except for patients with high baseline sBCMA (≥90th percentile) where more than dose proportional increase in exposure with dose is observed reflecting a potential impact of high baseline sBCMA on free elranatamab exposure. A trend for lower free elranatamab exposure was observed in participants with high baseline sBCMA* *The median accumulation ratio for the 76 mg QW dosing regimen of elranatamab was calculated for Cmax (4.8 for total and 6.6 for free), as well as for AUCtau (8.0 for total and 11.2 for free). The median time to 50% exposure reduction, i.e., time to half maximal concentration after 6 Cycles of 76 mg QW dosing of elranatamab, in the analysis population was approximately 25 days. Thus, participants who discontinue elranatamab after Cycle 6 are expected to have a 50% reduction from Cmax of elranatamab at a median (5th to*	Acceptable

	95th percentile) time of 25 (9.6 to 70) days after Tmax and a 97% reduction from Cmax at a median time of 130 (43 to 275) days after Tmax.	
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.3 PK	(b) (4) Absorption The mean bioavailability of elranatamab-xxxx was 56.2% when administered subcutaneously. The median T_{max} after elranatamab SC administration (b) (4) 3 to 7 days. Distribution (b) (4) Elimination (b) (4)	Acceptable

	(b) (4)	
	Specific Populations No clinically relevant differences in the pharmacokinetics of elranatamab-xxxx were observed based on age (36 to 89 years), sex (b) (4) race ((b) (4) White, (b) (4) Asian, (b) (4) Black), body weight (37 to 160 kg), mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] by Modification of Diet in Renal Disease [MDRD] method 30 to 89 mL/min/(b) (4), or mild hepatic impairment (b) (4) total bilirubin 1 to ≤1.5 x ULN (b) (4) (b) (4)	
	(b) (4)	

Table 69: Applicant – Summary of Participant Categorical Characteristics

Variable	Category	1-1	1-1.1QW	1-1.1Q2W	1-2A	2	3-A	3-B	9-1	9-2A	Total
N (%)		53	6	15	13	4	123	64	33	10	321
Route	IV	23 (43%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	23 (7%)
	SC	30 (57%)	6 (100%)	13 (100%)	15 (100%)	4 (100%)	123 (100%)	64 (100%)	33 (100%)	10 (100%)	298 (93%)
Formulation Strength	2 mg/mL	29 (55%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	29 (9%)
	10 mg/L	24 (45%)	6 (100%)	13 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	43 (13%)
	40 mg/L	0 (0%)	0 (0%)	0 (0%)	15 (100%)	4 (100%)	123 (100%)	64 (100%)	33 (100%)	10 (100%)	249 (78%)
Sex	Male	26 (49%)	2 (33%)	9 (69%)	8 (53%)	3 (75%)	68 (55%)	30 (47%)	14 (42%)	7 (70%)	167 (52%)
	Female	27 (51%)	4 (67%)	4 (31%)	7 (47%)	1 (25%)	55 (45%)	34 (53%)	19 (58%)	3 (30%)	154 (48%)
Race	Black	11 (21%)	2 (33%)	2 (15%)	1 (7%)	0 (0%)	9 (7%)	2 (3%)	2 (6%)	0 (0%)	29 (9%)
	Asian	3 (6%)	0 (0%)	1 (8%)	2 (13%)	4 (100%)	16 (13%)	1 (2%)	19 (58%)	3 (30%)	49 (15%)
	White	36 (68%)	4 (67%)	10 (77%)	10 (67%)	0 (0%)	72 (59%)	44 (69%)	11 (33%)	6 (60%)	193 (60%)
	Missing	3 (6%)	0 (0%)	0 (0%)	2 (13%)	0 (0%)	26 (21%)	17 (27%)	1 (3%)	1 (10%)	50 (16%)
EMD from INV	No	18 (34%)	2 (33%)	5 (38%)	7 (47%)	2 (50%)	85 (69%)	28 (44%)	20 (61%)	6 (60%)	173 (54%)
	Yes	11 (21%)	3 (50%)	4 (31%)	2 (13%)	2 (50%)	38 (31%)	36 (56%)	13 (39%)	4 (40%)	113 (35%)
	Missing	24 (45%)	1 (17%)	4 (31%)	6 (40%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	35 (11%)

Version date: January 2020 (ALL NDA/ BLA reviews)

Table 69: Applicant – Summary of Participant Categorical Characteristics

Variable	Category	1-1	1-1.1QW	1-1.1Q2W	1-2A	2	3-A	3-B	9-1	9-2A	Total
ADAB	Negative	42 (79%)	4 (67%)	10 (77%)	12 (80%)	4 (100%)	102 (83%)	42 (66%)	30 (91%)	6 (60%)	252 (79%)
	Positive	8 (15%)	2 (33%)	1 (8%)	1 (7%)	0 (0%)	11 (9%)	13 (20%)	2 (6%)	2 (20%)	40 (12%)
	Not evaluable	3 (6%)	0 (0%)	2 (15%)	2 (13%)	0 (0%)	10 (8%)	9 (14%)	1 (3%)	2 (20%)	29 (9%)
ADAT	Negative	42 (79%)	6 (100%)	10 (77%)	13 (87%)	2 (50%)	101 (82%)	52 (81%)	30 (91%)	8 (80%)	264 (82%)
	Positive	8 (15%)	0 (0%)	1 (8%)	0 (0%)	2 (50%)	12 (10%)	3 (5%)	2 (6%)	0 (0%)	28 (9%)
	Not evaluable	3 (6%)	0 (0%)	2 (15%)	2 (13%)	0 (0%)	10 (8%)	9 (14%)	1 (3%)	2 (20%)	29 (9%)

Repository artifact ID FI-32714420.

PK=pharmacokinetic; ADA=anti-drug antibody; ADAT=treatment-induced or treatment boosted ADA; ADAB=baseline ADA; EMD=extramedullary disease; INV=investigator assessment; 1-1=C1071001 Part 1; 1QW=C1071001 Part 1.1 QW; 1Q2W=C1071001 Part 1.1 Q2W; 1-2A=C1071001 Part 2A; 2=C1071002; 3A=C1071003 Cohort A; 3B=C1071003 Cohort B; 9-1=C1071009 Part 1; 9-2A=C1071009 Part 2A.

Table 70: Applicant – Summary of Participant Continuous Characteristics

Variable	Cohort	N	Nm	Mean (SD)	Median (Range)
Age (years)	1-1	53	0	63.55 (9.61)	64.00 (46.00-82.00)
	1.1QW	6	0	59.50 (13.31)	58.50 (42.00-74.00)
	1.1Q2W	13	0	67.38 (7.26)	67.00 (53.00-79.00)
	1-2A	15	0	66.73 (9.65)	69.00 (50.00-80.00)
	2	4	0	64.00 (10.03)	68.50 (49.00-70.00)
	3-A	123	0	67.07 (9.45)	68.00 (36.00-89.00)
	3-B	64	0	65.69 (9.42)	67.00 (41.00-84.00)
	9-1	33	0	60.42 (10.14)	63.00 (36.00-79.00)
	9-2A	10	0	64.70 (8.38)	66.00 (49.00-78.00)
	Total	321	0	65.27 (9.68)	66.00 (36.00-89.00)
Body weight (kg)	1-1	53	0	79.13 (20.71)	75.10 (42.00-120.00)
	1.1QW	6	0	68.83 (13.45)	64.50 (56.00-87.30)
	1.1Q2W	13	0	73.57 (14.93)	71.10 (51.30-99.40)
	1-2A	15	0	75.17 (19.25)	67.50 (55.20-121.90)
	2	4	0	68.78 (5.17)	70.10 (61.40-73.50)
	3-A	123	0	74.05 (18.62)	72.00 (40.90-159.60)
	3-B	64	0	73.23 (16.73)	69.30 (36.50-119.30)
	9-1	33	0	68.19 (15.24)	66.30 (44.50-101.50)
	9-2A	10	0	75.38 (14.04)	79.60 (54.50-91.70)
	Total	321	0	74.04 (17.95)	71.50 (36.50-159.60)
eGFR (ml/mi/1.73m2)	1-1	53	0	76.33 (20.04)	74.46 (36.58-107.47)
	1.1QW	6	0	87.84 (23.40)	94.02 (44.58-110.63)
	1.1Q2W	13	0	77.81 (21.01)	79.97 (44.01-103.27)
	1-2A	15	0	81.87 (21.20)	92.52 (36.29-103.99)
	2	4	0	92.52 (13.02)	95.63 (74.12-104.70)
	3-A	123	0	75.07 (21.98)	74.83 (22.63-122.77)
	3-B	64	0	77.91 (24.47)	81.86 (22.50-114.86)
	9-1	33	0	86.67 (20.73)	96.52 (42.09-124.58)
	9-2A	10	0	92.22 (21.28)	97.38 (33.66-108.49)
	Total	321	0	78.46 (22.18)	81.21 (22.50-124.58)
Total sBCMA (nM)	1-1	53	0	16.24 (19.24)	8.44 (0.00-74.63)
	1.1QW	6	1	38.41 (64.72)	12.04 (2.83-153.52)
	1.1Q2W	13	2	21.73 (23.07)	18.70 (0.00-81.67)
	1-2A	15	1	14.31 (25.02)	4.19 (0.42-95.19)
	2	4	4	-	-
	3-A	123	0	16.31 (30.43)	7.52 (0.00-266.67)
	3-B	64	0	21.24 (29.26)	10.66 (0.00-161.67)
	9-1	33	0	8.72 (9.10)	5.91 (0.41-48.52)

Table 70: Applicant – Summary of Participant Continuous Characteristics

Variable	Cohort	N	Nm	Mean (SD)	Median (Range)
	9-2A	10	1	13.99 (14.30)	6.35 (0.67-38.52)
	Total	321	9	16.90 (27.01)	8.29 (0.00-266.67)
Albumin (g/dL)	1-1	53	0	3.54 (0.64)	3.70 (2.00-4.60)
	1.1QW	6	0	3.53 (0.39)	3.40 (3.20-4.30)
	1.1Q2W	13	0	3.56 (0.71)	3.70 (2.40-4.50)
	1-2A	15	0	3.41 (0.53)	3.30 (2.60-4.20)
	2	4	0	3.48 (0.26)	3.50 (3.20-3.70)
	3-A	123	0	3.61 (0.54)	3.60 (2.10-4.70)
	3-B	64	0	3.55 (0.53)	3.50 (2.60-4.50)
	9-1	33	0	3.67 (0.54)	3.70 (1.90-4.80)
	9-2A	10	0	3.76 (0.68)	3.75 (2.30-4.80)
	Total	321	0	3.59 (0.56)	3.60 (1.90-4.80)
Bilirubin (mg/dL)	1-1	53	0	0.53 (0.29)	0.50 (0.10-1.40)
	1.1QW	6	0	0.38 (0.31)	0.25 (0.20-1.00)
	1.1Q2W	13	0	0.62 (0.35)	0.50 (0.30-1.40)
	1-2A	15	0	0.47 (0.23)	0.40 (0.20-1.00)
	2	4	0	0.77 (0.43)	0.65 (0.40-1.40)
	3-A	123	0	0.53 (0.41)	0.40 (0.10-3.80)
	3-B	64	0	0.52 (0.29)	0.40 (0.20-1.40)
	9-1	33	0	0.56 (0.22)	0.50 (0.20-0.90)
	9-2A	10	0	0.52 (0.33)	0.45 (0.10-1.10)
	Total	321	0	0.53 (0.34)	0.40 (0.10-3.80)
AST (U/L)	1-1	53	0	30.96 (33.75)	23.00 (9.00-247.00)
	1.1QW	6	0	33.00 (30.92)	20.50 (12.00-93.00)
	1.1Q2W	13	0	26.00 (10.80)	22.00 (13.00-49.00)
	1-2A	15	0	19.47 (9.66)	18.00 (8.00-40.00)
	2	4	0	19.50 (7.85)	16.50 (14.00-31.00)
	3-A	123	0	24.60 (12.84)	21.00 (10.00-86.00)
	3-B	64	0	30.20 (12.78)	28.00 (12.00-79.00)
	9-1	33	0	22.06 (10.48)	19.00 (12.00-73.00)
	9-2A	10	0	23.60 (10.85)	21.00 (10.00-42.00)
	Total	321	0	26.39 (18.22)	23.00 (8.00-247.00)
Serum IgG (g/L)	1-1	53	16	11.59 (16.12)	3.44 (1.24-81.92)
	1.1QW	6	6	-	-
	1.1Q2W	13	13	-	-
	1-2A	15	15	-	-
	2	4	4	-	-
	3-A	123	41	15.51 (17.17)	9.79 (0.30-77.16)
	3-B	64	7	15.24 (17.36)	6.65 (0.43-63.84)
	9-1	33	33	-	-
	9-2A	10	10	-	-
	Total	321	145	14.60 (16.99)	5.54 (0.30-81.92)

Repository artifact ID FI-32711023. Line 1 substituted. Table abbreviations: BMI=body mass index; kg=kilogram; Max=maximum value; m2=meters squared; Min=minimum value; N=number of participants; Nm=number of participants with missing observations; SD=standard deviation; eGFR=estimated glomerular filtration rate; 1-1=C1071001 Part 1; 1QW=C1071001 Part

Table 70: Applicant – Summary of Participant Continuous Characteristics

Variable	Cohort	N	Nm	Mean (SD)	Median (Range)

1.1 QW; 1Q2W=C1071001 Part 1.1 Q2W; 1-2A=C1071001 Part 2A; 2=C1071002; 3A=C1071003 Cohort A; 3B=C1071003 Cohort B; 9-1=C1071009 Part 1; 9-2A=C1071009 Part 2A.

Table 71: Applicant – Final Model Parameter Estimates

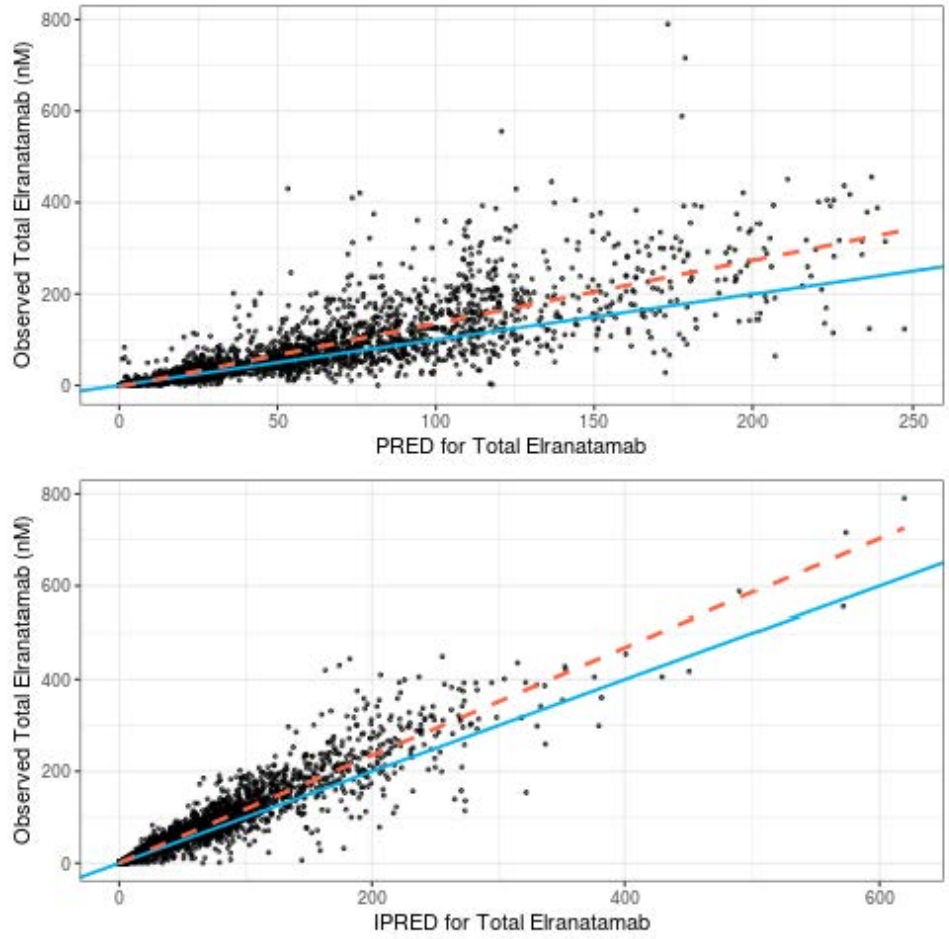
Parameter	Estimate	RSE	Shrinkage	CI
θCL elranatamab(*L/day*)	0.324	9.114	-	(0.266 ; 0.382)
θVc elranatamab(*L*)	4.777	5.745	-	(4.239 ; 5.315)
θ Vc sBCMA(*L*)	15.418	10.904	-	(12.123 ; 18.713)
θCL sBCMA(*L/day*)	0.273	21.030	-	(0.161 ; 0.386)
θCL complex(*L/day*)	0.164	9.201	-	(0.134 ; 0.193)
θVc complex(*L*)	3.802	4.848	-	(3.441 ; 4.164)
θBL sBCMA(*nM*)	6.914	7.793	-	(5.858 ; 7.970)
θVp elranatamab (*L*)	2.830	1.766	-	(2.732 ; 2.928)
θ_Q(*L/day*)	0.225	1.933	-	(0.217 ; 0.234)
θ_F	0.562	0.564	-	(0.556 ; 0.568)
θka (day-^{1})	0.287	4.432	-	(0.262 ; 0.311)
θ_{Kd}(*nM*)	3.138	3.312	-	(2.934 ; 3.342)
θResidual error total elranatamab	0.422	3.038	-	(0.397 ; 0.447)
θResidual error total sBCMA	0.347	4.028	-	(0.320 ; 0.375)
θResidual error free elranatamab	0.347	2.610	-	(0.330 ; 0.365)
θResidual error free sBCMA	0.518	3.503	-	(0.482 ; 0.553)
θSex on CL elranatamab	-0.492	12.533	-	(-0.613 ; -0.371)
θBwt on Vc elranatamab	1.017	22.351	-	(0.571 ; 1.462)
θAge on ka	-1.459	20.025	-	(-2.031 ; -0.886)
IIV	**CV (%)**	**RSE (%)**	**Shrinkage (%)**	**95% CI**
IIV on θVc elranatamab(%)	68.56	13.346	31.267	(58.91 ; 77.01)
IIV on θVc sBCMA(%)	135.98	31.910	24.118	(83.25 ; 173.38)
IIV on θCL sBCMA(%)	448.07	15.702	26.128	(372.8 ; 512.41)
IIV on θCL complex(%)	79.18	19.338	26.252	(62.45 ; 93.01)
IIV on θVc complex(%)	70.07	17.261	23.128	(57.01 ; 81.06)
IIV on θBL sBCMA(%)	134.61	13.078	0.276	(116.1 ; 150.9)
IIV on θVp elranatamab(%)	14.83	-	-	-
IIV on θ_Q(%)	14.83	-	-	-
IIV on θ_F(%)	14.83	-	-	-
IIV on θ_{ka}(%)	68.41	14.538	18.344	(57.88 ; 77.59)
IIV on θ_{Kd}(%)	14.83	-	-	-
OFV	52404.246	-	-	-

Repository artifact ID FI-36349537. Line 1 substituted.
Table abbreviations: CI=confidence interval; CL=clearance; CV=coefficient of variation; F=bioavailability; Prop=proportional; ka=first-order absorption rate constant; IIV=inter-individual variability; OFV=objective function value; Q=inter-compartmental clearance; RSE=relative standard error; sBCMA=soluble B-cell Maturation Antigen; Complex=elranatamab-sBCMA; Vc=central volume of distribution; Vp=peripheral volume of distribution; kd=dissociation constant of elranatamab:sBCMA.

Table 72: Applicant – Pharmacokinetic Parameters of Elranatamab-xxxx at the End of the Weekly Dosing (Week 24) at 76 mg

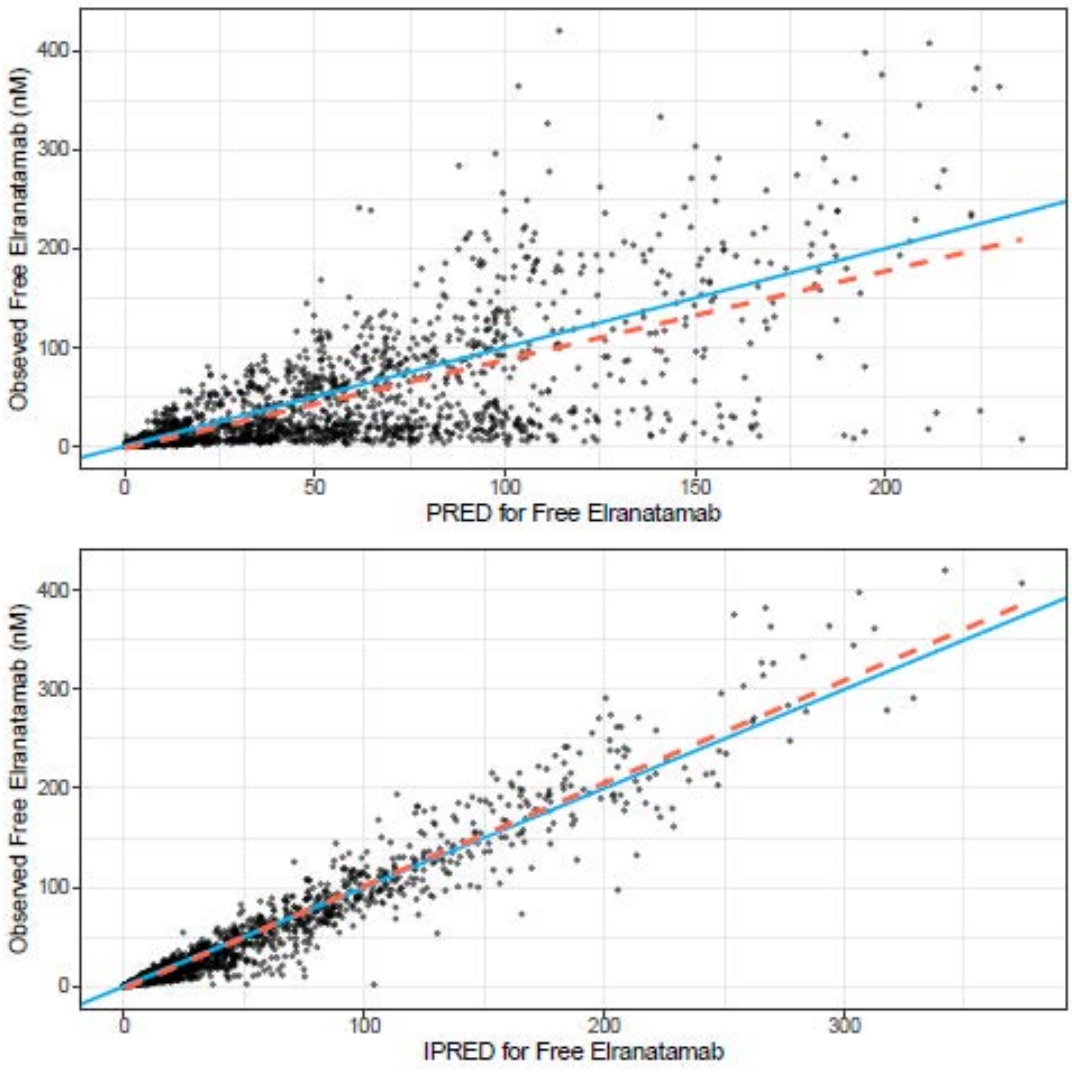
Pharmacokinetic Parameter	Geometric Mean (CV%)
C_{max} (mcg/mL)	25.8 (67%)
C_{trough} (mcg/mL)	23.9 (72%)
AUC_{tau} (mcg*day/mL)	173 (69%)

Figure 25: Applicant – Prediction-based Goodness-of-fit Plots for Total Elranatamab



Repository artifact ID FI-36317192.
Figure abbreviations: PRED=population predictions; IPRED=individual predictions.

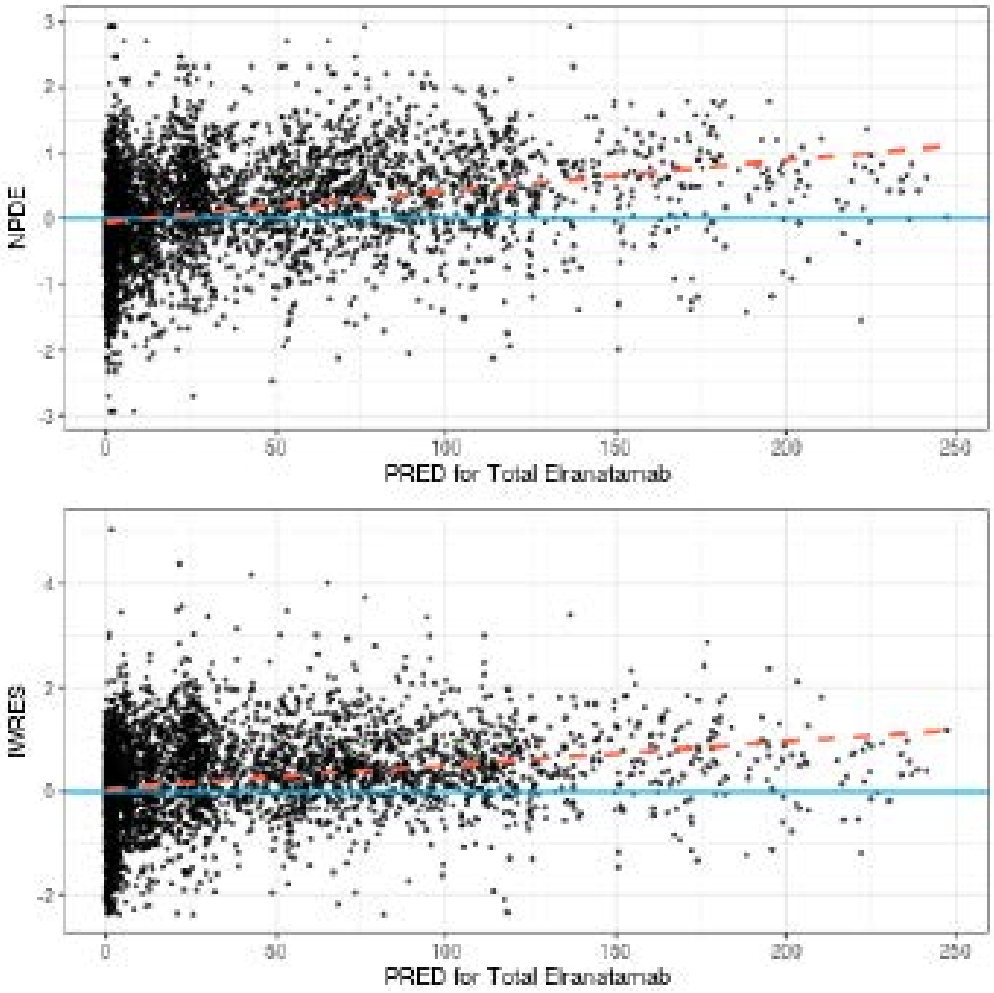
Figure 26: Applicant – Prediction-based Goodness-of-fit Plots for Free Elranatamab



Repository artifact ID FI-36317185.
Figure abbreviations: PRED=population prediction; IPRED=individual prediction.

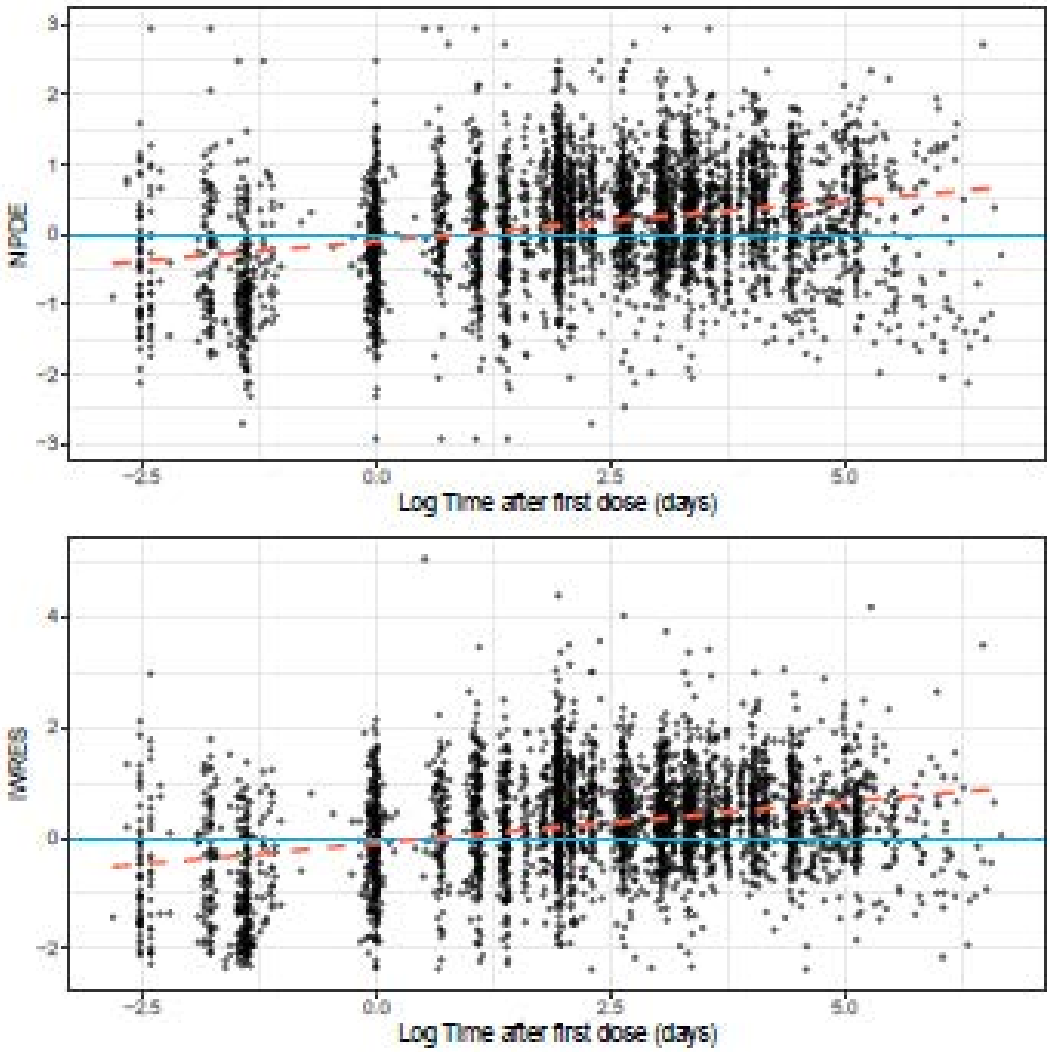
Residual-based diagnostic plots of NPDE and IWRES versus population predictions (PRED) and time (TAFD) are presented in Figure 27 and Figure 28 for total of elranatamab and in Figure 29 and Figure 30 for free elranatamab.

Figure 27: Applicant – Residuals Versus Population Predictions for Total Elranatamab



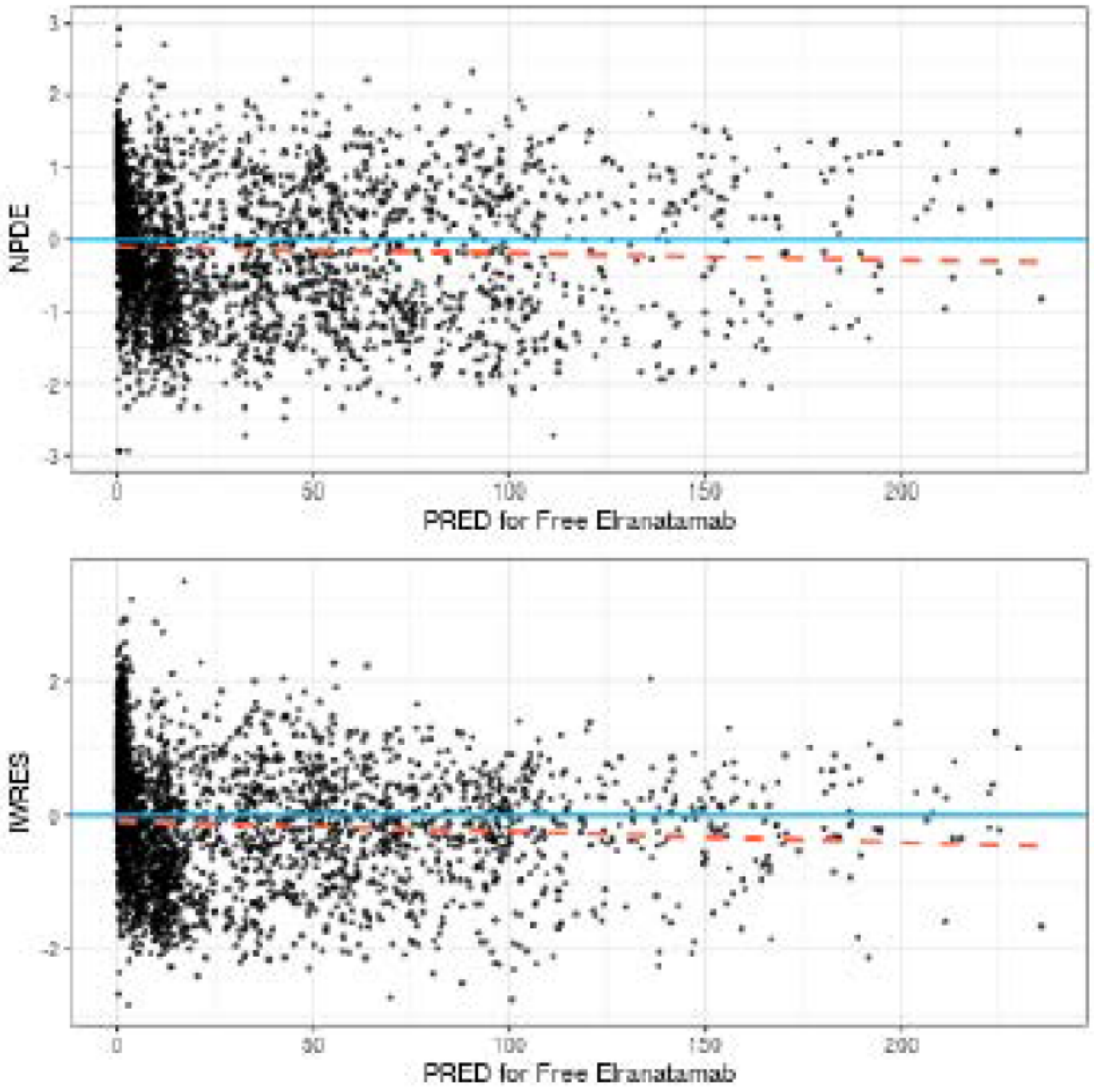
Repository artifact ID FI-36369898.
Figure abbreviations: NPDE=normalized prediction distribution error; PRED=population prediction; IWRES=individual weighted residual.

Figure 28: Applicant – Residuals Versus Time for Total Elranatamab



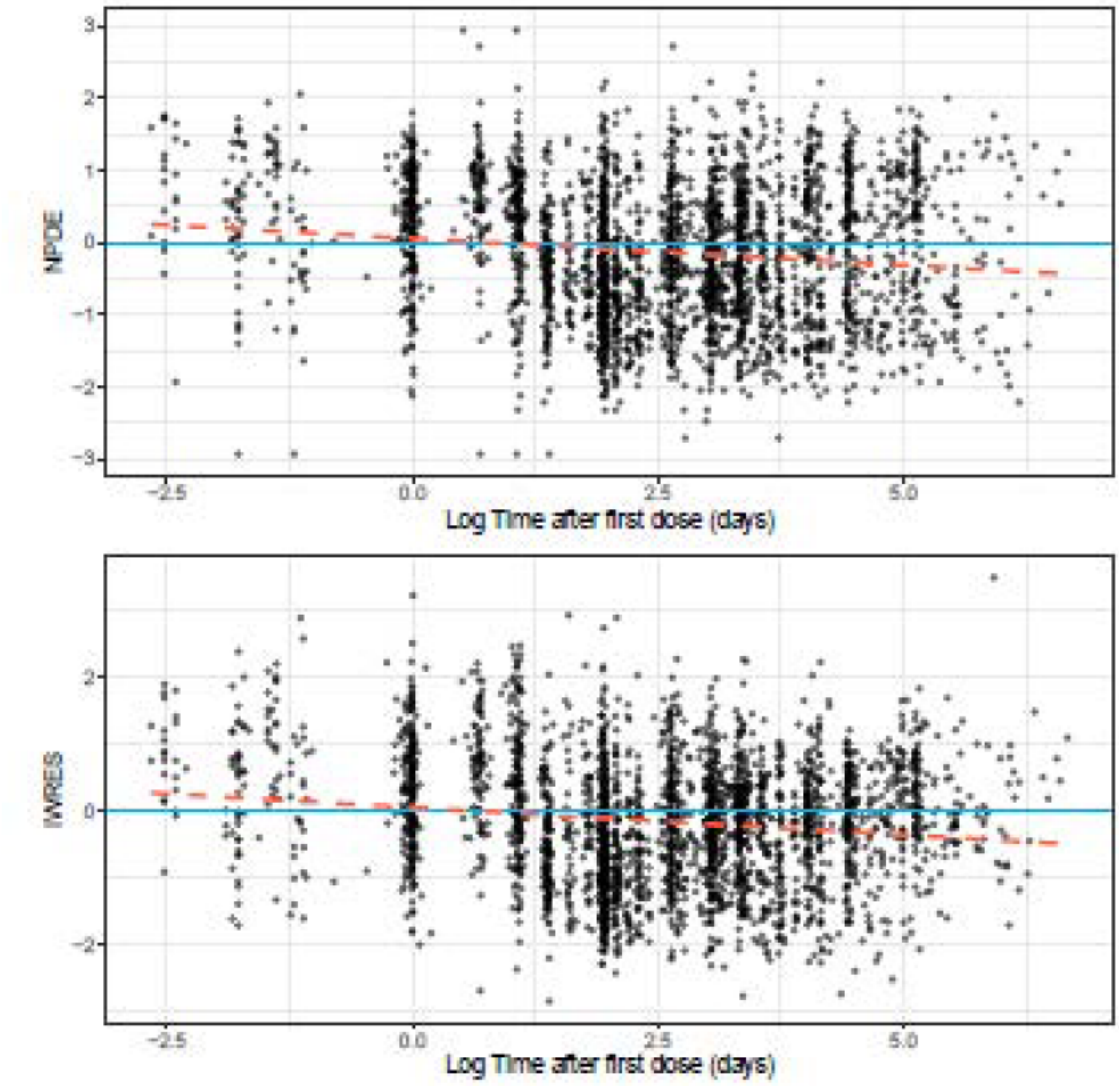
Repository artifact ID FI-36369899.
Figure abbreviations: NPDE=normalized prediction distribution error; IWRES=individual weighted residual.

Figure 29: Applicant – Residuals Versus Population Predictions for Free Elranatamab



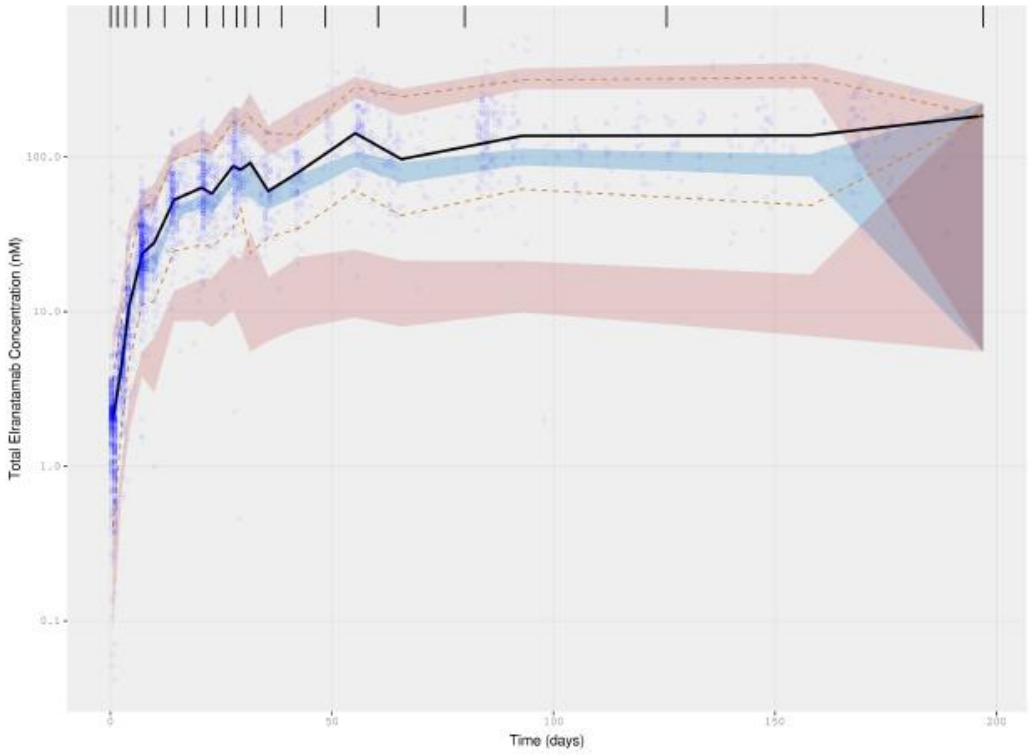
Repository artifact ID FI-36369890.
Figure abbreviations: NPDE=normalized prediction distribution error; PRED=population prediction; IWRES=individual weighted residual.

Figure 30: Applicant – Residuals Versus Time for Free Elranatamab



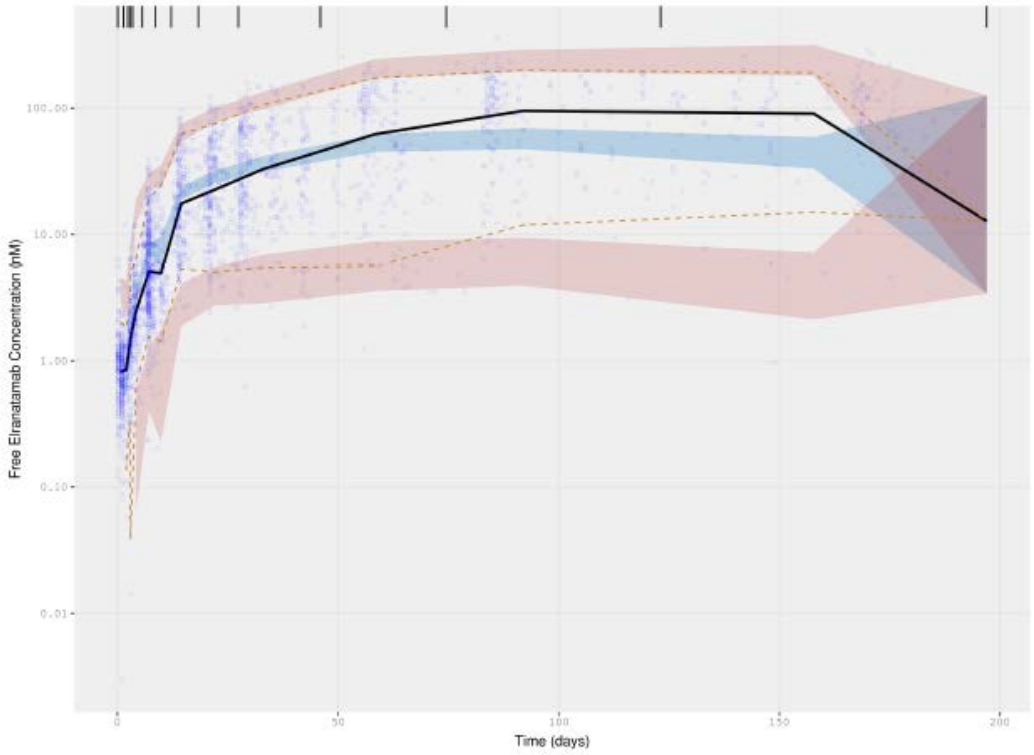
Repository artifact ID FI-36369891.
Figure abbreviations: NPDE=normalized prediction distribution error; IWRES=individual weighted residual.

Figure 31: Applicant – Final Model VPC for Total Elranatamab



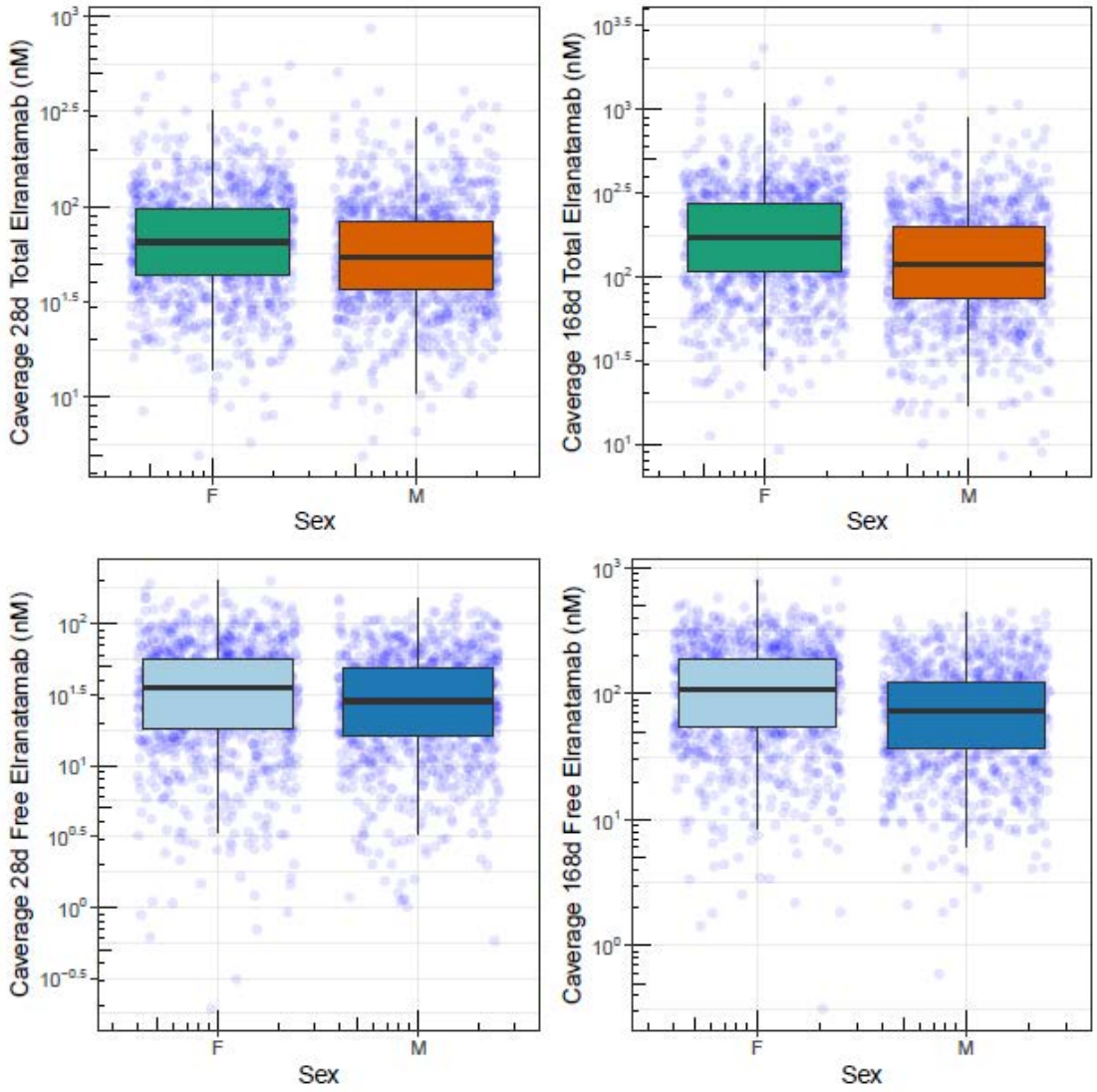
Repository artifact ID FI-36336821.
Blue circles represent the observed data and the solid black line represents the 50th percentile of the observed data. The dashed red lines represent the 5th and 95th percentiles of the observed data. The blue ribbon represents the 95% CI of the 50th percentile of the simulated data. The red ribbons represent the 95% CI of the 5th and 95th percentiles of the simulated data.
Figure abbreviations: VPC=visual predictive check.

Figure 32: Applicant – Final Model VPC for Free Elranatamab



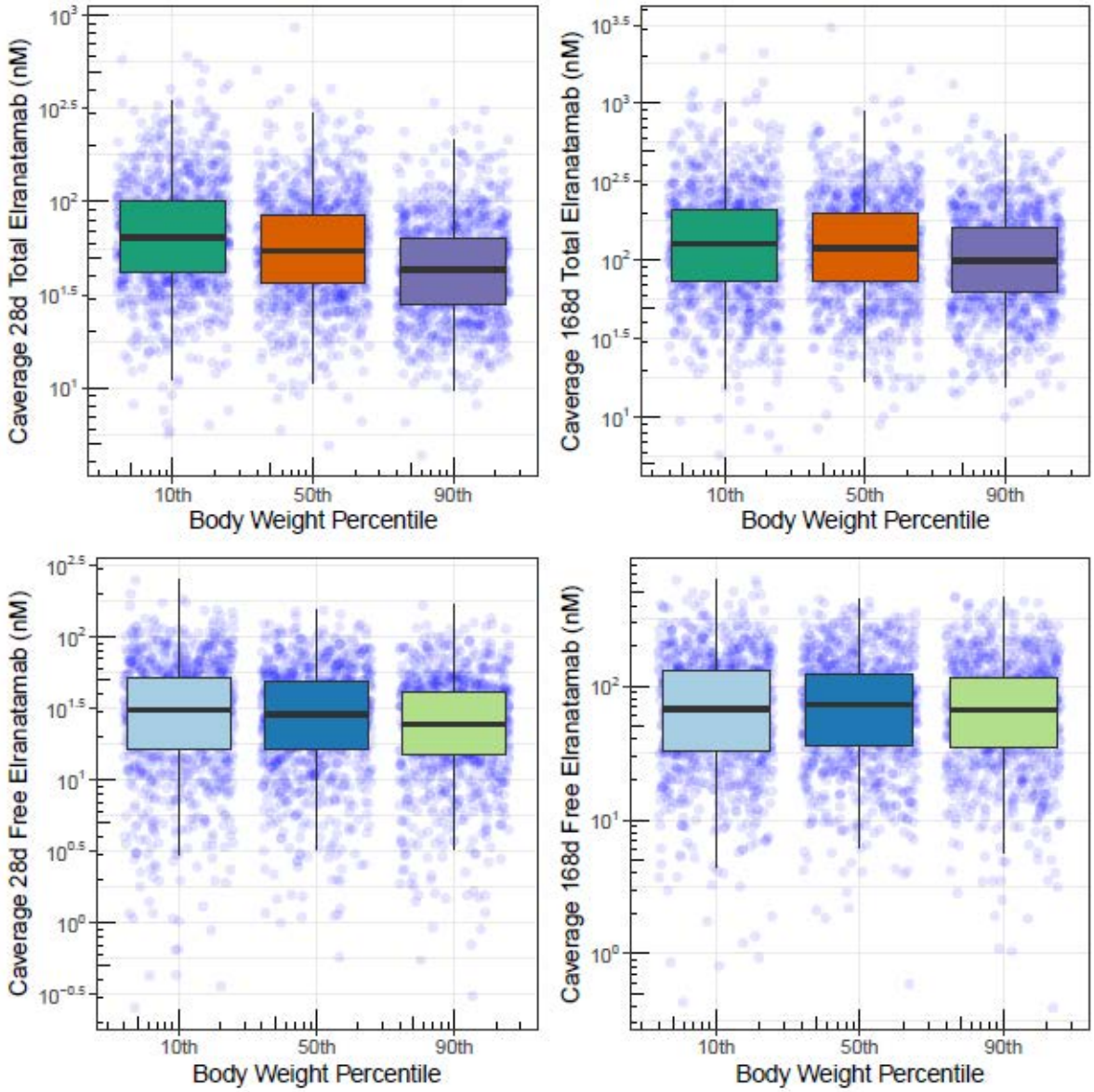
Repository artifact ID FI-36336824.
Blue circles represent the observed data and the solid black line represents the 50th percentile of the observed data. The dashed red lines represent the 5th and 95th percentiles of the observed data. The blue ribbon represents the 95% CI of the 50th percentile of the simulated data. The red ribbons represent the 95% CI of the 5th and 95th percentiles of the simulated data.
Figure abbreviations: VPC=visual predictive check.

Figure 33: Applicant – Elranatamab Exposure by Sex



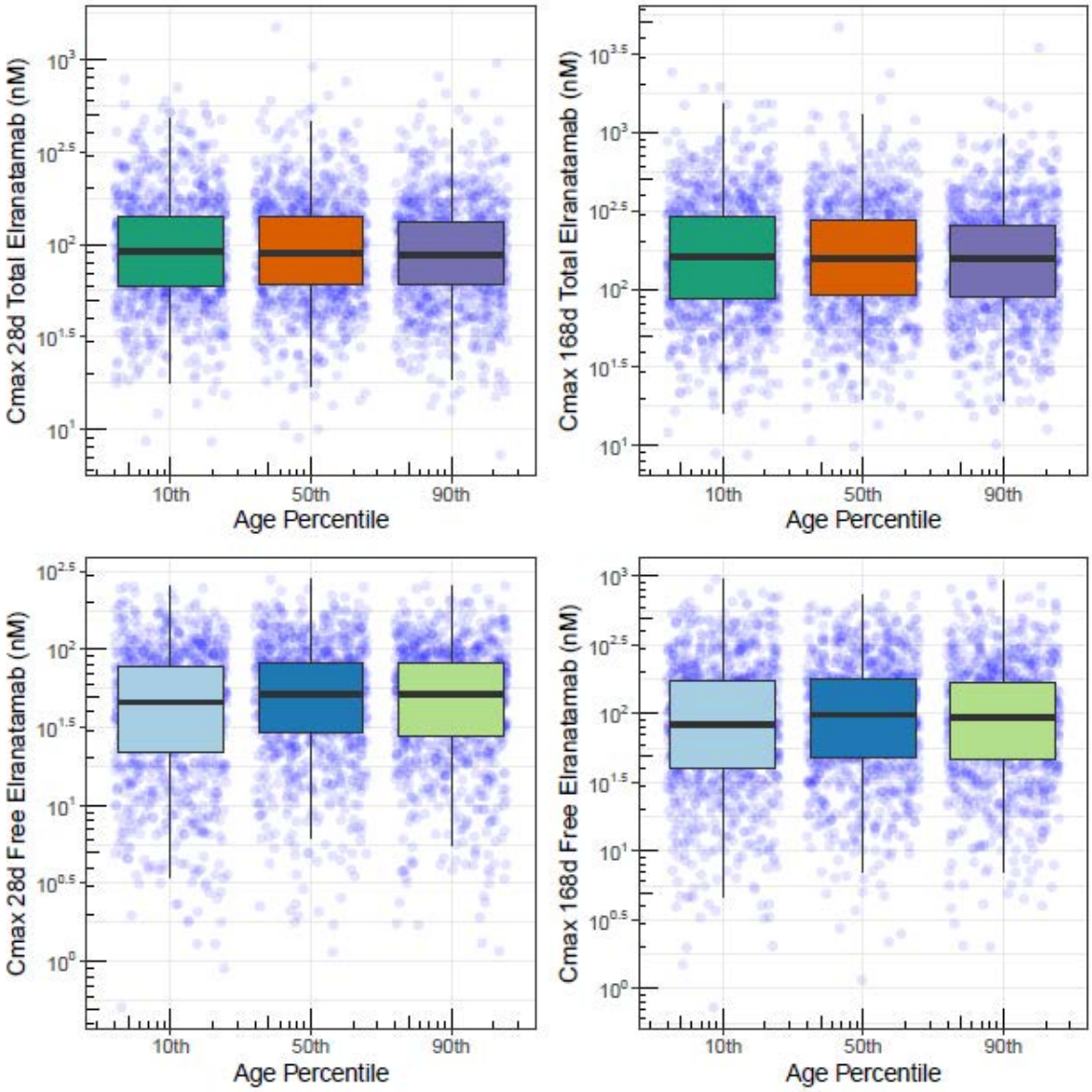
Repository artifact ID FI-36375389.
Assuming a typical patient with median values for age (66 years) and weight (71.5 kg)
Figure abbreviations: Caverage=average concentration.

Figure 34: Applicant – Elranatamab Exposure by Body Weight



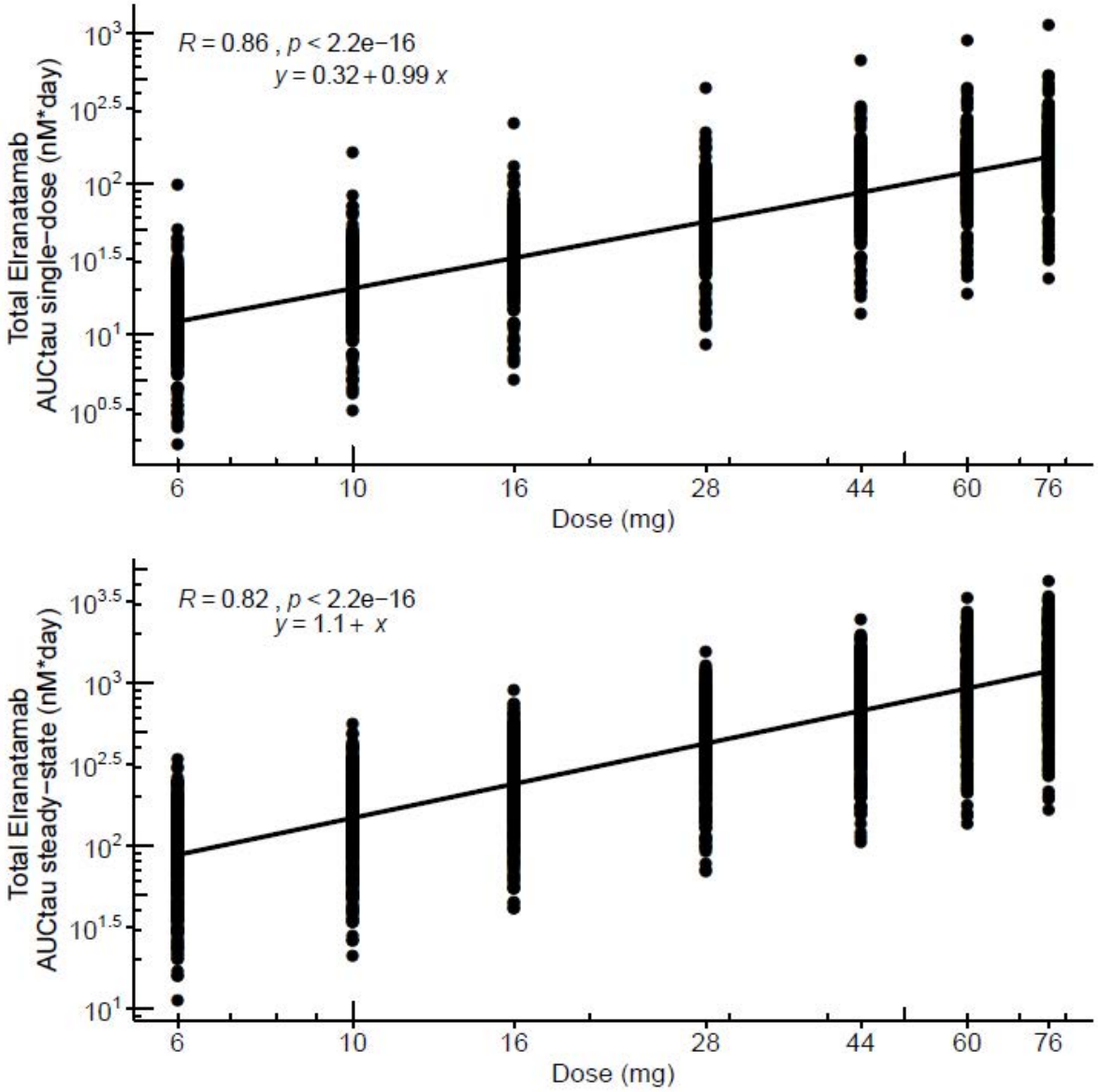
Repository artifact ID FI-36375388.
Assuming a typical male patient with median value for age (66 years)
Figure abbreviations: Caverage=average concentration.

Figure 35: Applicant – Elranatamab Exposure by Age



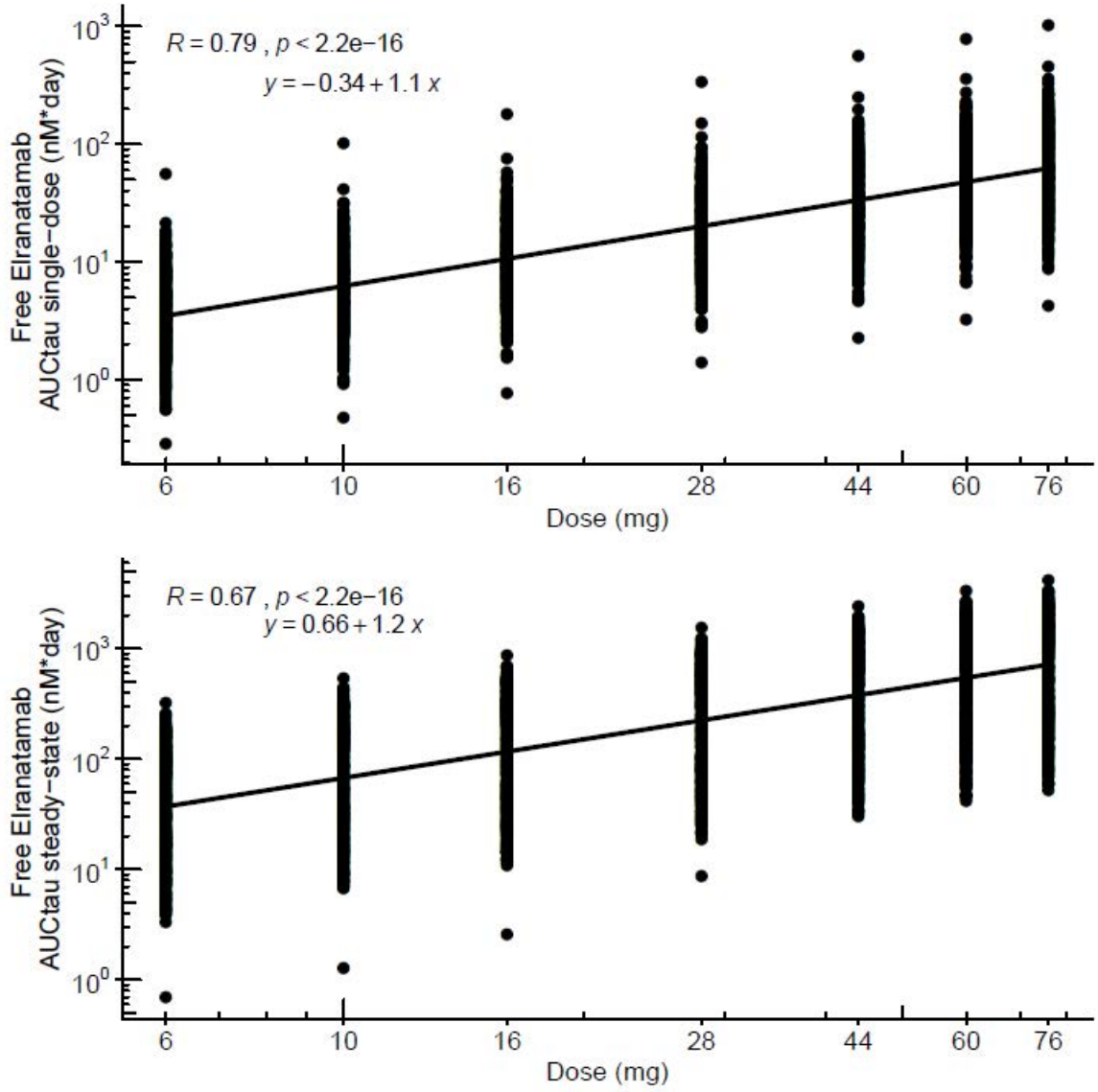
Repository artifact ID FI-36375387.
Assuming a typical male patient with median value for age (66 years)
Figure abbreviations: Cmax=maximum concentration.

Figure 36: Applicant – Simulated Individual Total Elranatamab AUC_{tau} Versus Dose Following Administration of Single (Upper Panel) or Multiple (Lower Panel) Elranatamab Administration



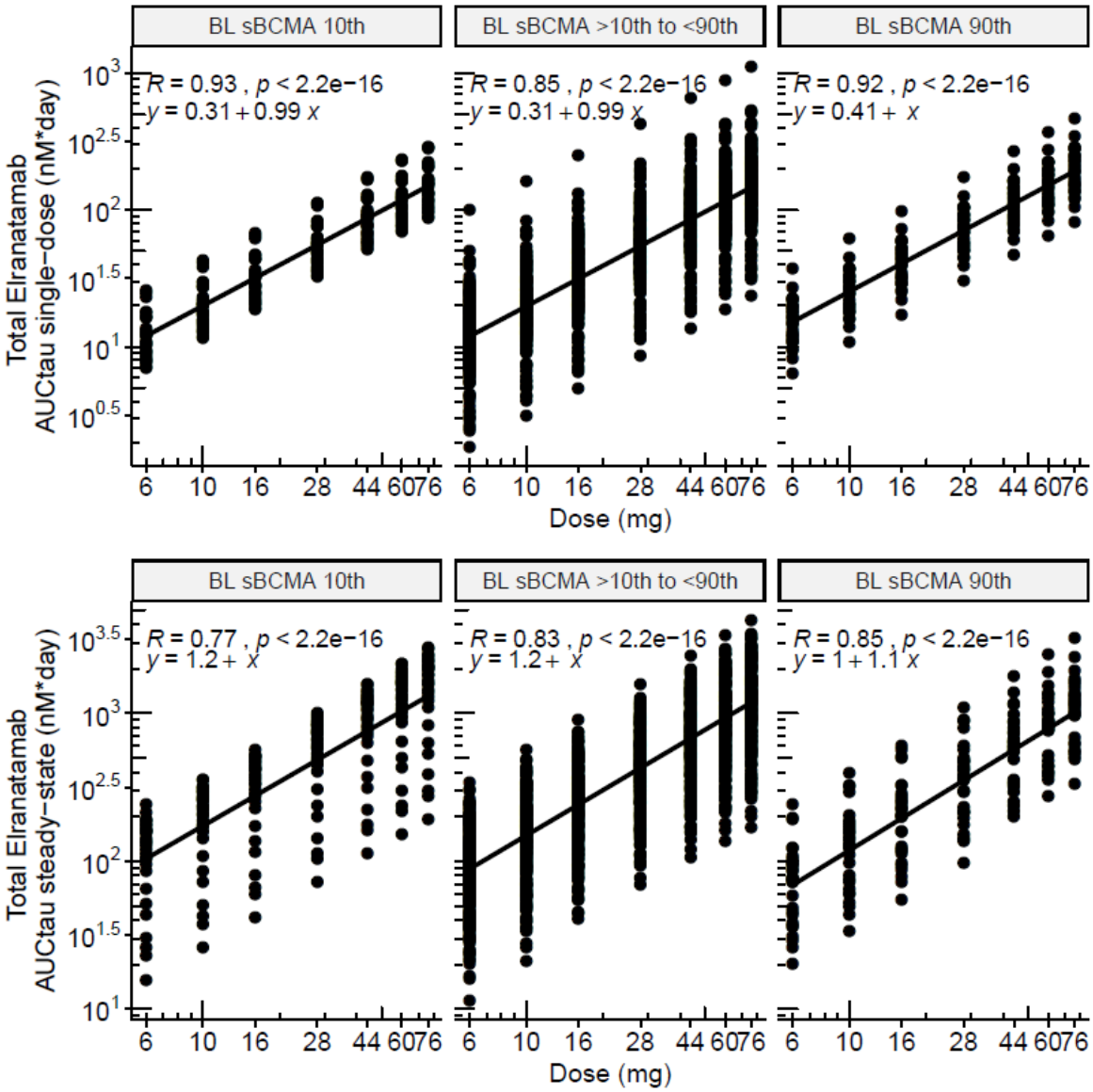
Black line is the linear regression. The x-axis and y-axis are on the logarithmic scale.

Figure 37: Applicant – Simulated Individual Free Elranatamab AUC_{tau} Versus Dose Following Administration of Single (Upper Panel) or Multiple (Lower Panel) Elranatamab Administration



Black line is the linear regression. The x-axis and y-axis are on the logarithmic scale.

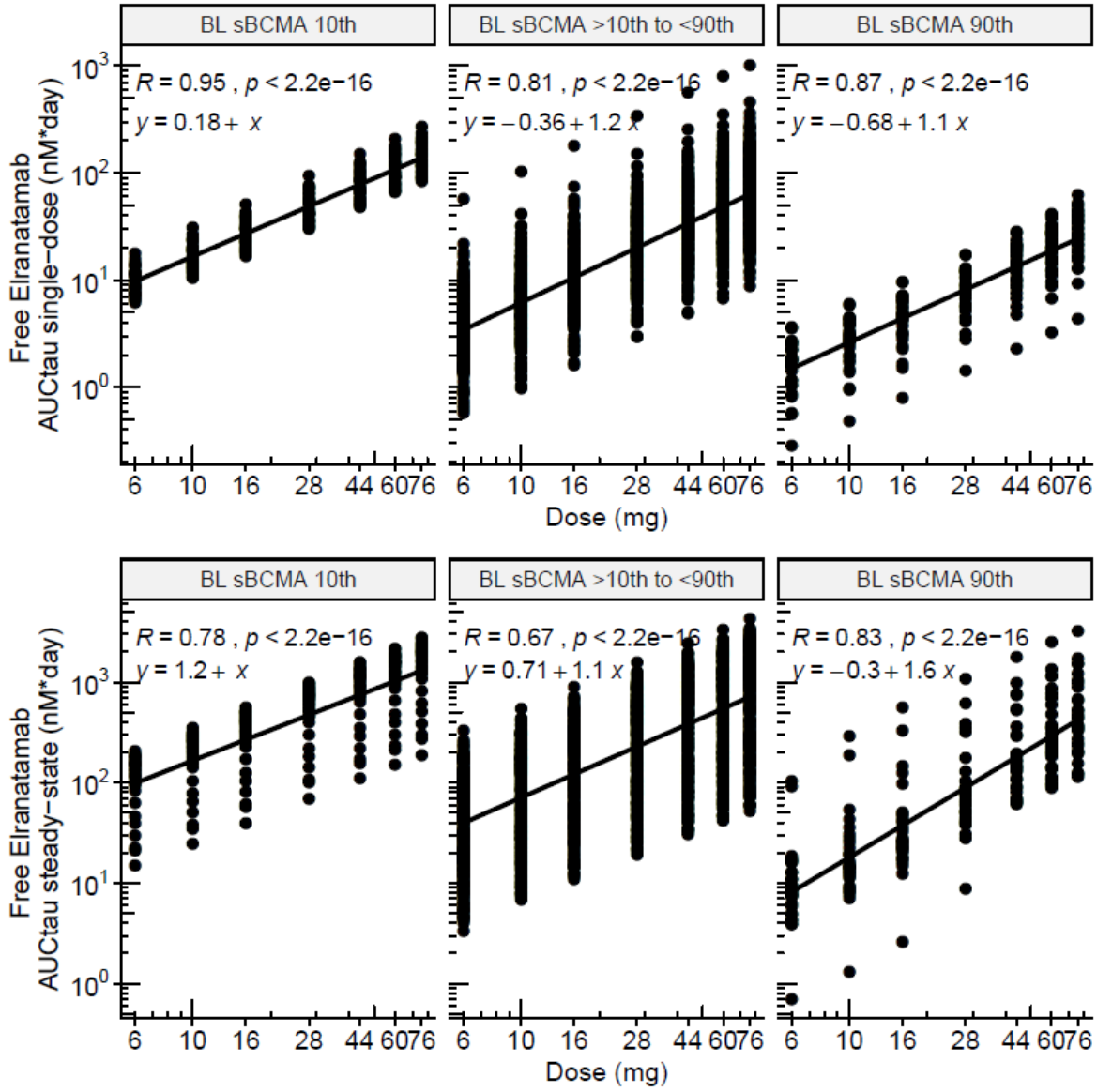
Figure 38: Applicant – Simulated Individual Total Elranatamab AUC_{tau} Versus Dose Following Administration of Single (Upper Panel) or Multiple (Lower Panel) Elranatamab Administration at Different Percentiles of Baseline sBCMA



Black line is the linear regression. The x-axis and y-axis are on the logarithmic scale.

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.

Figure 39: Applicant – Simulated Individual Free Elranatamab AUC_{tau} Versus Dose Following Administration of Single (Upper Panel) or Multiple (Lower Panel) Elranatamab Administration at Different Percentiles of Baseline sBCMA



Black line is the linear regression. The x-axis and y-axis are on the logarithmic scale.

The FDA's Assessment:

The FDA agrees with the Applicant's position. The Applicant population PK analysis of elranatamab is acceptable for the purpose of supporting analyses objectives. Covariate analysis showed that covariate includes age (36 to 89 years), sex, and body weight (37 to 160 kg) had a statistically significant effect on elranatamab exposure, however, the impact of these covariate on exposure was not considered clinically relevant.

19.4.3.3 PPK Review Issues

The FDA's Assessment:

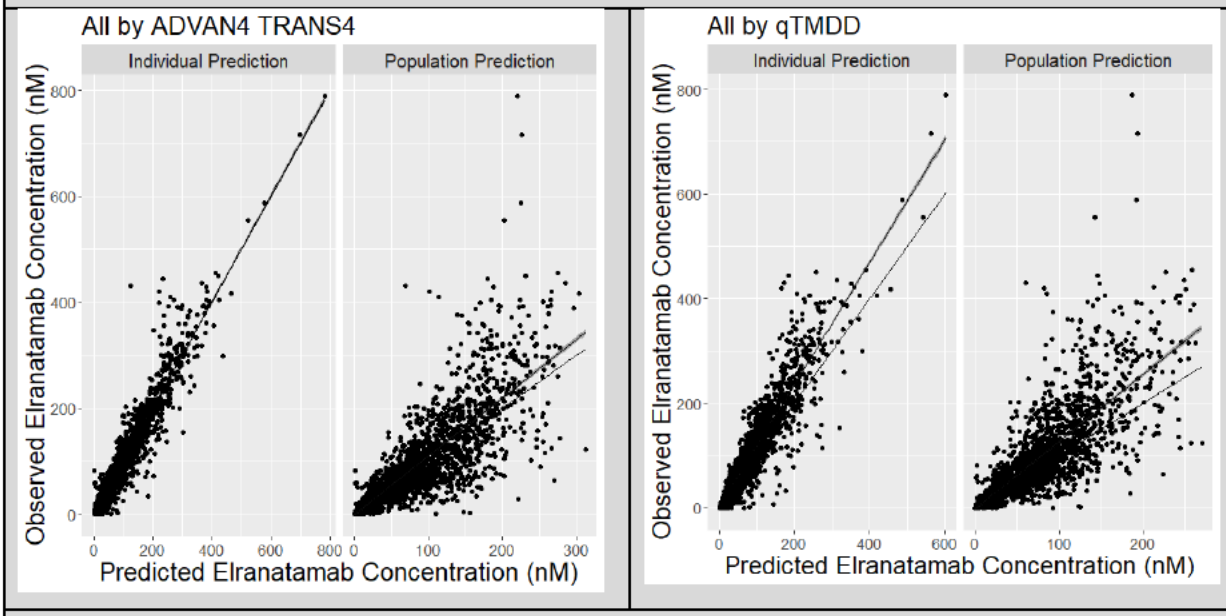
Although there were some overprediction for elranatamab concentrations under 20 ng/mL, the PopPK analysis is acceptable in general for describing the PK of elranatamab and deriving exposure metrics for subsequent exposure-response analyses.

19.4.3.4 Reviewer's Independent Analysis

The FDA's Assessment:

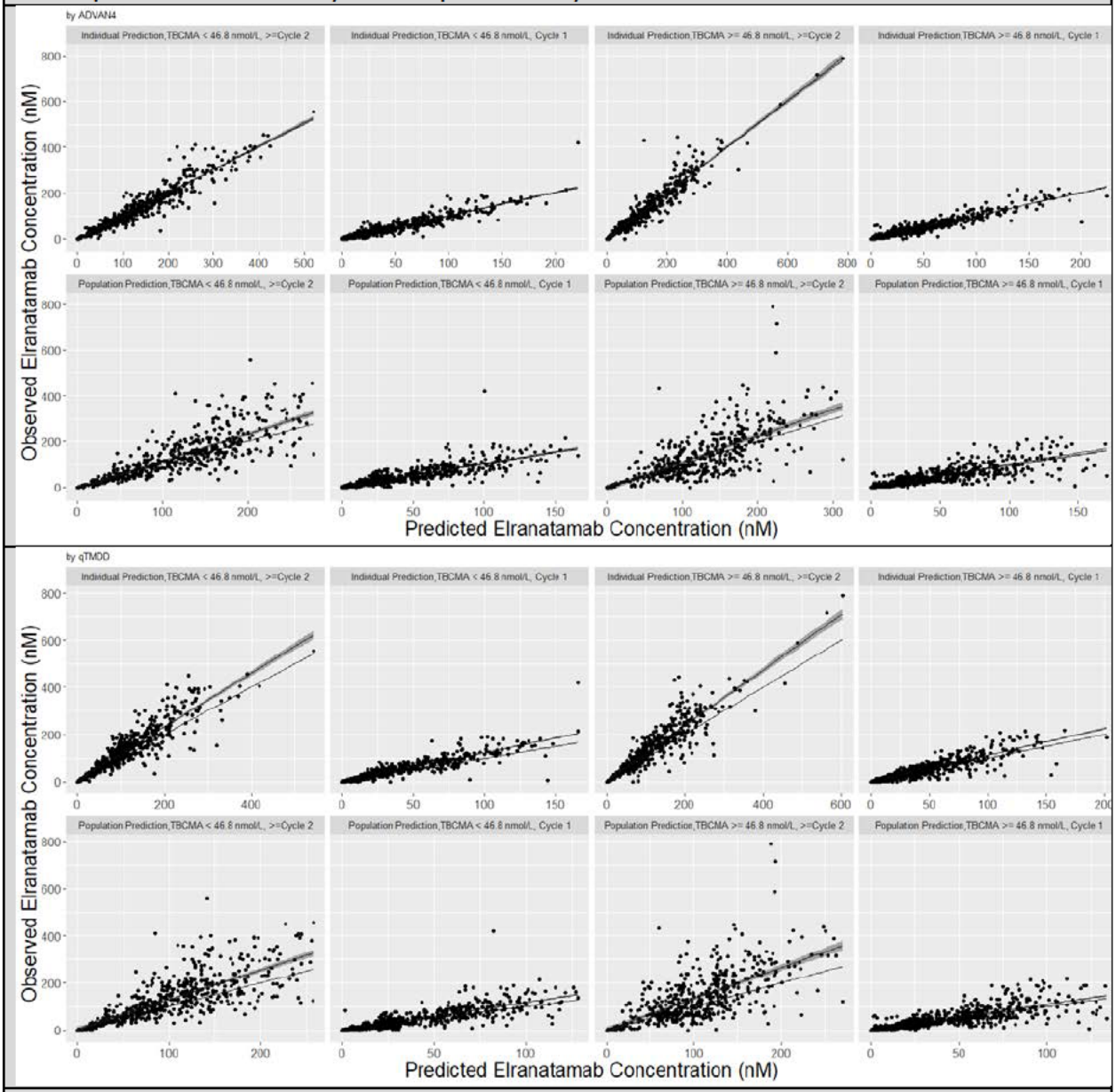
ADVAN4 TRANS4 was used to conduct the population analysis of elranatamab ADVAN4 TRANS4 appeared to better capture elranatamab concentration data than TMDD in general (Figure 40) and by time and sBCMA levels (Figure 41).

Figure 40: FDA – Goodness-of-Fit Plot of ADVAN4 TRANS4 versus the TMDD Model with the Assumption of Quasi-Steady-State Equilibrium (qTMDD)



Source: FDA Reviewer's Analysis.

Figure 41: FDA – Goodness-of-Fit Plot of ADVAN4 TRANS4 versus the TMDD Model with the Assumption of Quasi-Steady-State Equilibrium by Time and sBCMA Level



Source: FDA Reviewer's Analysis.

19.4.4 Exposure-Response Analysis

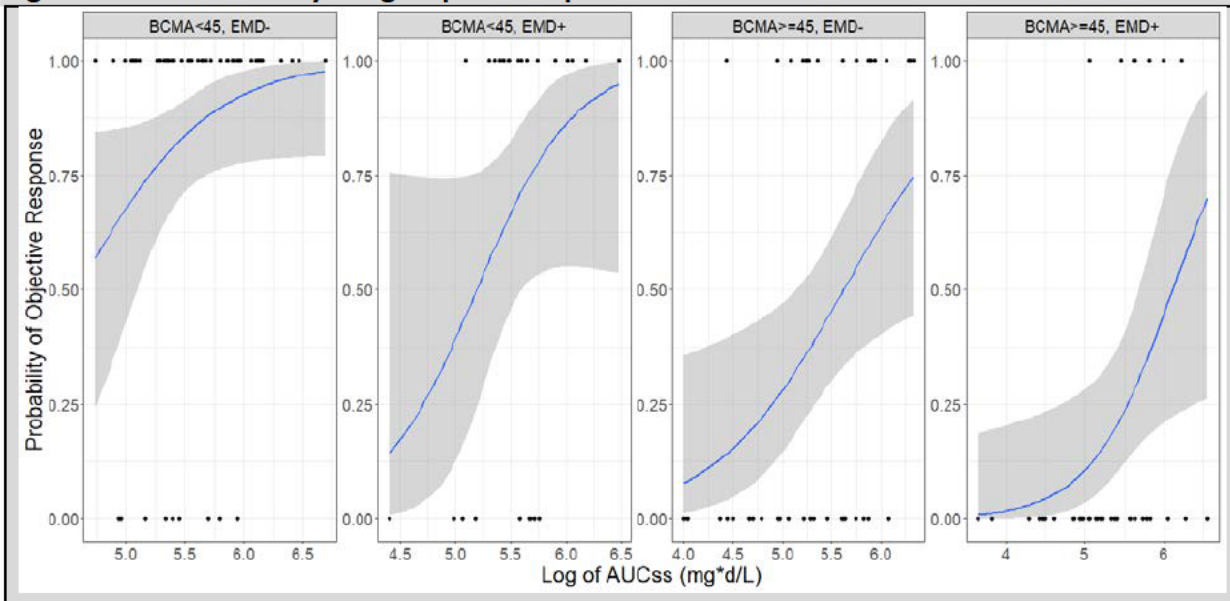
19.4.4.1 ER (efficacy) Executive Summary

<u>The FDA's Assessment:</u>

The exposure generated from the TMDD model appears not to be the best for ER analysis. Particularly, using time-to-event mean exposure to conduct exposure-safety analysis resulted

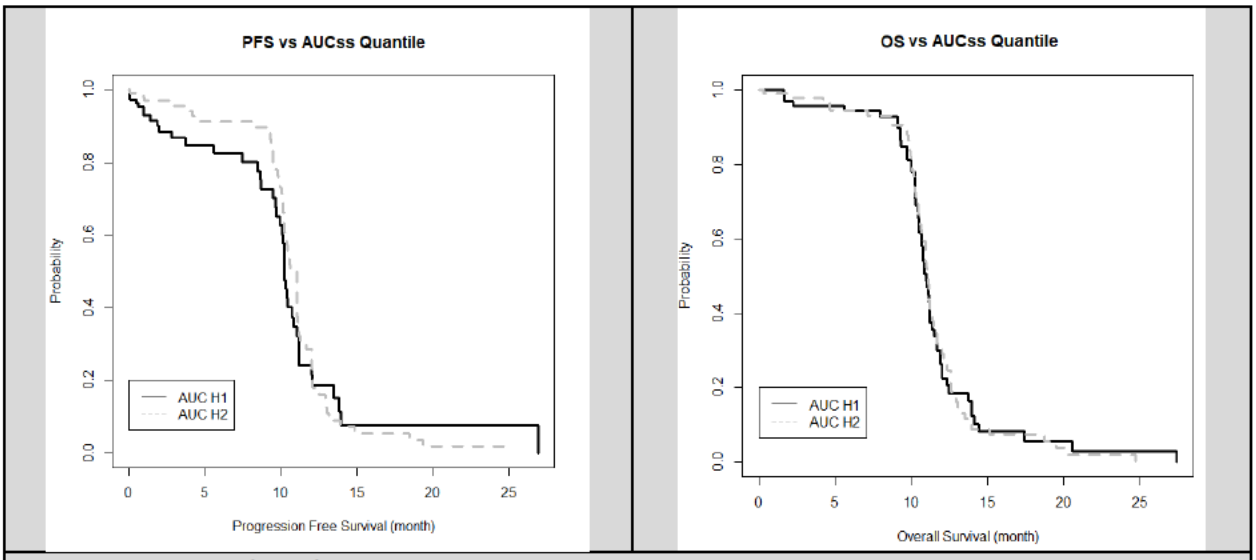
reverse/negative relationship. In comparison, the steady-state exposure generated from ADVAN4 TRANS4 resulted in more appropriate ER result, as shown below.

Figure 42: FDA – ORR by Subgroup with Exposure from ADVAN4 TRANS4



Source: FDA Reviewer's Analysis.

Figure 43: FDA – The ER Relationship of Progression-Free Survival and Overall Survival with Exposure from ADVAN4 TRANS4.



Source: FDA Reviewer's Analysis.

19.4.4.2 ER (efficacy) Assessment Summary

The Applicant's Position:

General Information		
Goal of ER analysis		*Explore the E-R relationships for efficacy endpoints of ORR (primary) and DOR in participants who received elranatamab monotherapy, using both free and total elranatamab PK*
Study Included		*C1071001, C1071002, C1071003, and C1071009*
Endpoint		*Primary: ORR* *Secondary: DOR*
No. of Patients (total, and with individual PK)		*297*
Population Characteristics (Table 69, Table 70)	General	*Age median (range): 66.00 (36.00-89.00)* *Weight median (range): 71.30 (36.50-159.60)* *N (%) male: 151 (51%) male; 146 (49%) female* *N (%) race: 178 (60%) White; 55(15%) Asian; 27 (9%) black or African American; 48 (16%) Missing/Unknown*
	Pediatrics (if any)	*Not applicable*
Dose(s) Included		*IV: 0.1, 0.3, 1, 3, 10, 30, and 50 µg/kg; SC: 80, 130, 215, 360, 600, and 1000 µg/kg, and 4, 12, 20, 32, 44, and 76 mg*
Exposure Metrics Explored (range)		*Total and free elranatamab exposure metrics:* • *Average concentration on Day 28 ($C_{ave,Day28}$)* • *Average elranatamab concentration up to the time of first response or progression/end of treatment ($C_{ave,Event}$)*
Covariates Evaluated		*Continuous: Age, baseline body weight, baseline creatinine clearance, baseline total and free sBCMA, baseline platelet count* *Categorical: Sex, race (White or others, and Asian or others), EMD status, Type of myeloma (IgG, or non-IgG/Light chain only), % bone marrow plasma cells (<70% or ≥70%), baseline cytogenetics (high or standard), prior stem cell transplant, disease stage (1-2 or 3), whether participant was refractory to last therapy, penta-refractory status, ECOG performance status (0 or 1-3), number of prior lines of therapy (>5 or ≤5), ADA baseline status (positive or negative), treatment induced and boosted ADA status, tumor burden (high or others), prior BCMA therapy*
Final Model Parameters	**Summary**	**Acceptability**

		[FDA's comments]
Model Structure	*For ORR: Binomial logistic regression model* *For DOR: Cox proportional hazard model*	Acceptable
Model Parameter Estimates	Table 73 *for ORR* Table 74 *and* Table 75 *for DOR*	Acceptable
Model Evaluation	• A significant E-R relationship was identified for ORR with total and free elranatamab exposure $C_{ave,Day28}$ and $C_{ave,Event}$. Patients with higher total and free elranatamab exposure were more likely to achieve objective responses. • Overall, the results of the $C_{ave,Event}$ analysis were consistent with that of $C_{ave,Day28}$. • The Cox proportional hazard analysis and KM analysis of DOR revealed that there was no significant association between total or free elranatamab exposure, or Q2W switch	Acceptable
Covariates and Clinical Relevance	Number of prior lines of therapy and baseline EMD were inversely associated with achieving objective responses. In the total elranatamab E-R analysis, baseline sBCMA was identified as a significant predictor of ORR.	Acceptable
Simulation for Specific Population	*Not applicable*	Acceptable
Visualization of E-R relationships	Figure 44 *for total elranatamab* Cave,Day28 Figure 45 *for free elranatamab* Cave,Day28	Acceptable
Overall Clinical Relevance for ER	The E-R analysis revealed that higher elranatamab exposures were associated with higher probability of achieving objective responses. In the total PK logistic regression	Acceptable

	analysis, baseline sBCMA level was inversely associated with ORR. EMD status at baseline and >5 prior lines of therapy were also significant covariates inversely associated with the probability of achieving objective responses. The 76 mg QW regimen is the highest tested full dose/dosing intensity and achieves the highest free elranatamab exposure at a given baseline sBCMA level in the dose range evaluated, and results in higher probability of achieving an objective responses vs lower doses. Elranatamab exposures and the Q2W switch did not impact DOR.	
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	(b) (4)	Acceptable

Table 73: Applicant – Final Model for ORR Using Total Elranatamab Exposure

Elranatamab PK	Exposure Metrics	Effects	Estimate (95% CIs)	Odds Ratio (95% CIs)	Pr(>|Z|)
Total	$C_{ave,\ Day\ 28}$	sBCMA at baseline*	-0.01 (-0.01 - -0.01)	0.991 (0.986 - 0.994)	<0.0001
		Log $C_{ave,\ Day28}$	1.56 (0.77 - 2.55)	4.78 (2.16 – 12.81)	0.0006
		Prior lines of Therapy >5	-0.991 (-1.59 - -0.408)	0.371 (0.204 – 0.665)	0.0010
		Positive EMD at baseline	-0.871 (-1.48 - -0.277)	0.419 (0.229 - 0.758)	0.0043
		Intercept	-4.08 (-7.80 - -1.07)	-	0.0175
	$C_{ave,\ event}$	sBCMA at baseline*	-0.009 (-0.013 - -0.006)	0.991 (0.987 - 0.994)	<0.0001
		Log $C_{ave,\ event}$	1.34 (0.65 - 2.18)	3.82 (1.92 – 8.83)	0.0006
		Prior lines of Therapy >5	-0.954 (-1.55 - -0.37)	0.385 (0.211 – 0.691)	0.0015
		Positive EMD at baseline	-0.992 (-1.61 - -0.387)	0.371 (0.200 - 0.679)	0.0015
		Intercept	-3.37 (-6.62 - -0.68)	-	0.0260
Free	$C_{ave,\ Day\ 28}$	Intercept	-15.8 (-20.3 - -11.9)	-	<0.0001
		Log $C_{ave,\ Day28}$	4.89 (3.74 – 6.21)	133.1 (42.2 – 498.5)	<0.0001
		Prior lines of Therapy >5	-0.976 (-1.69 - -0.292)	0.377 (0.185 – 0.747)	0.0058
		Positive EMD at baseline	- 0.917 (-1.63 - -0.226)	0.400 (0.196 - 0.798)	0.0100
	$C_{ave,\ event}$	Intercept	-12.9 (-16.7 - -9.6)	-	<0.0001
		Log $C_{ave,\ event}$	3.93 (2.99 – 5.01)	50.9 (19.9 – 150)	<0.0001
		Positive EMD at baseline	-1.45 (-2.20 - -0.75)	0.388 (0.194 - 0.760)	0.0001
		Prior lines of Therapy	-0.946 (-1.64 - -0.274)	0.234 (0.111 – 0.474)	0.0065

Table 73: Applicant – Final Model for ORR Using Total Elranatamab Exposure

Elranatamab PK	Exposure Metrics	Effects	Estimate (95% CIs)	Odds Ratio (95% CIs)	Pr(>|Z|)

*Baseline sBCMA was used from the free sBCMA assay based on the results from base models of free and total sBCMA baseline levels.

Based on the odds ratio, with a 1 unit increase of log $C_{ave,Day28}$, the odds of achieving ORR are multiplied by a factor of 4.78 and 133.1, respectively, for total and free exposures; when number of prior lines of therapy is more than 5 at baseline, the odds of achieving ORR are multiplied by a factor of 0.371 and 0.377, respectively, for total and free exposures; when EMD is present at baseline, the odds of achieving ORR are multiplied by a factor of 0.419 and 0.400, respectively, for total and free exposures. For total log $C_{ave,Day28}$ analysis, with a 1 unit increase in baseline sBCMA, the odds of achieving ORR are multiplied by a factor of 0.991.

Based on the odds ratio, with a 1 unit increase of log $C_{ave,Event}$, the odds of achieving ORR are multiplied by a factor of 3.82 and 50.9, respectively, for total and free exposures; when number of prior lines of therapy is more than 5 at baseline, the odds of achieving ORR are multiplied by a factor of 0.385 and 0.388, respectively, for total and free exposures; when EMD is present at baseline, the odds of achieving ORR are multiplied by a factor of 0.371 and 0.234, respectively, for total and free exposures. For total log $C_{ave,Event}$ analysis, with a 1 unit increase in baseline sBCMA, the odds of achieving ORR are multiplied by a factor of 0.991.

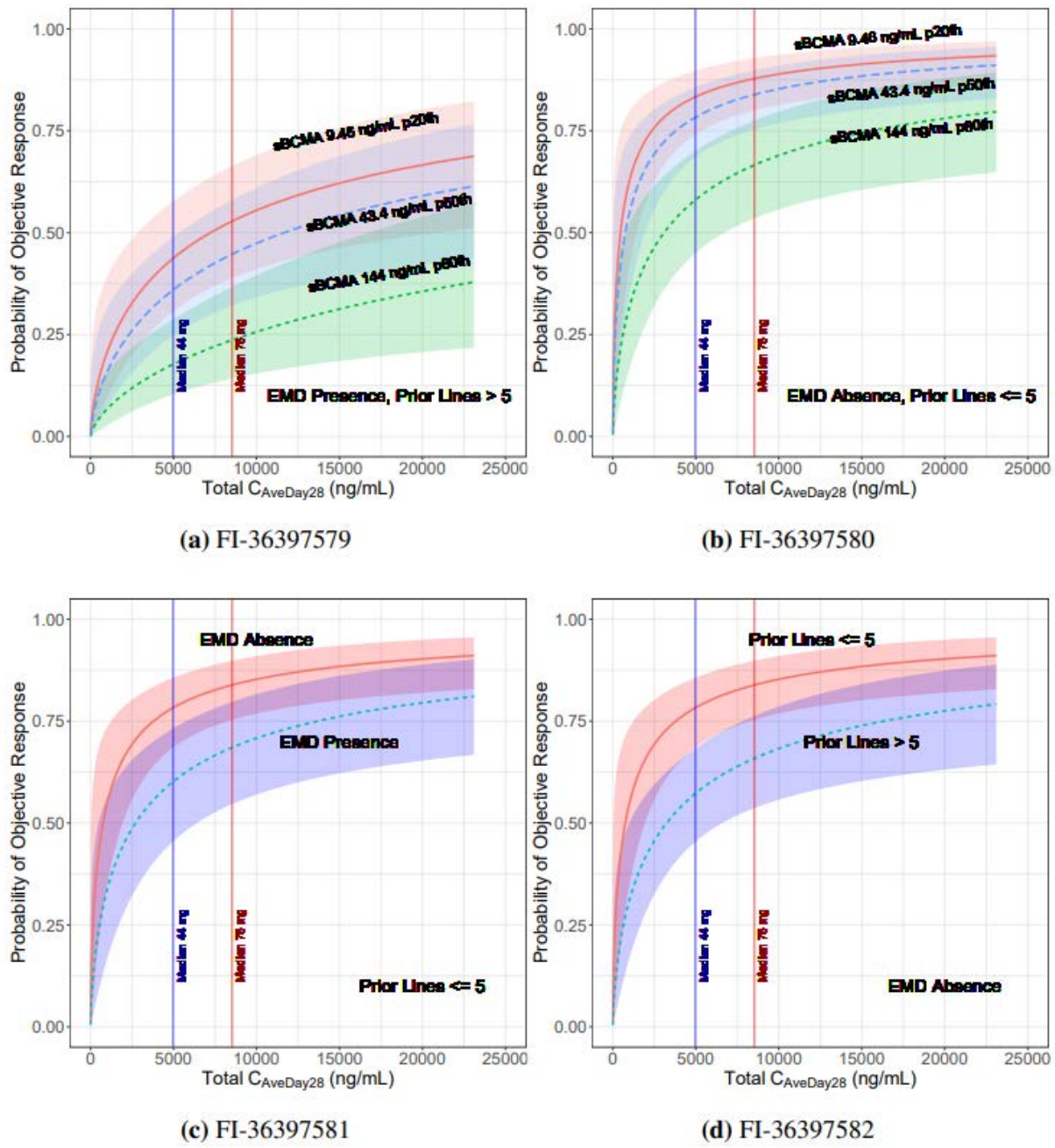
Table 74: Applicant – Univariate Analysis of Cox Proportional Hazard Model for DOR Study (Studies 1001, 1002, 1003, 1009)

Variable	Coefficient	Hazard Ratio (95% CI)	p-value
Log $C_{ave, Day 28}$	-0.262	0.769 (0.494 – 1.20)	0.247
Log $C_{ave, event}$	-0.218	0.804 (0.546 – 1.19)	0.271

Table 75: Applicant – Univariate and Multivariate Analysis of Cox Proportional Hazard Model for DOR Study

Analysis	Variable	Coefficient	Hazard Ratio (95% CI)	p-value
Q2W Switch	Q2W Switch	-0.462	0.630 (0.0797 – 4.98)	0.661
Q2W Switch + $C_{ave, Day 28}$	Q2W Switch	-0.517	0.596 (0.0749 – 4.75)	0.625
	Log $C_{ave, Day 28}$	-0.431	0.650 (0.300 – 1.41)	0.274
Q2W Switch + $C_{ave, event}$	Q2W Switch	-0.454	0.635 (0.0803 – 5.02)	0.667
	Log $C_{ave, event}$	-0.349	0.706 (0.302 – 1.65)	0.421

Figure 44: Applicant – Final Model for ORR Illustrating the Association of Total Elranatamab $C_{ave,Day28}$, Baseline sBCMA, Number of Prior Lines of Therapy, and EMD Status

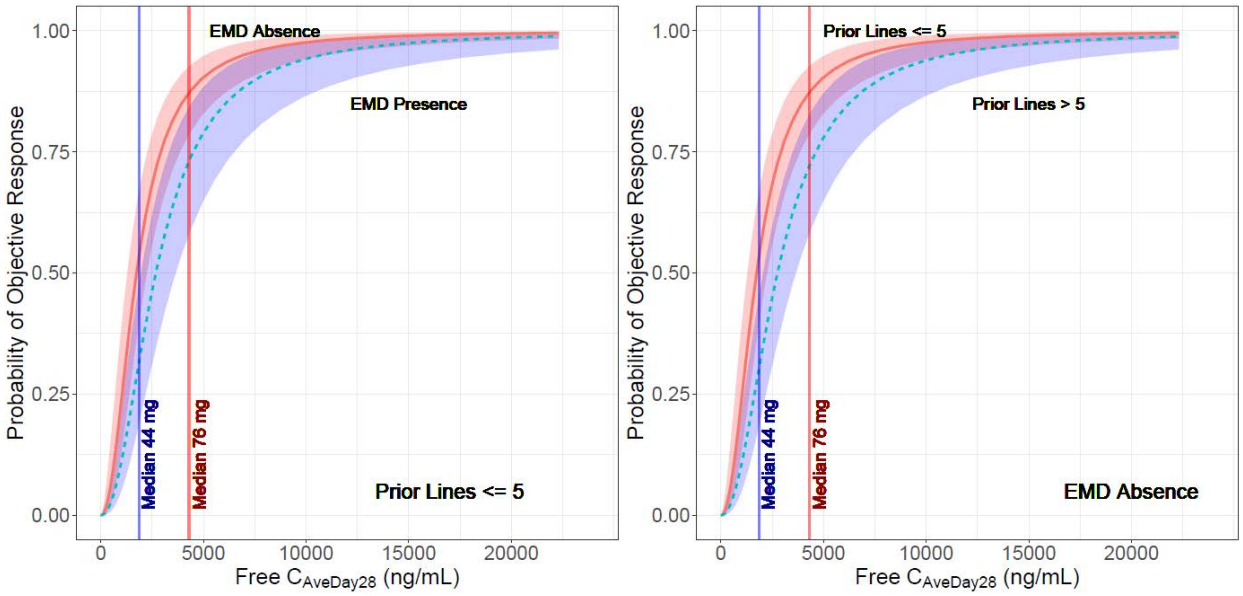


(a) FI-36397579 (b) FI-36397580

(c) FI-36397581 (d) FI-36397582

In figures (a) and (b), red, blue, and green curved lines and shaded regions represent median and 95% CI predicted probability of objective Response for patients with 20th, 50th, and 80th percentiles of sBCMA, respectively. In figures (c) and (d), simulations utilizing 50th percentile of sBCMA are displayed.

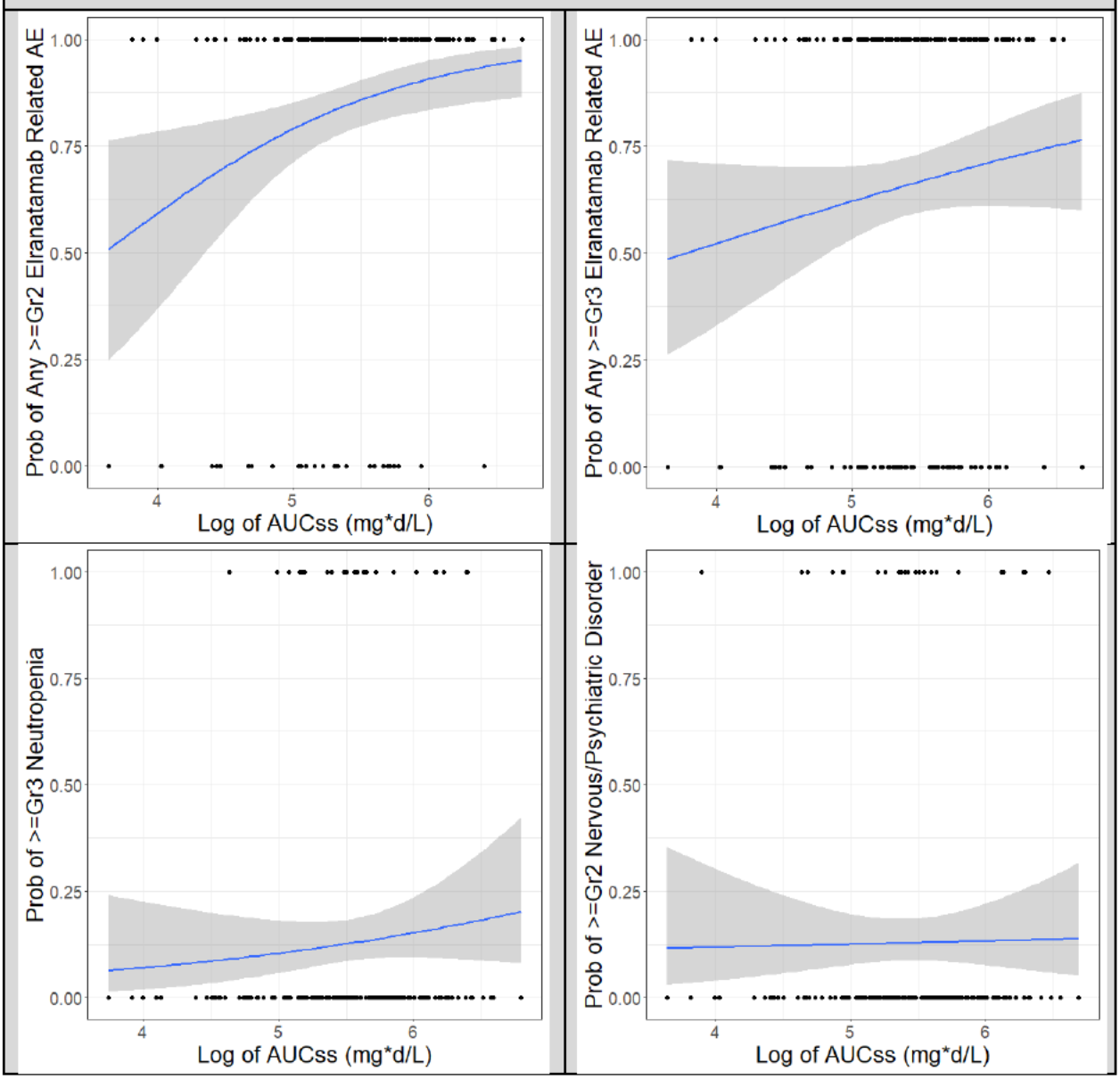
Figure 45: Applicant – Final Model for ORR Illustrating the Association of Free Elranatamab Cave,Day28, Baseline sBCMA, Number of Prior Lines of Therapy, and EMD Status

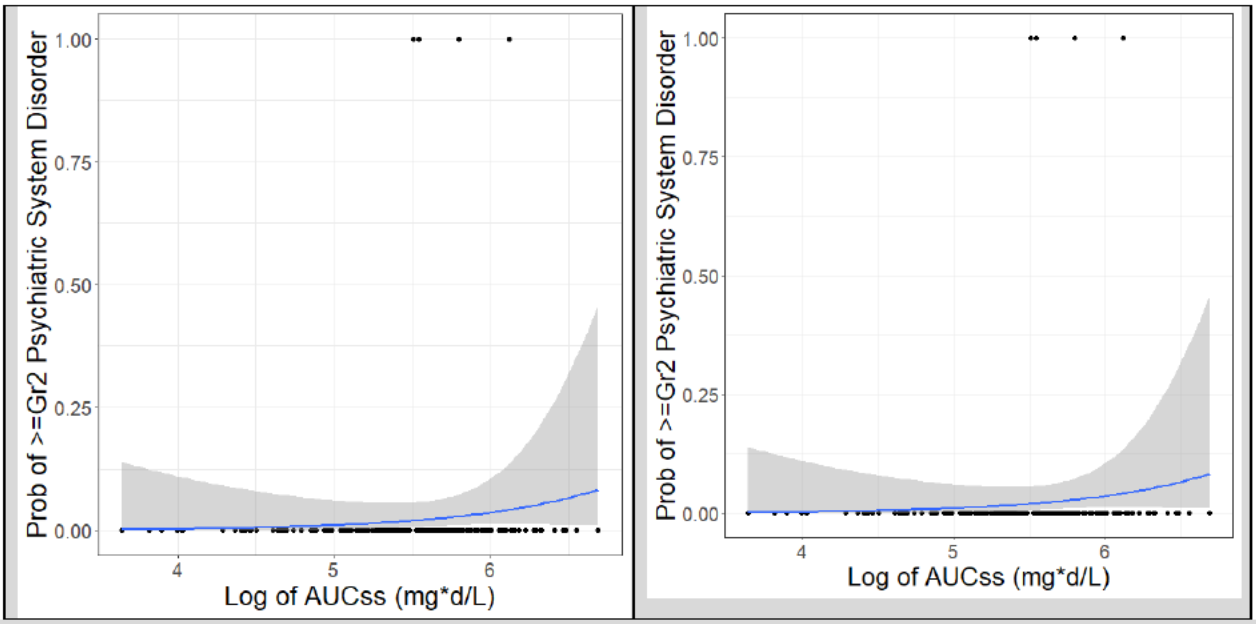


19.4.4.3 ER (safety) Executive Summary

The FDA's Assessment:
As mentioned previously, the steady-state exposure generated from ADVAN4 TRANS4 could be more appropriate for ER safety analysis. FDA such analysis resulted in the following results:

Figure 46: FDA – The ER Relationship of Safety with Exposure from ADVAN4 TRANS4





Source: FDA Reviewer's Analysis.

19.4.4.4 ER (safety) Assessment Summary

The Applicant's Position:

19.4.2.4.1. ER-Safety analysis for CRS

General Information		
Goal of ER analysis		*Explore the E-R relationships for Grade ≥1 CRS and Grade ≥2 CRS in participants who received elranatamab monotherapy, using both free and total elranatamab PK*
Study Included		*C1071001, C1071002, C1071003, and C1071009*
Population Included		*Adult participants with relapsed or refractory multiple myeloma*
Endpoint		*Grade ≥1 CRS and Grade ≥2 CRS*
No. of Patients (total, and with individual PK)		*324*
Population Characteristics (Table 69, Table 70)	General	*- Age median (range): 66 (36-89)* *- Weight median (range): 71.45 (36.5-159.6)* *- 168 (51.9%) male; 156 (48.1%) female* *- 29 (9%) Black; 51 (15.7%) Asian; 194 (59.9%) White; 49 (15.1%) Missing; 1 (0.3%) Not Reported*
	Organ impairment	*- Renal (based on eGFR, mL/min/1.73m^2):* *128 (39.5%) ≥90 mL/min/1.73 m^2 (normal)* *123 (38.0%) ≥60-<90 mL/min/1.73 m^2 (mild impairment)* *70 (21.6%) ≥30-<60 mL/min/1.73 m^2 (moderate impairment)* *3 (0.9%) <30 mL/min/1.73 m^2 (severe impairment)*

	Pediatrics (if any)	*Not applicable*
	Geriatrics (if any)	*- Age median (range): 71 (65-89)* *184 (56.8%) participants ≥65 yr; 50 (15.4%) participants ≥75 yr* *- 92 (50.0%) male; 92 (50.0%) female*
Dose(s) Included		*IV: 0.1, 0.3, 1, 3, 10, 30, and 50 µg/kg, SC: 80, 130, 215, 360, 600, and 1000 µg/kg, 4, 12, 20, 32, 44, and 76 mg*
Exposure Metrics Explored (range)		• *Predicted maximum concentration within the first 24 hours following the first treatment dose (C_{max},24)* • *Predicted maximum concentration within the first 48 hours following the first treatment dose (C_{max},48)*
Covariates Evaluated		*Age, body weight, creatinine clearance, platelet count, lactate dehydrogenase, total soluble BCMA, sex, type of myeloma, on-treatment ADA status, baseline ADA status, premedication, prior BCMA CAR-T therapy, prior BCMA ADC therapy*

Final Model Parameters	**Summary**	**Acceptability [FDA's comments]**
Model Structure	*logistic regression*	Acceptable
Model Parameter Estimates	Table 81	Acceptable
Model Evaluation	*Early elranatamab exposure ($C_{max,24}$) was retained as a significant predictor in all E-R models analyzed for CRS, where a higher $C_{max,24}$ indicated a greater probability of experiencing CRS.*	Acceptable
Covariates and Clinical Relevance	*Baseline total soluble BCMA; Since increasing levels of baseline total soluble BCMA indicated a lower probability of experiencing CRS in the E-R model for Grade ≥1 CRS using total elranatamab PK, the safety impact is estimated to be minimal.*	Acceptable
Simulation for Specific Population	*Not applicable*	Acceptable
Visualization of E-R relationships	Figure 47 *for Grade ≥1 and Grade ≥2 CRS using total elranatamab PK* Figure 48 *for Grade ≥1 and Grade ≥2 CRS using free elranatamab PK*	Acceptable

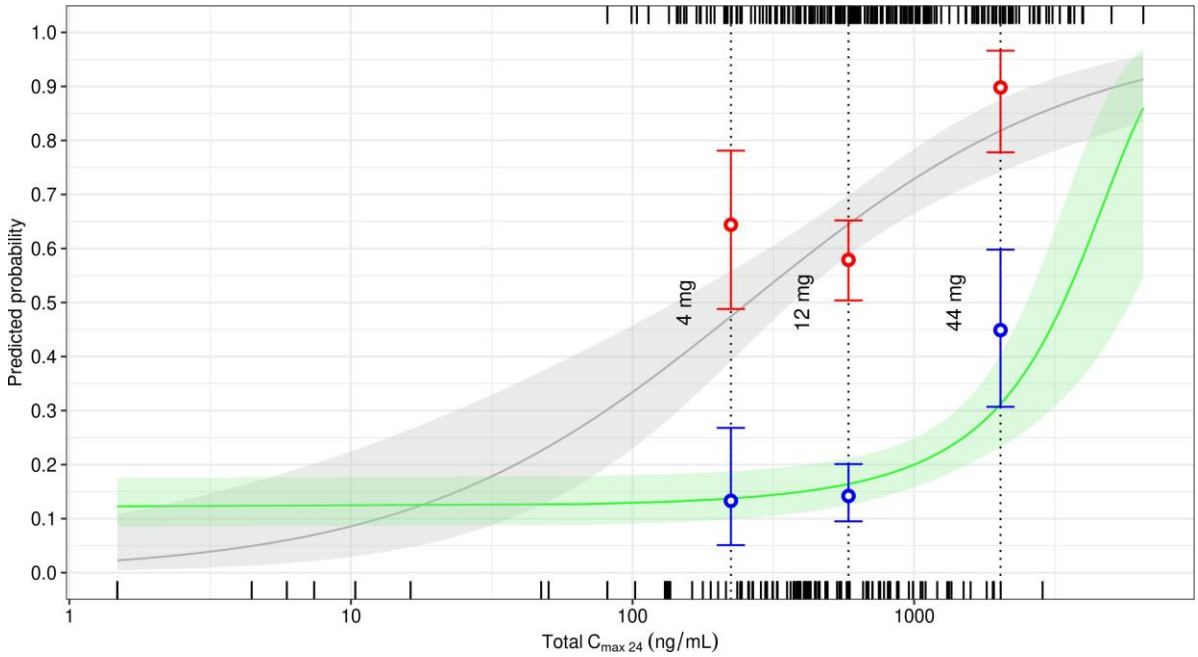
Overall Clinical Relevance for ER	*Higher, early elranatamab exposure ($C_{max,24}$) indicated a greater probability of experiencing Grade ≥1 CRS and Grade ≥2 CRS using both free and total elranatamab PK*	Acceptable
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	Not applicable.	N/A

Table 76: Applicant – Final Models for Any Grade and Grade ≥2 CRS vs Elranatamab Exposure

Elranatamab PK (Free or Total)	CRS Endpoint	Effects	Estimate (95% CIs)	Odds Ratio (95% CIs)	Pr(>|Z|)
Total PK	Any Grade CRS	Intercept	-3.11 (-4.95, -1.42)	-	< 0.001
		Log (Total $C_{max, 24h}$) (ng/mL)	0.728 (0.465, 1.02)	2.07 (1.59, 2.78)	< 0.001
		Log (Total Baseline sBCMA) (ng/mL)	-0.245 (-0.423, -0.0822)	0.783 (0.655, 0.921)	0.0051
	Grade ≥2 CRS	Intercept	-1.97 (-2.4, -1.56)	-	< 0.001
		Log (Total $C_{max, 24h}$) (ng/mL)	0.000581 (0.000294, 0.000883)	1.00 (1.00, 1.00)	< 0.001
Free PK	Any Grade CRS	Intercept	-4.05 (-5.59, -2.64)	-	< 0.001
		Log (Free $C_{max, 24h}$) (ng/mL)	0.905 (0.631, 1.21)	2.47 (1.88, 3.35)	< 0.001
	Grade ≥2 CRS	Intercept	-4.63 (-6.26, -3.12)	-	< 0.001
		Log (Free $C_{max, 24h}$) (ng/mL)	0.596 (0.328, 0.879)	1.81 (1.39, 2.41)	< 0.001

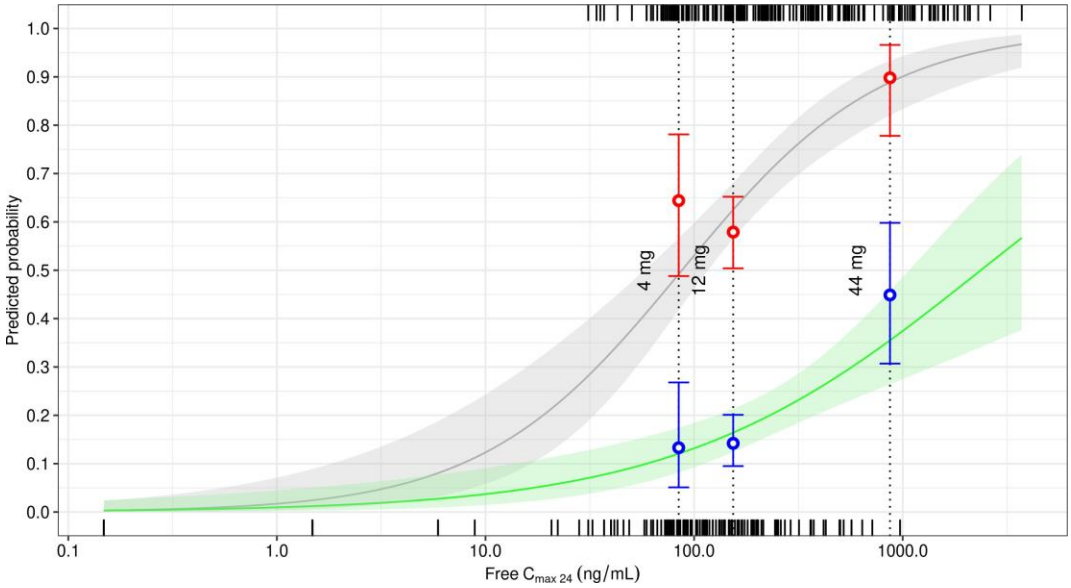
N = 324 participants.

Figure 47: Applicant – ER Curves of CRS vs Total Elranatamab $C_{max,24}$ in 324 Patients



These simulations show the relationships between the probabilities of CRS any Grade and CRS Grade 2 or worse using total elranatamab PK and the covariates from the final models, respectively. The vertical dotted lines indicate the median observed $C_{max,24}$ values at initial elranatamab doses of 4, 12, and 44 mg. The red dots and whiskers represent the observed proportions and 95 % CIs of any Grade CRS at each of the initial elranatamab doses of 4, 12, and 44 mg, respectively. The blue dots and whiskers represent the observed proportions and 95 % CIs of Grade 2 or worse CRS at each of the initial elranatamab doses of 4, 12, and 44 mg, respectively. The solid grey line and ribbon represent the simulated probabilities and 95% CI of any Grade CRS, respectively, using the overall median Log(Baseline Total Soluble BCMA (ng/mL)) (LTBCMA). The solid green line and ribbon represent the simulated probabilities and 95% CI of Grade 2 or worse CRS, respectively. The rug lines indicate the $C_{max,24}$ values for those participants who did (top) and did not (bottom) experience any Grade CRS. **Note:** These simulations are derived from two separate models for CRS using total elranatamab PK.

Figure 48: Applicant – ER Curves of CRS vs Free Elranatamab $C_{max,24}$ in 324 Patients



19.4.2.4.2. ER-Safety Analysis for Neutropenia

General Information		
Goal of ER analysis		*Explore the E-R relationships for Grade ≥3 neutropenia in participants who received elranatamab monotherapy, using both free and total elranatamab PK*
Study Included		*C1071001, C1071002, C1071003, and C1071009*
Population Included		*Adult participants with relapsed or refractory multiple myeloma*
Endpoint		*Grade ≥3 neutropenia*
No. of Patients (total, and with individual PK)		*324*
Population Characteristics (Table 69, Table 70)	General	*Age median (range): 66 (36-89)* *-Weight median (range): 71.4 (36.5-159.6)* *-168 (51.9%) male; 156 (48.1%) female* *-29 (9%) Black; 51 (15.7%) Asian; 194 (59.9%) White; 50 (15.4%) Missing*
	Organ impairment	*Please refer to baseline characteristics.*
	Pediatrics (if any)	*Not applicable*
	Geriatrics (if any)	*Age median (range): 66 (36-89)*
Dose(s) Included		*IV: 0.1, 0.3, 1, 3, 10, 30, and 50 µg/kg, SC: 80, 130, 215, 360, 600, and 1000 µg/kg, 4, 12, 20, 32, 44, and 76 mg*
Exposure Metrics Explored (range)		Free and total average concentration up to the event time ($C_{ave,event}$)
Covariates Evaluated		*sex, age, baseline body weight, race, baseline soluble B-cell Maturation Antigen, baseline creatinine clearance, % bone marrow plasma cells , baseline platelet count baseline platelet Count, absolute neutrophil counts, extramedullary disease, prior stem cell transplant, disease stage, refractoriness to last therapy, penta-refractory status, and Eastern Cooperative Oncology Group (ECOG) performance status, baseline alanine aminotransferase, baseline aspartate aminotransferase, baseline total bilirubin , baseline alkaline phosphatase, baseline albumin, baseline hemoglobin, baseline cytogenetics , baseline neutropenia, treatment-induced/boosted anti-drug antibody status and baseline immunogenicity*
Final Model Parameters	**Summary**	**Acceptability [FDA's comments]**
Model Structure	*Not applicable*	Acceptable

Model Parameter Estimates	*Not applicable*	Acceptable
Model Evaluation	*Not applicable*	Acceptable
Covariates and Clinical Relevance	*Not applicable*	Acceptable
Simulation for Specific Population	*Not applicable*	Acceptable
Visualization of E-R relationships	*Not applicable*	Acceptable
Overall Clinical Relevance for ER	The relatively flat exposure-response relationship suggests that selection of a lower dose would not mitigate the risk for AEs.	Acceptable
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics		

19.4.2.4.3. ER-Safety Analysis for Infections

General Information			
Goal of ER analysis		*Explore the E-R relationships for Grade ≥3 infection in participants who received elranatamab monotherapy, using both free and total elranatamab PK*	
Study Included		*C1071001, C1071002, C1071003, and C1071009*	
Population Included		*Adult participants with relapsed or refractory multiple myeloma*	
Endpoint		*Grade ≥3 infection*	
No. of Patients (total, and with individual PK)		*324*	
Population Characteristics (Table 69, Table 70)	General	*Age median (range): 66 (36-89)* *-Weight median (range): 71.4 (36.5-159.6)* *-168 (51.9%) male; 156 (48.1%) female* *-29 (9%) Black; 51 (15.7%) Asian; 194 (59.9%) White; 50 (15.4%) Missing*	
	Organ impairment		
	Pediatrics (if any)	*Not applicable*	
	Geriatrics (if any)	*Age median (range): 66 (36-89)*	
Dose(s) Included		*IV: 0.1, 0.3, 1, 3, 10, 30, and 50 µg/kg, SC: 80, 130, 215, 360, 600, and 1000 µg/kg, 4, 12, 20, 32, 44, and 76 mg*	
Exposure Metrics Explored (range)		Free and total average concentration up to the event time ($C_{ave,event}$)	
Covariates Evaluated		*sex, age, baseline body weight, race, baseline soluble B-cell Maturation Antigen, baseline creatinine clearance, % bone marrow plasma cells , baseline platelet count baseline platelet Count, absolute neutrophil counts, extramedullary disease, prior stem cell transplant, disease stage, refractoriness to last therapy, penta-refractory status, and Eastern Cooperative Oncology Group (ECOG) performance status, baseline alanine aminotransferase, baseline aspartate aminotransferase, baseline total bilirubin , baseline alkaline phosphatase, baseline albumin, baseline hemoglobin, baseline cytogenetics , baseline infection, treatment-induced/boosted anti-drug antibody status and baseline immunogenicity*	
Final Model Parameters		**Summary**	**Acceptability [FDA's comments]**
Model Structure		*Not applicable*	**N/A**
Model Parameter Estimates		*Not applicable*	**N/A**

Model Evaluation	*Not applicable*	**N/A**
Covariates and Clinical Relevance	*Not applicable*	**N/A**
Simulation for Specific Population	*Not applicable*	**N/A**
Visualization of E-R relationships	*Not applicable*	**N/A**
Overall Clinical Relevance for ER	The relatively flat exposure-response relationship suggests that selection of a lower dose would not mitigate the risk for AEs.	**Acceptable**
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics		

19.4.2.4.4. ER-Safety Analysis for Peripheral Neuropathy

General Information			
Goal of ER analysis		*Explore the E-R relationships for Grade ≥2 PN in participants who received elranatamab monotherapy, using both free and total elranatamab PK*	
Study Included		*C1071001, C1071002, C1071003, and C1071009*	
Population Included		*Adult participants with relapsed or refractory multiple myeloma*	
Endpoint		*Grade ≥2 PN*	
No. of Patients (total, and with individual PK)		*324*	
Population Characteristics (Table 69, Table 70)	General	*-Age median (range): 66 (36-89)* *-Weight median (range): 71.45 (36.5-159.6)* *-168 (51.9%) male; 156 (48.1%) female* *-29 (9%) Black; 51 (15.7%) Asian; 194 (59.9%) White; 49 (15.1%) Missing; 1 (0.3%) Not Reported*	
		Organ impairment	*-Renal (based on eGFR, mL/min/1.73m^2):* *128 (39.5%) ≥90 mL/min/1.73 m^2 (normal)* *123 (38.0%) ≥60-<90 mL/min/1.73 m^2 (mild impairment)* *70 (21.6%) ≥30-<60 mL/min/1.73 m^2 (moderate impairment)* *3 (0.9%) <30 mL/min/1.73 m^2 (severe impairment)*
		Pediatrics (if any)	*Not applicable*
		Geriatrics (if any)	*-Age median (range): 71 (65-89)* *184 (56.8%) participants ≥65 yr; 50 (15.4%) participants ≥75 yr* *-92 (50.0%) male; 92 (50.0%) female*
Dose(s) Included		*IV: 0.1, 0.3, 1, 3, 10, 30, and 50 µg/kg, SC: 80, 130, 215, 360, 600, and 1000 µg/kg, 4, 12, 20, 32, 44, and 76 mg*	

Exposure Metrics Explored (range)	• *Predicted maximum concentration within the first 24 hours following the first treatment dose ($C_{max,24}$)* • *Predicted average concentration 28 days following the first treatment dose ($C_{ave,28}$)* • *Predicted average concentration up to event time ($C_{ave,event}$)*	
Covariates Evaluated	*Not applicable*	
Final Model Parameters	**Summary**	**Acceptability [FDA's comments]**
Model Structure	*Boxplots by incidence of Grade ≥2 PN.*	**Acceptable**
Model Parameter Estimates	*Not applicable*	**Acceptable**
Model Evaluation	*There was not an apparent E-R relationship by visual inspection of the boxplots*	**Acceptable**
Covariates and Clinical Relevance	*Not applicable*	**Acceptable**
Simulation for Specific Population	*Not applicable*	**Acceptable**
Visualization of E-R relationships	Figure 49 *for Grade ≥2 PN using free elranatamab PK* Figure 50 *for Grade ≥2 PN using total elranatamab PK*	**Acceptable**
Overall Clinical Relevance for ER	*There was no apparent E-R relationship for Grade ≥2 PN using either free or total elranatamab PK*	**Acceptable**
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics		

Figure 49: Applicant – PN Grade ≥2 by Free Elranatamab PK Exposures in 324 Participants

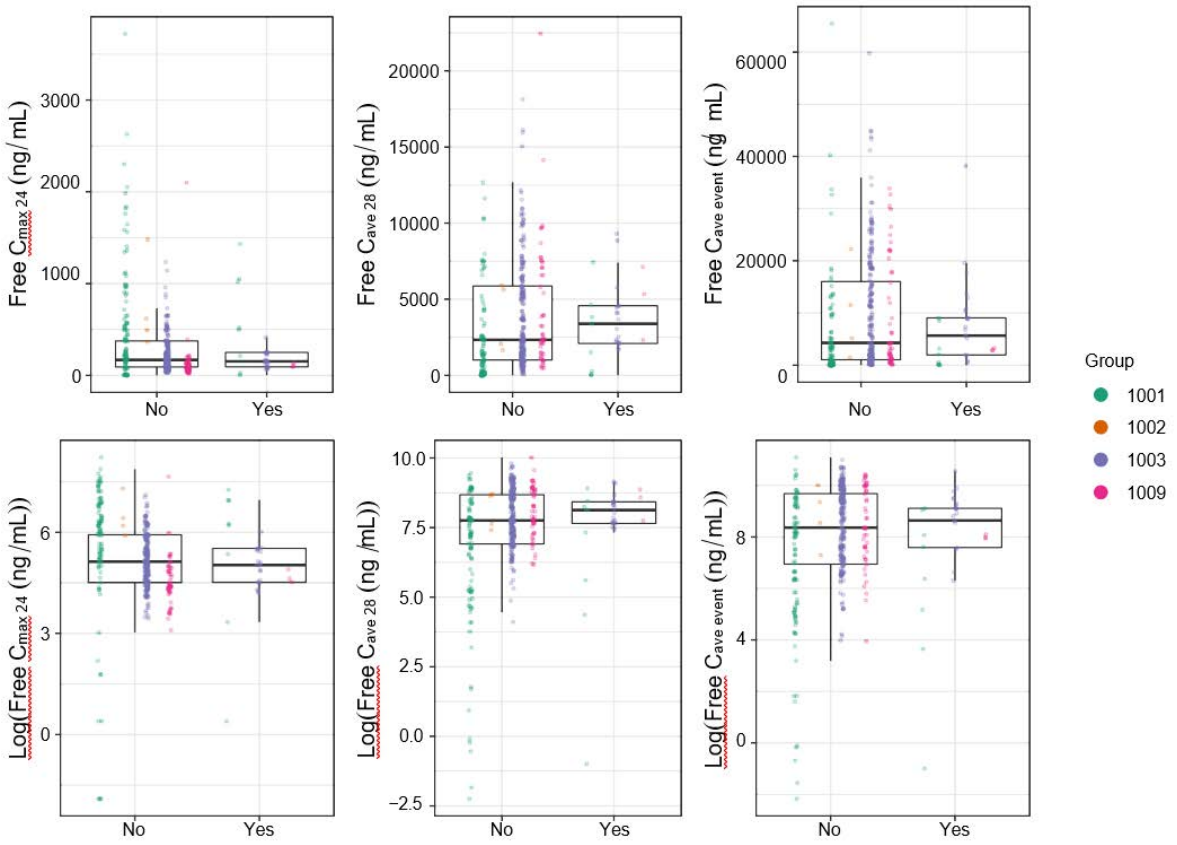
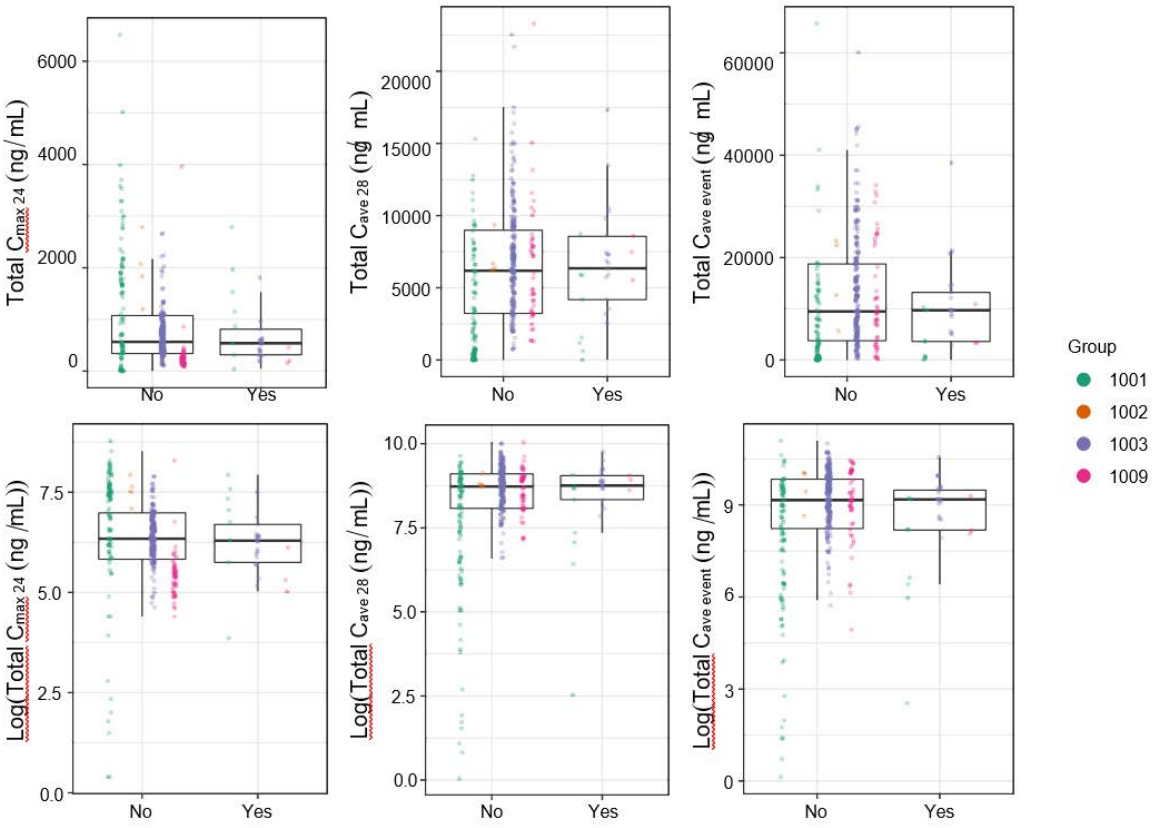


Figure 50: Applicant – PN Grade ≥2 by Total Elranatamab PK Exposures in 324 Participants



19.4.2.4.5. ER- Safety Analysis for QTc Prolongation

General Information		
Goal of ER analysis		*To characterize the effects of total and free elranatamab concentration on the QTc interval in participants with relapsed or refractory multiple myeloma.*
Study Included		*C1071001, C1071002, C1071003, and C1071009*
Population Included		*Adult participants with relapsed or refractory multiple myeloma*
Endpoint		• *QT interval corrected for heart rate using Fridericia's formula.*
No. of Patients (total, and with individual PK)		*324* *Total elranatamab analysis: 302 (22 excluded)* *Free elranatamab analysis: 295 (29 excluded)*
Population Characteristics (Table 69, Table 70)	General	*Total elranatamab analysis:* *- Age median (range): 66 yrs (36 yrs-89 yrs)* *- Sex: 157 men and 145 women* *- Race: 27 black, 49 Asian, 180 white, 46 unknown* *- QT interval median (range):* *Baseline: 391 msec (282 msec-516 msec)* *During Treatment: 396 (253 msec- 506 msec)* *- RR interval* *Baseline: 791 msec (510 msec-1272 msec)* *During Treatment: 786 (97 msec-1192 msec)* *-QTcF Median (range* *Baseline: 426 msec (325 msec-520 msec)* *During Treatment: 428 (312 msec- 564 msec)* *Free elranatamab analysis:* *- Age median (range): 66 yrs (36 yrs-89 yrs)* *- Sex: 151 men and 144 women* *- Race: 25 black, 48 Asian, 175 white, 47 unknown* *- QT interval median (range):* *Baseline: 391 msec (282 msec-516 msec)* *During Treatment: 396 (253 msec- 506 msec)* *- RR interval* *Baseline: 786 msec (510 msec-1272 msec)* *During Treatment: 784 (97 msec-1192 msec)* *- QTcF Median (range* *Baseline: 426 msec (325 msec-520 msec)* *During Treatment: 428 (312 msec- 564 msec)*
	Pediatrics (if any)	*Not applicable*

Dose(s) Included	*IV: 0.1, 0.3, 1, 3, 10, 30, and 50 µg/kg, SC: 80, 130, 215, 360, 600, and 1000 µg/kg, 4, 12, 20, 32, 44, and 76 mg*	

Elranatamab Concentrations (ng/ml)	• *Total elranatamab analysis median (range):*
	  ○ *6270.0 (0.0-117000.0)*
	• *Free elranatamab analysis*
	  ○ *1960.0 (0.0-101000.0)*
	Table 77 *and* Table 78– *Summary Statistics of Total and Free Elranatamab Concentrations and ECG Measurements for Baseline and During Treatment, respectively.*	

Covariates Evaluated	*Age, sex, race*	
Final Model Parameters	**Summary**	**Acceptability [FDA's comments]**
Model Structure	*Linear Regression Analysis*	**Acceptable**
Model Parameter Estimates	*Model Parameter Estimates for RR Versus Total Elranatamab Concentration Relationship* (Table 79) *Model Parameter Estimates for RR Versus Free Elranatamab Concentration Relationship* (Table 80) *Total Elranatamab Final Base Model Parameter Estimates and Bootstrap for QTcF* (Table 81) *Free Elranatamab Final Base Model Parameter Estimates and Bootstrap for QTcF* (Table 82)	**Acceptable**

Model Evaluation	*Neither total or free elranatamab concentrations were found to effect RR intervals.* *The correction factor QTcF was determined to be appropriate and was used as the primary endpoints in this analysis.* *The results of both analyses demonstrated a lack of an effect of both total and free elranatamab concentrations on QTcF.*	**Acceptable**
Covariates and Clinical Relevance	*The population covariates (e.g. age, race and gender) tested did not have a statistically significant impact QTcF.*	**Acceptable**
Simulation for Specific Population	Table 83 *Simulated 2.5th, Median, and 97.5th Percentiles of the Changes in QTcF (msec) from Baseline at Observed Serum Cmax at Therapeutic Concentrations*	**Acceptable**
Visualization of E-R relationships	Figure 51 *QTcF Versus Total Elranatamab Concentration* Figure 52 *QTcF Versus Free Elranatamab Concentration*	**Acceptable**
Overall Clinical Relevance for ER	*Total and free elranatamab concentrations had no clinically meaningful effect on the QT interval corrected for heart rate over a range of serum concentrations observed across all four clinical studies.*	**Acceptable**
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics		

Table 77: Applicant – Summary Statistics of Total Elranatamab Concentrations and ECG Measurements for Baseline and During Treatment

Group	During Treatment	Baseline	Total
Total Elranatamab Concentration (ng/ml)			
Median	6270.0	0.0	4345.0
Mean (Std. Dev.)	10940.35 (12617.94)	0.00 (0.00)	9165.92 (12233.10)
Range (Min; Max)	(0.0; 117000.0)	(0.0; 0.0)	(0.0; 117000.0)
N (%)	1565 (83.8%)	302 (16.2%)	1867 (100.0%)
QT interval (msec)			
Median	396	391	395
Mean (Std. Dev.)	395.7 (36.4)	393.7 (35.8)	395.4 (36.3)
Range (Min; Max)	(253; 506)	(282; 516)	(253; 516)
N (%)	1565 (83.8%)	302 (16.2%)	1867 (100.0%)
RR interval (msec)			
Median	786	791	787
Mean (Std. Dev.)	793.9 (139.1)	809.5 (145.9)	796.4 (140.3)
Range (Min; Max)	(97; 1192)	(510; 1272)	(97; 1272)
N (%)	1565 (83.8%)	302 (16.2%)	1867 (100.0%)
QTcF (msec)			
Median	428	426	427
Mean (Std. Dev.)	428.5 (25.5)	424.4 (23.8)	427.8 (25.3)
Range (Min; Max)	(312; 564)	(325; 520)	(312; 564)
N (%)	1565 (83.8%)	302 (16.2%)	1867 (100.0%)

Repository artifact ID FI-35416482.
For each subject, average of the triplicate ECG measurements were used for summary statistics calculation. For observations with missing triplicate values, the first observation was taken into account.
BL=Baseline; N=number of observations; QT interval=time from the start of the Q wave to the end of the T wave; RR interval=time from the peak of 1 QRS complex to the peak of the next; QTcF=QT interval corrected for heart rate using Fridericia's formula; Std.Dev.=Standard Deviation; msec=millisecond; min=minimum; max=maximum.

Table 78: Applicant – Summary Statistics of Free Elranatamab Concentrations and ECG Measurements for Baseline and During Treatment

Group	During Treatment	Baseline	Total
Free Elranatamab Concentration (ng/ml) Median	1960.0	0.0	1020.0
Mean (Std. Dev.)	6679.36 (10720.61)	0.00 (0.00)	5584.68 (10109.49)
Range (Min; Max)	(0.0; 101000.0)	(0.0; 0.0)	(0.0; 101000.0)
N (%)	1507 (83.6%)	295 (16.4%)	1802 (100.0%)
QT interval (msec) Median	396	391	395
Mean (Std. Dev.)	395.8 (36.6)	393.7 (36.0)	395.5 (36.5)
Range (Min; Max)	(253; 506)	(282; 516)	(253; 516)
N (%)	1507 (83.6%)	295 (16.4%)	1802 (100.0%)
RR interval (msec) Median	784	786	785
Mean (Std. Dev.)	792.8 (140.2)	808.5 (145.6)	795.4 (141.2)
Range (Min; Max)	(97; 1192)	(510; 1272)	(97; 1272)
N (%)	1507 (83.6%)	295 (16.4%)	1802 (100.0%)
QTcF (msec) Median	428	426	428
Mean (Std. Dev.)	428.9 (25.6)	424.7 (24.0)	428.2 (25.4)
Range (Min; Max)	(312; 564)	(325; 520)	(312; 564)
N (%)	1507 (83.6%)	295 (16.4%)	1802 (100.0%)

Repository artifact ID FI-35416481.
For each subject, average of the triplicate ECG measurements were used for summary statistics calculation. For observations with missing triplicate values, the first observation was taken into account.
BL=Baseline; N=number of observations; QT interval=time from the start of the Q wave to the end of the T wave; RR interval=time from the peak of 1 QRS complex to the peak of the next; QTcF=QT interval corrected for heart rate usingFridericia's formula; Std.Dev.=Standard Deviation; msec=millisecond; min=minimum; max=maximum.

Table 79: Applicant – Model Parameter Estimates for RR Versus Total Elranatamab Concentration Relationship

Parameter, Units	Typical Value	RSE%	ω^2	95% CI
Intercept, msec	782.4	0.953	111.7	(767.8-797.0)
Slope, msec/(ng/mL)	-0.000089	473.9	-	(-0.00092-0.00074)
Additive residual error (σ)	89.32	5.44	-	(78.8-98.8)

Artifact ID:FI-32510078
RSE% was calculated as 100·SE/TV. 95% CI was calculated using equation: TV±1.96×SE; TV=typical value; SE= standard error. ω2= The estimate of interindividual variability presented as variance.

Table 80: Applicant – Model Parameter Estimates for RR Versus Free Elranatamab Concentration Relationship

Parameter, Units	Typical Value	RSE%	ω^2	95% CI
Intercept, msec	779.2	0.928	111.6	(765.0-793.4)
Slope, msec/(ng/mL)	0.000404	130.0	-	(-0.00063-0.00143)
Additive residual error (σ)	89.6	5.55	-	(79.9-99.4)

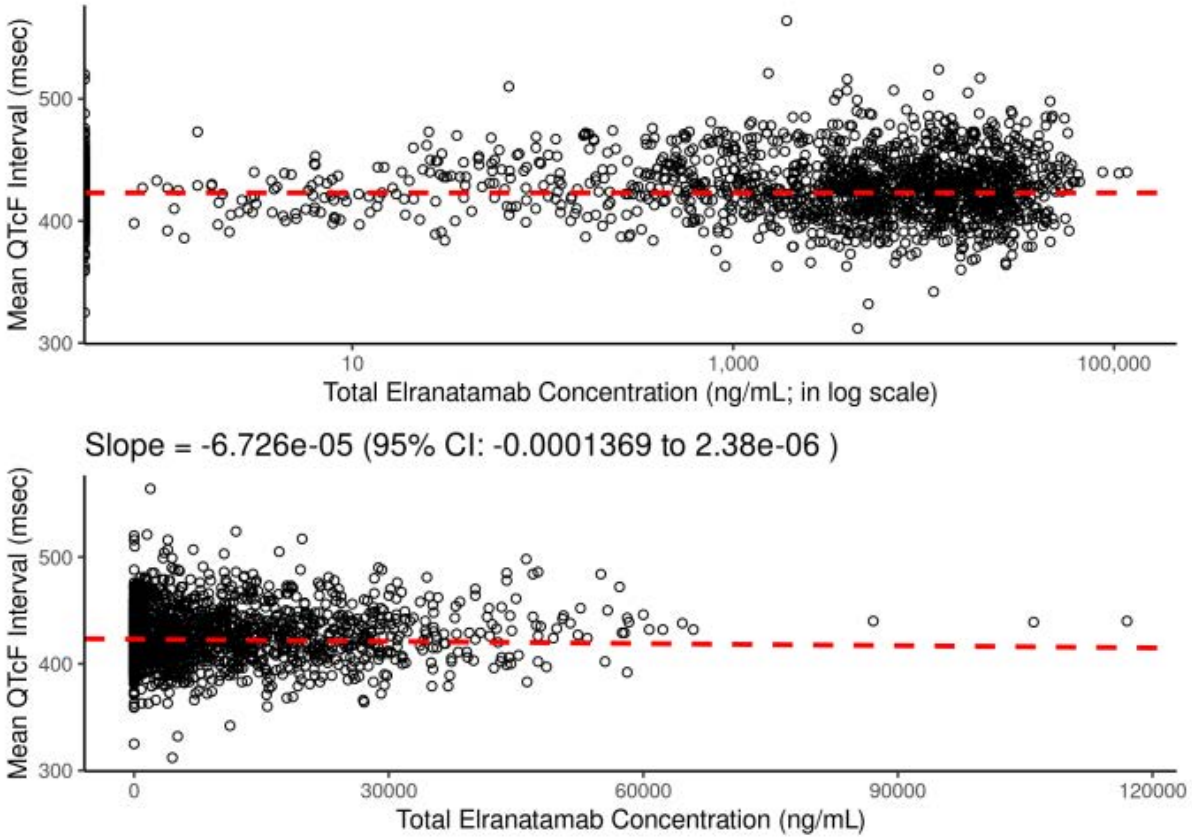
Artifact ID: FI-32511398
RSE% was calculated as 100·SE/TV. 95% CI was calculated using equation: TV2= The estimate of interindividual variability presented as variance.±1.96×SE; TV=typical value;
SE= standard error. ω

Table 81: Applicant – Total Elranatamab Final Base Model Parameter Estimates and Bootstrap for QTcF

		Base Model			Bootstrap
Parameter	**Estimate**	**RSE (%)**	**Shrinkage (%)**	**Median**	**95% CI**
θIntercept (msec)	423	0.312	-	423.6	(420.8; 426.3)
θSlope (msec/(ng/ml))	-6.726e-05	52.8	-	-0.0000690	(-0.000145; -0.00000738)
θAdd.Res.Error	13.77	4.26	-	13.8	(12.7; 15.0)
IIV	Estimate	RSE (%)	Shrinkage (%)	Median	95% CI
$\omega^2_{Intercept}$	430.6	5.09	5.4	425.2	(346.6; 519.4)
OFV	12401.53	-	-	12361.08	-

Repository artifact ID FI-35600169. Line 1 substituted.
The median and 95% CI are generated from a bootstrap run of 1000 resampled datasets.

Figure 51: Applicant – QTcF Versus Total Elranatamab Concentration



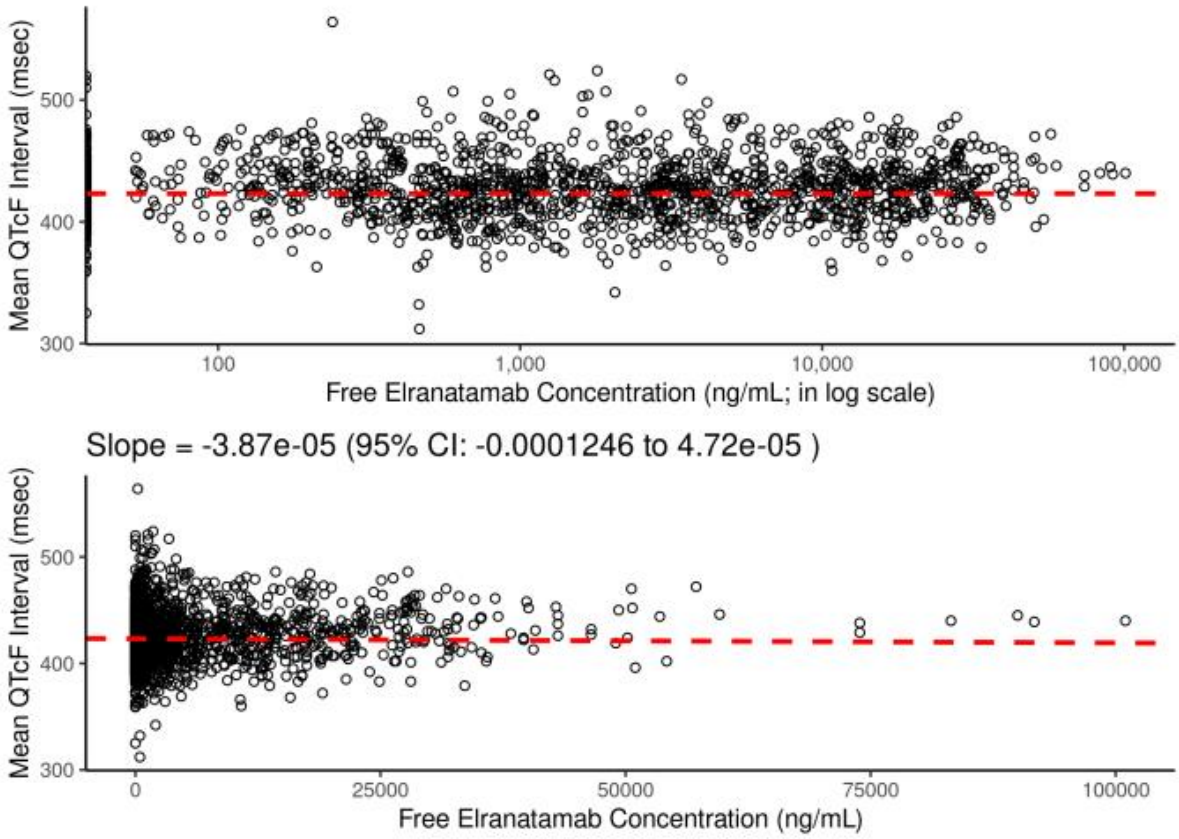
Repository artifact ID FI-32568961.
Red dashed line represents the mean model predicted response. For better visualization, horizontal axis in the first plot is presented in log scale. Slope and 95% CI from the model fit are presented in the second plot.
msec=millisecond; CI=confidence interval.
95% CI was calculated using equation: TV±1.96×SE; TV=typical value; SE= standard error.

Table 82: Applicant – Free Elranatamab Final Base Model Parameter Estimates and Bootstrap for QTcF

		Base Model			Bootstrap
Parameter	**Estimate**	**RSE (%)**	**Shrinkage (%)**	**Median**	**95% CI**
θIntercept (msec)	423.1	0.321	-	423.3	(420.8 ; 426.2)
θSlope (msec/(ng/ml))	-3.87e-05	113.3	-	-0.0000419	(-0.000139 ; 0.0000329)
θAdd.Res.Error	13.89	4.39	-	13.8	(12.7 ; 15.2)
IIV	Estimate	RSE (%)	Shrinkage (%)	Median	95% CI
ω^2Intercept	436.8	5.09	5.4	435.5	(353.3 ; 525.4)
OFV	12000.52	-	-	11968.29	-

Repository artifact ID FI-35650522. Line 1 substituted.
The median and 95% CI are generated from a bootstrap run of 1000 resampled datasets.
RSE=relative standard error; CI=confidence interval; Prop.=Proportional; Res. Error=residual error; IIV=inter-individual variability; CV=coefficient of variation; OFV=objective function value; ω2=variance; θ=typical value.

Figure 52: Applicant – QTcF Versus Free Elranatamab Concentration



Repository artifact ID FI-32622418.
Red dashed line represents the mean model predicted response. For better visualization, horizontal axis in the first plot is presented in log scale. Slope and 95% CI from the model fit are presented in the second plot.
msec=millisecond; CI=confidence interval.
95% CI was calculated using equation: TV±1.96×SE; TV=typical value; SE= standard error.

Table 83: Applicant – Simulated 2.5th, Median, and 97.5th Percentiles of the Changes in QTcF (msec) from Baseline at Observed Serum Cmax at Therapeutic Concentrations

Analyte	Mean C_{max}	ΔQTcF (2.5th percentile)	ΔQTcF (Median)	ΔQTcF (97.5th percentile)
Free Elranatamab (ng/mL)	13941.9	-1.929	-0.583	0.454
Total Elranatamab (ng/mL)	22760.5	-3.303	-1.572	-0.178

Repository artifact ID FI-36345169.
Unit of ΔQTcF is milliseconds; Cmax=maximum concentration.

The FDA's Assessment:
FDA agreed with Applicant elranatamab concentrations (either free or total) did not affect heart rate. QTcF intervals have a negative correlation with elranatamab serum concentrations (both total and free). The upper bound of 95% CI for both of the models predicted changes in QTcF at the mean observed plasma Cmax for therapeutic concentrations were less than 5 milliseconds, suggesting the effect of total or free elranatamab exposure on QTc prolongation is very minimal. The population covariates (e.g., age, race and gender) tested did not have a statistically significant impact on the change in QTc interval.

These findings are consistent with the fact that elranatamab is a large, targeted protein and bispecific antibody that has a low likelihood of direct ion channel interactions and therefore is not expected to cause concentration dependent prolongation of QT interval. In general, FDA does not recommend concentration-QTc analysis for large molecules, which are unlikely to interact or block with hERG ion channels.

19.4.4.5 ER Review Issues

The FDA's Assessment:
In general, the applicant ER analysis is acceptable. However, the TMDD model could not capture the steady-state drug concentration as well as ADVAN4 TRANS4 therefore the submitted ER results may not reflect the true ER relationship for both efficacy and safety. Refer to FDA reviewer's analysis for more information. The FDA reviewer's E-R analysis for overall survival (OS) indicated that there may be no OS difference between the two exposure quantiles. However, the positive E-R for ORR appeared to support the 76mg for the proposed RRMM patient population.

19.4.4.6 Overall Benefit-Risk Evaluation Based on E-R Analyses

The Applicant's Position:
A significant association between elranatamab exposure (both free and total) was observed with ORR. These results support the full dose of 76 mg QW regimen aiming to saturate sBCMA and maximize elranatamab free drug exposure to increase the probability of ORR.

Exposure-safety analyses support a full dose of 76 mg QW and do not suggest that selection of a lower dose would mitigate the risk for AEs.

A significant association between elranatamab exposure (both free and total) was observed with ORR. Baseline sBCMA was inversely associated with ORR. The 76 mg QW regimen is the highest tested full treatment dose/dosing intensity and achieves the highest free elranatamab exposure at a given baseline sBCMA level in the dose range evaluated. This regimen results in higher probability of achieving an objective response vs lower doses with no expected impact on safety given the flat exposure-safety relationship for Grade ≥3 neutropenia, Grade ≥3 infections, and Grade ≥2 peripheral neuropathy. The 2 step-up priming dose regimen of 12 mg/32 mg with premedications demonstrated predictable and manageable CRS profile.

Therefore, elranatamab at the recommended dosing regimen is considered to have a positive benefit-risk profile for the proposed indication based on meaningful and durable ORR and a manageable safety profile. No dose adjustments based on efficacy, safety, and/or clinical pharmacology findings are needed.

The FDA's Assessment:
FDA agreed with Applicant's position that exposure-efficacy and safety analyses appeared to support the recommended full treatment dosing regimen of 76 mg QW. While there is no OS difference between the two exposure quantiles, the ER for both ORR and ≥ Grade 3 adverse events (AEs) showed positive relationship, and there is no positive E-R relationship identified for any serious AEs, suggesting the overall benefit and risk are balanced for the proposed dose of 76 mg. Refer to FDA reviewer's analysis for more information.

19.4.4.7 Reviewer's Independent Analysis

The FDA's Assessment:
Not Applicable.

19.4.5 Quantitative System Pharmacology (QSP) Analysis

19.4.5.1 QSP Executive Summary

The objective of this QSP analysis is to explore the predicted efficacy at different dosing regimens in high and low baseline (BL) soluble B-cell Maturation Antigen (sBCMA) populations, as well as to compare the maintenance of responses with and without transition from once a week (QW) to twice a week (Q2W) after 24 weeks for participants with persistent responses.

The Division of Pharmacometrics has reviewed the QSP analysis report (Study: PMAR-EQDD-C107a-DP4-1513), supporting modeling files, and the Applicant's responses to Clinical Pharmacology Information Requests (IR). The QSP review team concluded that QSP analysis, in addition to the observations from clinical trials, can be used to support the approval of elranatamab based on:

- The QSP analysis can describe the pharmacokinetic profiles of elranatamab and dynamics of biomarkers (i.e., integrated paraproteins, sBCMA) and biochemical response rate (BRR) after elranatamab treatment
- The QSP analysis provided supportive evidence for the recommended dosing regimen of 76 mg QW SC with a priming regimen and a QW to Q2W dosing interval change after 6 Cycles with weekly dosing for participants with IMWG responses of partial response (PR) or better for at least 2 Cycles.

19.4.5.2 QSP Assessment Summary

Table 84: Applicant – QSP Model Analysis

General Information		
Goal of QSP analysis	QSP modeling was used to explore: i) whether there is a predicted increase in efficacy over different dose and regimens for virtual patient sub-cohorts with high versus low sBCMA, ii) whether the simulated virtual patient response for SC QW differed from a simulated regimen with a QW to Q2W regimen change after 6 Cycles for participants with response of PR or better for at least 2 Cycles.	
Study Included	C1071001 and C1071003 Cohort A interim analysis population	
Endpoint	Response based on serum M-protein and involved FLC	
No. of Patients	N= 101 for C1071001 and N=94 for C1071003	
Dose(s) Included	C1071001: IV from to, SC from 80- 1000 µg/kg, SC 600 then 1000 µg/kg (Part 1.1), SC 600 then 1000 ug/kg Q2W (Part 1.1), SC 44 mg then 76 mg QW (Part 2A) C1071003: SC 12 then 32 then 76 mg QW	
Exposure Metrics Explored (range)	Not applicable	
Covariates Evaluated	Not applicable	
Final Model Parameters	**Summary**	**Acceptability [FDA's comments]**
Model Structure	*A multi-compartment non-linear ODE model was used as described in* ***Error! Reference source not found.***	**Appears to be reasonable**
Model Parameter Estimates	*(parameters varied to generate plausible population simulations)*	The methodologies used to generate plausible patients and virtual population are acceptable
Model Evaluation	-Uncertainty in model parameters and heterogeneity in participant response are captured by a virtual population (VPop) approach outlined in Error! Reference source not found. -Efficacy calibrations of each VPop (ten VPops, each with N = 100 virtual patients) were performed by fitting studies 1001 and 1003 Cohort A IA efficacy biomarker dynamics (time-course and best responses) of serum myeloma protein/monoclonal spike (M-protein) or involved free light chain (FLC), shown in Error! Reference source not found.. -Study 1001 and 1003 Cohort A IA sBCMA longitudinal participant data were set	The QSP model evaluation/validation strategy and results seem to be reasonable.

Table 84: Applicant – QSP Model Analysis

	aside for model validation and not used in the objective function for VPop construction, shown in **Error! Reference source not found.**	
Covariates and Clinical Relevance	*Not applicable*	*Not applicable*
Simulation for Specific Population	*Not applicable*	*Not applicable*
Visualization of model results	*Total sBCMA at baseline was explored through simulated virtual cohorts of patients stratified by sBCMA levels at baseline* *Error! Reference source not found. illustrates simulated biochemical response rate (BRR) for different dose QW or Q2W regimens across multiple VPops stratified by sBCMA levels at baseline.* QSP simulations demonstrated 76 mg QW full treatment dose to provide maximum BRR for all virtual patients including those with high baseline sBCMA	Visualization of model results is acceptable.
Overall Clinical Relevance for Model results	The model virtual population simulations support the recommended dose of 76 mg SC QW with transition to Q2W on Cycle ≥7 upon confirmed response.	*The QSP model predictions showed slightly decrease in average progressive disease among responders under QW to Q2W versus constant QW scenarios with substantial overlap of the 90% prediction intervals of plotted biomarkers. Although the predicted differences might not be clinically relevant, the simulations suggest that the proposed switch to Q2W is as efficacious as a QW (no transition) regimen, supporting the*

Table 84: Applicant – QSP Model Analysis

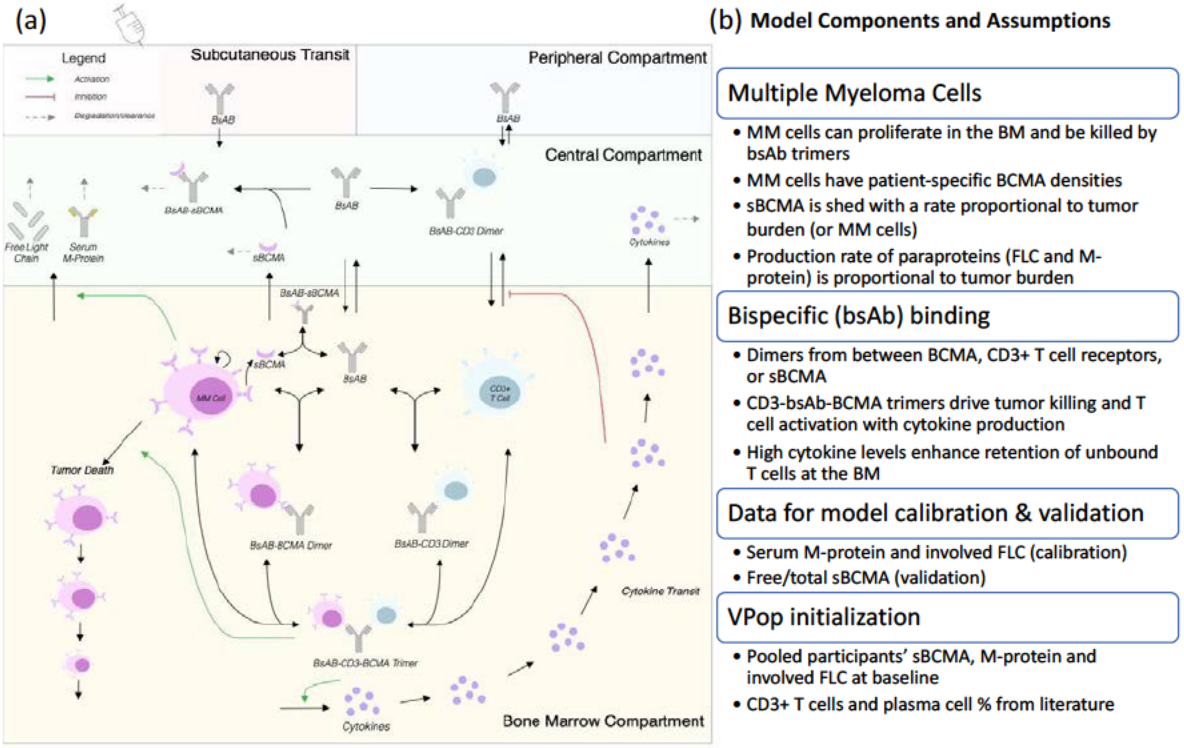
		recommended regimen and the reduction of the dosing interval to 76 mg Q2W after 24 weeks for participants who have achieved a response.
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics		

Table 85: Applicant – Parameters Varied to Generate PP

Parameter Name	Definition	Units	Default Value	VPop range determined by LSA
CD3_density	Density of CD3 receptors on T cell	Receptor/cell	$6x10^4$	±25%
Beta_resis	Rate of resistance maximal effect on trimer kill IC_{50} due to weakened T cell activation	1/hr.	0.1	±2 fold
Alpha_resis	Maximal effect of resistance on trimer kill IC_{50} due to weakened T cell activation	Hr.	0.5	±2 fold
BCMA_density	Density of BCMA receptors on tumor cell	Receptor/cell	$1.259x10^4$	±25%
K_g0	Exponential-phase tumor growth rate	1/hr.	$3.32x10^{-4}$	±10 fold
K_g1	Linear-phase tumor growth rate	Cells/hr.	15000	±10 fold
Tau_mm	Transit time between tumor cell death compartments	hr.	27	24-30
Alpha_kill	Trimer tumor kill rate constant	1/hr.	0.02	±10 fold
N_kill	Trimer tumor kill rate hill coefficient	Unitless	0.8	0.5-1.5

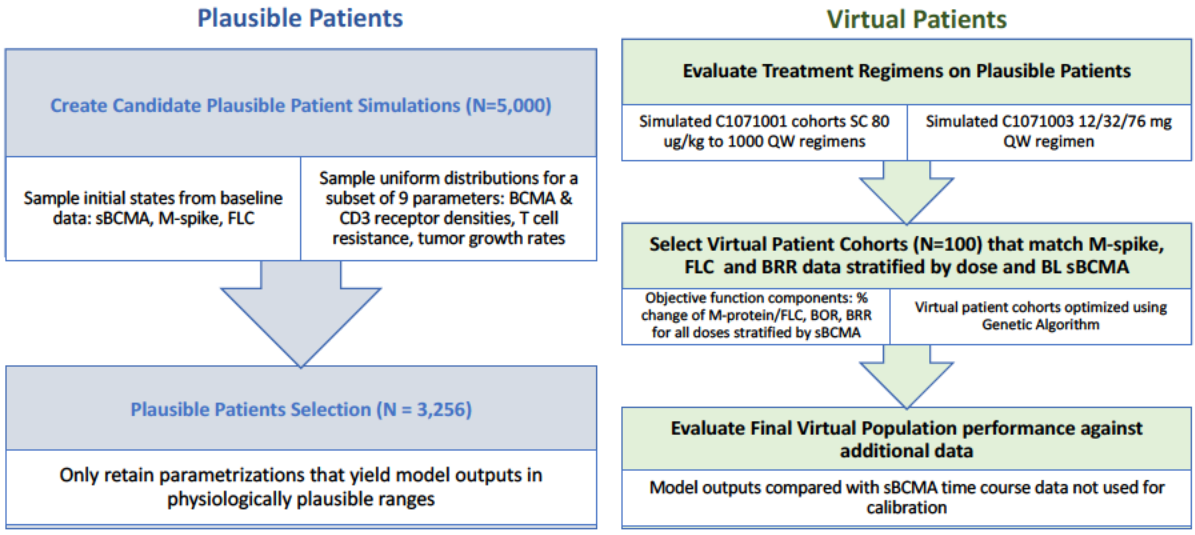
Each parameter was independently sampled from the ranges using uniform distributions. Ranges were assessed using local sensitivity analysis (LSA), which was iteratively applied for the upper and lower parameter bounds that preserved the local sensitivity metric for the listed subset of sensitive of model parameters.

Figure 53: Applicant – Simplified QSP Model Schematic



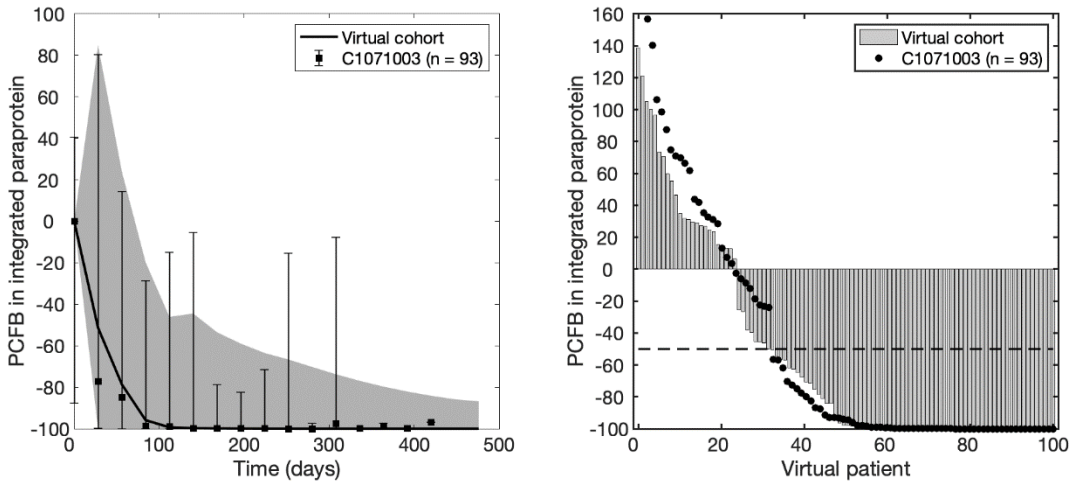
The model describes the dynamic changes in MM cells over time in the bone marrow (BM) which provides a generalized site of action compartment. A bispecific antibody (bsAb) engages CD3 receptors of T cells and BCMA receptors on MM cells to form bsAb-CD3-BCMA trimers, which in turn initiate MM cell death. MM cells produce paraproteins such as M-protein and free light chain (FLC) that serve as key biomarkers that can be measured in circulation and used for virtual patient assessment. Trimers also can activate bound T cells and lead to generic pro-inflammatory cytokine production that helps attenuate T cell migration out of the BM and enhances a pro-inflammatory state, mimicking T cell activation due to trimer formation. MM cells can shed BCMA receptors to generate soluble BCMA (sBCMA) both in the BM and in circulation. A bsAb can bind to sBCMA, as well as T cells in circulation in the central compartment.

Figure 54: Applicant – Overview of Virtual Population Generation Workflow



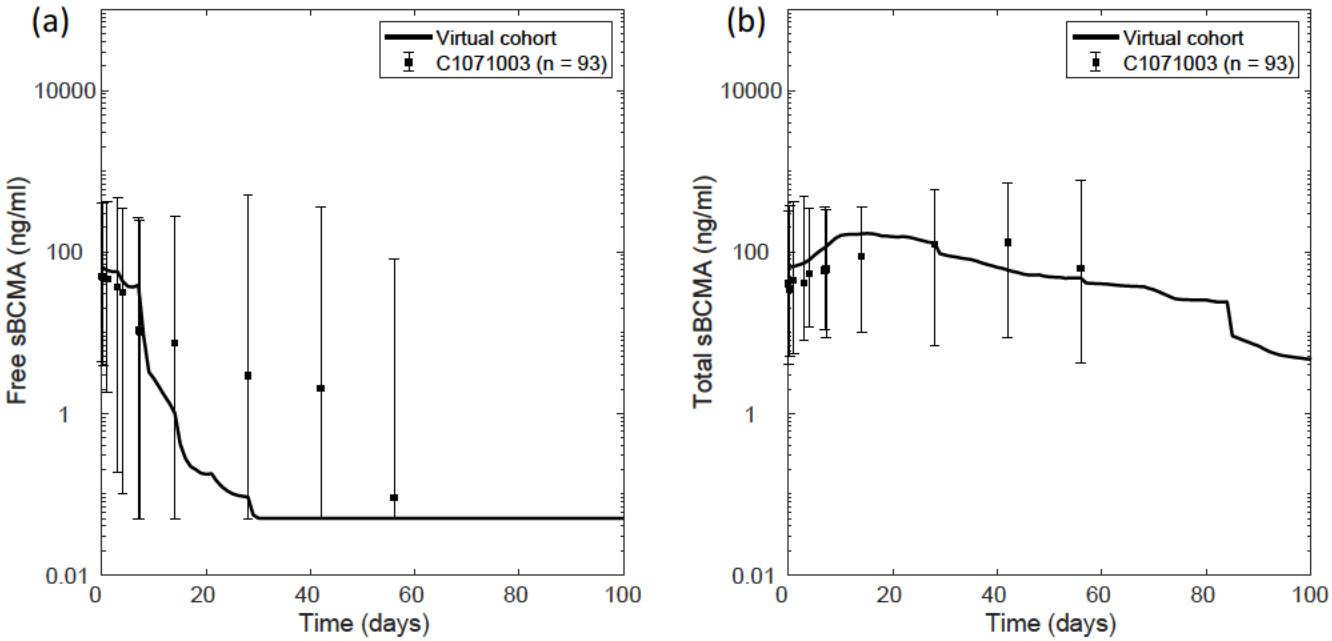
VPop workflow starts with a generation of plausible patients (PP), and through calibration steps with participant data, selection of virtual populations (VPop) cohorts (simulation of only one VPop from PP set shown here). Initial states from plausible patients are sampled from empirical distributions built from pooled participant data. Plausible patient distributions of model parameters are sampled from a uniform distribution, then model parametrizations are filtered according to doubling times of plasma cells and serum M-protein to obtain the PP. These parametrizations are further refined by matching to clinical data (Studies C1071001 and C1071003) to obtain each VPop (N=100). BL sBCMA = baseline sBCMA.

Figure 55: Applicant – Spider and Waterfall Plots of Integrated Paraproteins in Simulations and Clinical Data



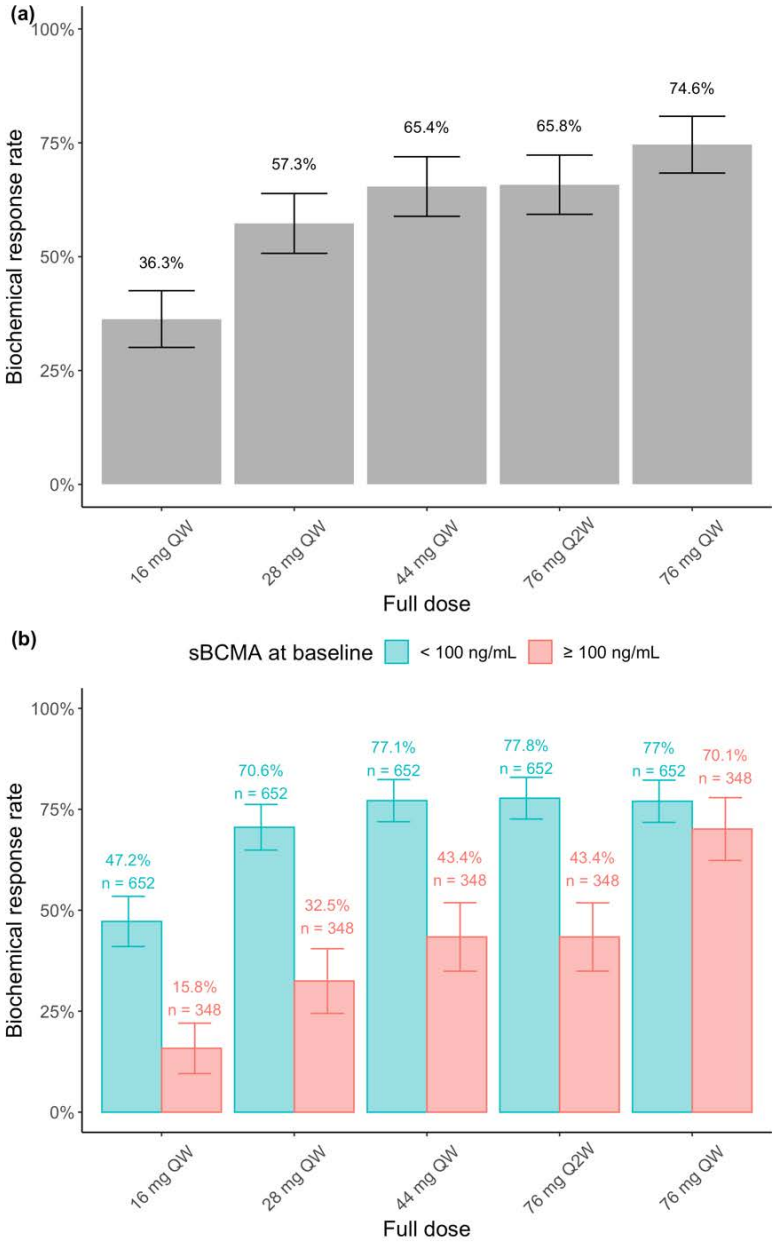
Plots showing spider and waterfall plots from simulations of a QSP virtual population (N=100) against participant paraprotein integrated paraprotein for the two-step-up dose regimen used in study 1003-cohort A (n = 93). (a) Spider plot showing percentage change from baseline (PCFB), black solid line marks the VPop median dynamics with the 95% prediction interval shaded in grey. The median of pooled participant data with 2 standard errors is shown in black solid squares and error bars, respectively. (b) Best percent change in simulated integrated paraprotein protein (as described in methods) shown in the waterfall plot. The horizontal line marks the IMWG criteria thresholds of -50% change from baseline (PR and better). Solid black circles represent best percentage change in integrated paraprotein from participants in study 1003-cohort A (n=93).

Figure 56: Applicant – Visual Predictive Checks of VPop sBCMA to 1003 Participant Trajectories



Comparison of VPop simulated medians for (a) free and (b) total sBCMA shown in solid black lines, with 95% CI shown in grey shaded area with Study C1071003-cohort A participant data. Longitudinal participant data from Study C1071003 (n = 93) are summarized in medians and 2 standard errors, shown in black dots and error bars, respectively. The QSP model simulations show good agreement with longitudinal sBCMA participant levels for Study C1071003.

Figure 57: Applicant – BRR Simulations for Different Dose QW or Q2W Regimens Across Multiple VPops



(a) Simulated BRR across doses for all ten aggregated VPops. Averages of BRR from ten VPops are shown by the grey bars with one standard error represented by the error bars. (b) Simulated BRR stratified by baseline sBCMA levels across doses for the same ten VPops. Averages and standard errors (bar plots and error bars, respectively) were appropriately weighted by cohort sizes before being aggregated. Doses are selected to correspond to efficacious dose range as follows: 16 mg is the fixed dose equivalent of 215 µg/kg; 28 mg is the fixed dose equivalent of 360 µg/kg; 44mg is the fixed dose equivalent of 600 µg/kg; and 76 mg is the fixed dose equivalent of 1000 µg/kg.

Quantitative Systems Pharmacology (QSP) Modeling Review

Division Of Pharmacometrics, Office of Clinical Pharmacology

EXECUTIVE SUMMARY

The objective of this QSP analysis is to explore the predicted efficacy at different dosing regimens in high and low baseline (BL) soluble B-cell Maturation Antigen (sBCMA) populations, as well as to compare the maintenance of responses with and without transition from once a week (QW) to twice a week (Q2W) after 24 weeks for participants with persistent responses.

The Division of Pharmacometrics has reviewed the QSP analysis report (Study: PMAR-EQDD-C107a-DP4-1513), supporting modeling files, and the Applicant's responses to Clinical Pharmacology Information Requests (IR). The QSP review team concluded that QSP analysis, in addition to the observations from clinical trials, can be used to support the approval of elranatamab based on:

- The QSP analysis can describe the pharmacokinetic profiles of elranatamab and dynamics of biomarkers (i.e., integrated paraproteins, sBCMA) and biochemical response rate (BRR) after elranatamab treatment
- The QSP analysis provided supportive evidence for the recommended dosing regimen of 76 mg QW SC with a priming regimen and a QW to Q2W dosing interval change after 6 Cycles with weekly dosing for participants with IMWG responses of >= partial response (PR) for at least 2 Cycles.

A. BACKGROUND

Elranatamab is a heterodimeric humanized full-length bispecific antibody (BsAb) that binds BCMA on MM cells and CD3 on T cells, which directs T cells to myeloma target cells, circumvents the need for the interaction of the T-cell receptor and antigen and expands the T cell repertoire to all CD3+ T cells, thus reacting against BCMA-expressing cells, including myeloma cells. The Applicant developed a QSP model to describe tumor dynamics in response to elranatamab in relapsed/refractory multiple myeloma (RRMM) patients and the QSP model was used to explore the predicted efficacy at different dosing regimens in RRMM patients, and to compare the maintenance of responses with and without transition from QW to Q2W for participants with persistent responses.

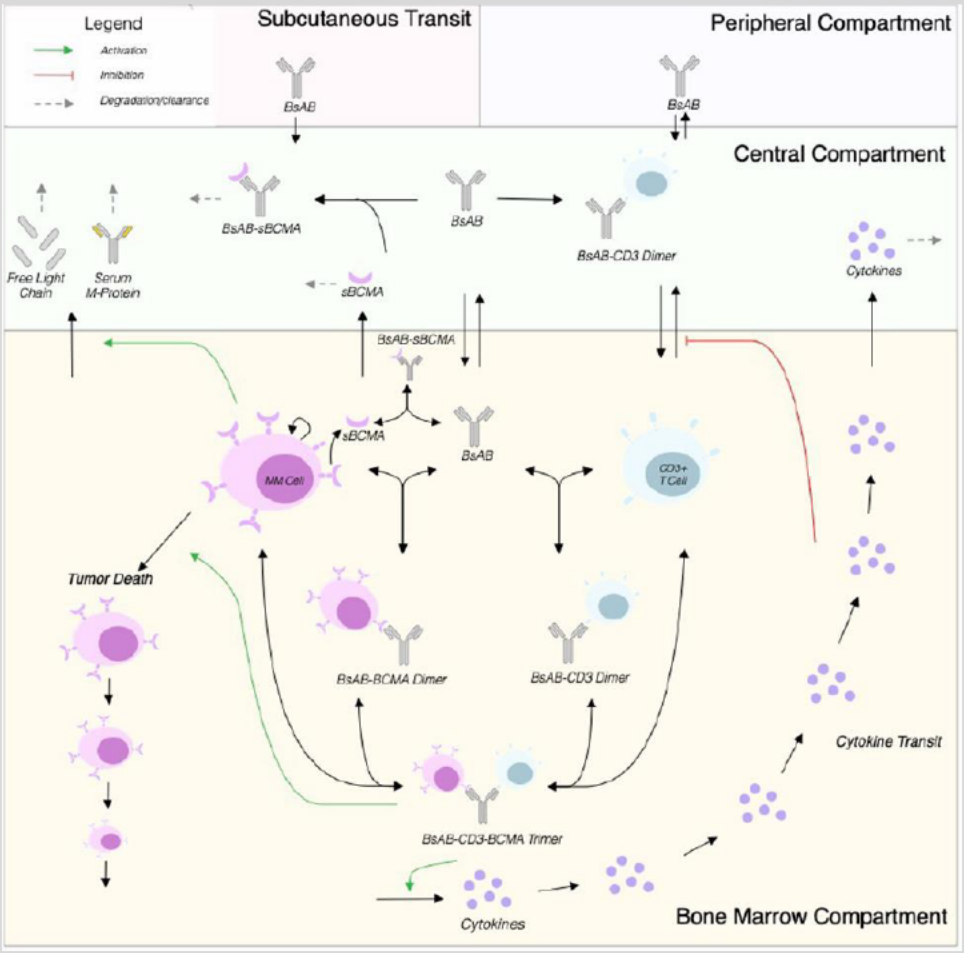
B. METHODS

1. Model Structure

A simplified schematic of the QSP model is depicted in Figure 58. The major disease components involve MM cells at the site of action (bone marrow (BM) compartment) which express BCMA receptors that can be shed in the central compartment. Paraproteins (M-protein and free light chain (FLC)) are also produced at a rate proportional to the total number of MM cells and shed in the central compartment to allow calibration with clinical data. T cell

expressing CD3 receptors can bind BsAb either at the site of action or central compartment. BsAB-CD3 -BCMA trimers are the driving force of MM cell killing and production of a generic pro-inflammatory cytokine species.

Figure 58: FDA – Simplified schematic of the QSP model



Source: Figure 1 of the Applicant's QSP report

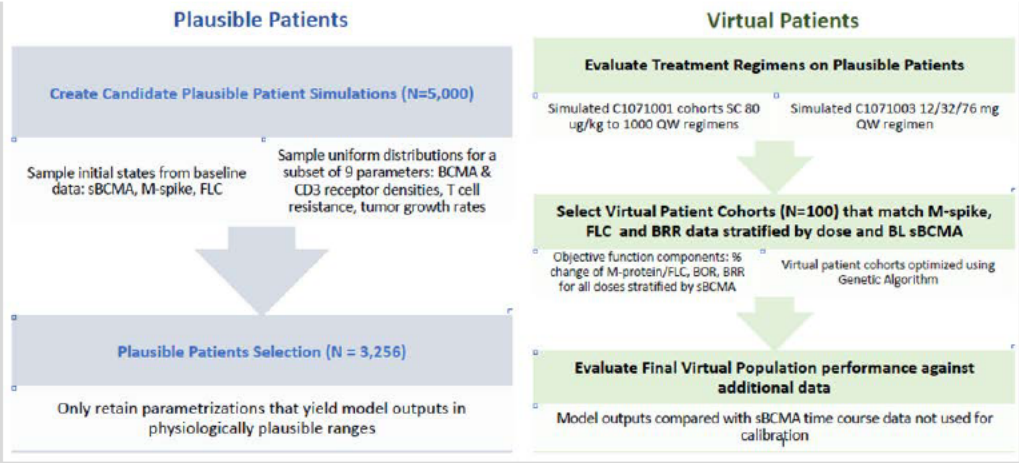
The main model interactions in the central and BM compartments are outlined below. Briefly, in the central compartment, the key interactions described by the model involve binding of BsAb to sBCMA receptors in circulation and to circulatory T cell CD3 receptors. The synthesis of sBCMA in the central compartment is assumed to be proportional to total tumor burden. Besides binding drug, T cells can transit between the central and the BM compartments. To retain T cell steady state dynamics in circulation, a zero-order proliferation term, proportional to baseline T cell density and clearance rate, was incorporated in the T cell model equations. Serum FLC and M-protein dynamics are described by a balance of synthesis rates (following the same form as those for sBCMA, i.e., proportional to total tumor burden) and degradation rates. In the BM compartment (tumor site of action) where MM cells are produced and proliferate, a BsAb can bind: i) myeloma cell BCMA receptors, ii) T cell CD3 receptors, and iii) shed sBCMA.

The rate of BCMA shedding is assumed to be proportional to tumor burden. The total bound receptor counts in the BM were computed using the total numbers of MM and CD3 cells and published BCMA and CD3 T cell receptor densities. MM cell dynamics in the BM follow a standard Simeoni model with kill term driven by trimer concentrations.

2. Generating a Virtual Population (VPop)

To generate virtual patients, as shown in Figure 59, plausible patients (PP) were firstly created by sampling a subset of biologically relevant parameters with high sensitivity and uncertainty independently from their ranges using uniform distributions. Next, model solutions were checked to ensure that these parameters all fell within anticipated physiological ranges, the lower and upper bounds of which were based on literature data or local sensitivity analysis. Initial conditions for serum FLC, serum M-protein, and total sBCMA for plausible patient simulations were obtained from sampling of continuous distributions fitted to pooled studies 1001 and 1003 Cohort A IA participant data at baseline. Each VPop was formed by selecting a subset of PP whose simulated serum M-protein and/or FLC time courses, including biochemical response rate (BRR) based on these biomarkers, best matched corresponding participant biomarkers in Part 1 and Part 1.1 (QW) cohorts in the 1001 study and Cohort A IA in 1003 study.

Figure 59: FDA – Virtual clinical trial simulation strategy



Source: Figure 2 of the Applicant's QSP report

For each virtual patient, serum M-protein was selected as the integrated paraprotein for a participant if it was above detectable levels at baseline, otherwise FLC was used. A virtual patient was marked as a biochemical responder if its corresponding integrated paraprotein had a 50% decrease or greater from baseline and lasting over two treatment Cycles. For each VPop simulated under a particular regimen, percentage of biochemical responders was estimated and used as a metric of efficacy that was compared to a corresponding BRR obtained from study 1001 and 1003 Cohort A IA participant data. To explore variability in simulated BRR, multiple VPops that fit the relevant 1001/1003 Cohort A IA participant data were generated. In addition, to compare potential loss of efficacy due to Q2W switching, progressive disease

events (25% increase from integrated paraprotein nadir) were calculated for virtual patients and this metric was used to explore the possible rebound of disease after patients have been switched to a Q2W regimen.

3. Data for Analysis

Various sources of data were used to inform the development of the QSP model as summarized in **Table 86.**

Table 86: FDA – Description of data used to inform the development of QSP model parameters

Modeling stage	Study	Description	QSP modeling parameters obtained*
Development		Nonclinical data	$k_{on1}, k_{off1}, k_{\deg\_sBCMA}$
Development	NCT02514239	Clinical data, AMG 420 (Topp, M., et al. 2020)	$k_{TC\_c\_BM}, k_{TC\_BM\_c}, k_{\deg\_cyt}, ktr_{cyt}, k_m, \beta_{prod}$
Development/ Validation	C1071001	Clinical data (part 1 (IV: 0.1, 0.3, 1, 3, 10, 30, and 50 ug/kg QW; SC: 80, 130, 215, 360, 600, and 1000 ug/kg QW); part 1.1 (SC: 600 ug/kg for the first week, then 1000 ug/kg QW; SC: 600 ug/kg for the first week, then 1000 ug/kg Q2W); part 2A: SC: 44 mg for the first week, then 76 mg QW)	$CL, F, k_a, V_c, V_p, MM_{max}, \tau_{resis}$
Validation	C1071003 IA	Clinical data (part A: SC: 12/32/76 mg C1D1/C1D4/C1D8 then 76 mg QW)	Parameters perturbed in VPop: $\beta_{resis}, \alpha_{resis}, \alpha_{kill}, n_{kill}, k_{g0}, k_{g1}, BCMA_{density}, \tau_M, CD3_{density}$

$*$ *selected QSP parameters.* k_{on1}: *Binding of BsAB to BCMA;* k_{off1}: *Unbinding rate;*
$k_{deg_{sBCMA}}$: *Degradation of sBCMA;* $k_{TC_{c_{BM}}}$: *T cell transport from central to BM;*
$k_{TC_{BM_c}}$: *T cell transport from BM to central;* $k_{deg_{cyt}}$: *Degradation of cytokines;*
ktr_{cyt}: *Cytokine transit rates from BM to central;* k_m: *Half saturation for tumor killing;*
β_{prod}: *Basal cytokine production;* CL: *Clearance;* F: *Drug bioavailability;*
k_a: *Drug absorption rate;* V_c: *Volume in central;* V_p: *Volume of peripheral;*

MM_{max}: *Maximum tumor burden;* τ_{resis}: *Time to resistance;*

β_{resis}: *Rate of change of resistance;* α_{resis}: *Maximum addition resistance,*
α_{kill}: *Kill constant ,* n_{kill}: *Cooperativity coefficient kill constant,*
k_{g0}: *Exponential tumor growth rate;* k_{g1}: *Linear tumor growth rate;*
$BCMA_{density}$: *Density of BCMA receptors per tumor cell;*
τ_M: *Transit time to MM cell death;* $CD3_{density}$: *Density of CD3 receptors per T cell*

Source: IR response dated on Feb 10th, 2023, and Table 1 from QSP report

Reviewer's comments:

Although Applicant's QSP report is well-organized. Information request was issued to request technical documentation to facilitate a timely review. Example of technical documentation requested by reviewers include:

- *Executable scripts implicated in the studies/simulations in the QSP report: the scripts need to be well documented, with each line/block of scripts followed by relevant descriptions and notes.*
- *Datafiles (input, intermediate and output datasets) implicated in all the studies and simulations in the QSP report.*
- *Model equation files: a complete list of ODEs and any other mathematical equations used in the final QSP model, followed by proper definitions/descriptions.*
- *Parameter definition files: a complete list of parameters each with its description, value, units, sources, and parameter specific assumptions.*
- *Data utility file: a table describing all sources of data informing the QSP model parameters at different modeling stages.*
- *Model assumption files: a complete list of model assumptions and corresponding justifications involved in the FINAL QSP model.*
- *Hardware definition files: a complete list of hardware specifications, operating system, and all the software and tools used to reproduce the simulations in the QSP report.*

4. Model Output Uncertainty Analysis

The plausible and virtual patient generation strategy was utilized by the Applicant to assess model output uncertainty with respect to parameters and initial conditions sampled ranges. To assess model uncertainty in the computed BRR, 10 virtual populations (VPops) were independently sampled from the total pool of 3,256 plausible patients. The variance of the summary statistics across VPops can be interpreted as a metric of uncertainty from multiple

sources. Thus, the Applicant reported summary statistics of simulated regimens by aggregating ten VPops (total of N = 1,000 virtual patients). For each VPop and sub-cohort (i.e., groups defined by baseline sBCMA levels), BRR and its standard error were calculated, and then each estimate was averaged across all ten VPop and sub-cohort weighted by number of virtual patients.

5. Model Validation

The QSP model was validated by comparing simulated sBCMA from one VPop to observed participant time-courses from study 1003 Cohort A IA. The study 1001 and 1003 Cohort A IA sBCMA longitudinal participant data were set aside for model validation and not used in the objective function for VPop construction.

6. Model application

The following assessment were proposed by Applicant:

- Identification of clinical doses that yield highest response rates among patients with different sBCMA levels at baseline. The QSP model was utilized to investigate, for studies 1001 and 1003 Cohort A IA, if there is a predicted increase in efficacy over different dose and regimen levels for virtual patient sub-cohorts with high versus low baseline sBCMA levels across tested dose levels.
- Identification of maintenance of responses after transition from QW to Q2W after 6 Cycles. The QSP model was employed to investigate, for study 1003 Cohort A IA, if the simulated virtual patient maintenance response of elranatamab QW regimen is different than a regimen with a QW to Q2W dosing interval change after 6 Cycles with weekly dosing for participants with IMWG responses of ≥ partial response (PR) for at least 2 Cycles.

Reviewer's comments

It is critical to determine potential CRS risk associated with restarting therapy with elranatamab after dosage delay. Therefore, information request was issued to predict cytokine profiles following elranatamab treatment for several different dose delay scenarios (Table 2 from IR dated on March 07th, 2023) with the QSP model. The results from these simulations have been used to guide elranatamab re-start recommendations following dose delays. For more details of the above QSP simulations, refer to IR response dated on March 24th, 2023.

7. Software and Code Verification

The QSP analysis was conducted using MATLAB® R2019b (The MathWorks, Natick, MA) based upon data pooled from different studies. R statistical software© (version 4.1.3) (The R Foundation, Vienna, Austria) was used for data tabulation, and visualization activities.

Reviewer's comments:

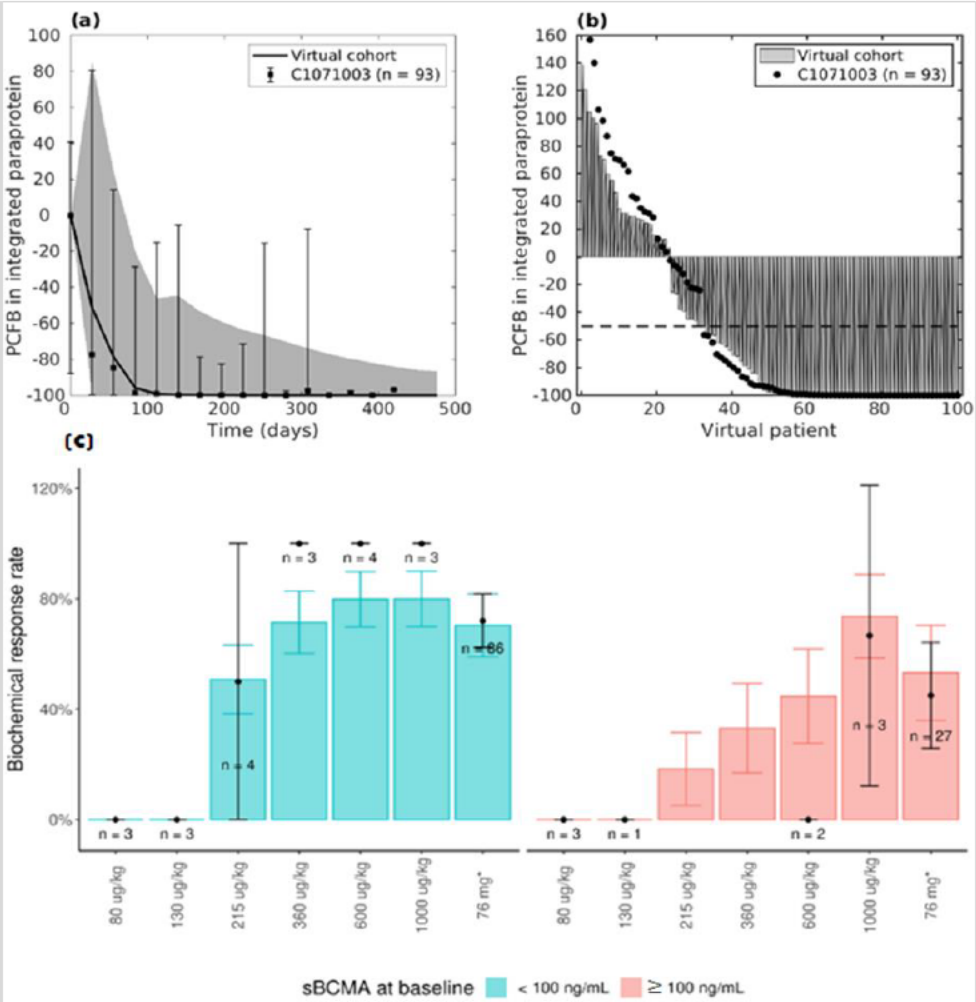
- *Applicant was able to provide all the required documentation following FDA's information requests.*
- *Mathematical equation and methodology have been checked against the reference code and reviewer can reproduce the results in the report.*

C. RESULTS

1. Can the QSP model describe the PK profiles of elranatamab and dynamics of* biomarkers (i.e., integrated paraproteins, sBCMA) and biochemical response rate (BRR) *after elranatamab treatment?

Yes. The model can describe the dynamics of biomarkers, such as integrated paraproteins and sBCMA and BRR in patients following the clinical treatment of elranatamab. As shown in Figure 60(a), the spider plots which describe dynamic changes of integrated paraprotein of one VPop (N = 100) simulated with the dosing regimen implemented in study 1003 Cohort A IA, virtual patients' dynamics align with the 95% confidence intervals of study participant paraproteins. Similarly, the waterfall plots (Figure 60 (b)) also show good alignment with the best overall response (BOR) observed in study 1003 Cohort A IA. Notably, about 70% of virtual patients achieve a decrease of 50% or greater from baseline in paraproteins (Figure 60(b)). Figure 60(c) shows the simulated BRR from 10 aggregated VPops compared to the corresponding observed BRR for 1001 and 1003 Cohort A IA participants stratified by baseline sBCMA levels (low versus high). Consistent with clinical observation, the VPops did not show biochemical response at SC doses 130 mg/kg regardless of baseline sBCMA levels. Moreover, the Applicant compared the simulated sub-cohorts results in virtual patient with high and low sBCMA following 1003 two-step-up priming regimen with participant data pooled from priming regimens Part 1.1, 2A and 1003 Cohort A IA. As shown in Figure 60(c). In agreement with observed participant BRRs, VPop sub-cohorts with high sBCMA had lower simulated BRR as compared to those with low sBCMA.

Figure 60: FDA –Percentage change from baseline, best percent change in simulated integrated paraprotein and soluble BCMA stratified by dose

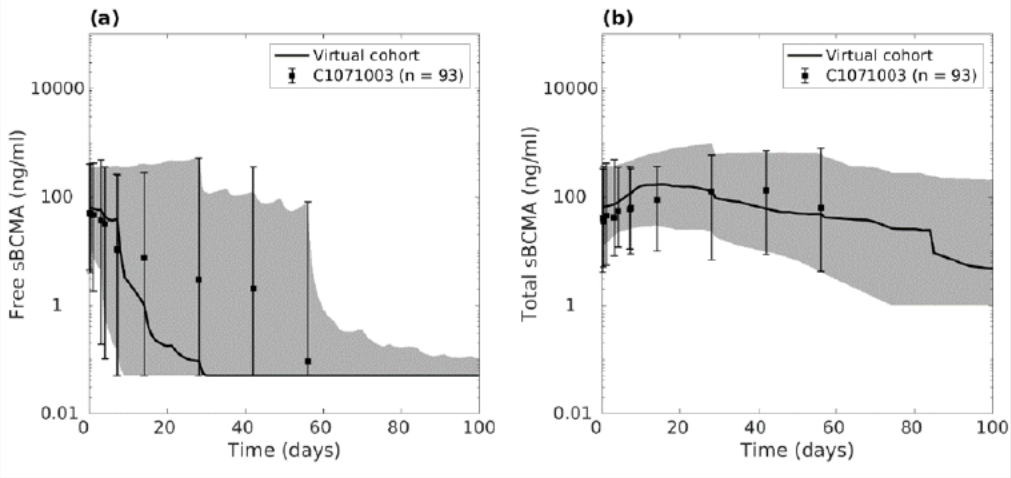


(a) Spider plot showing percentage change from baseline (PCFB). Black solid line marks the VPop median dynamics with the 95% prediction interval shaded in grey. The median of pooled participant data with 2 standard errors is shown in black solid squares and error bars; (b) waterfall plot showing best percent change in simulated integrated paraprotein protein. The horizontal line marks the IMWG criteria thresholds of -50% change from baseline (PR and better). Solid black circles represent best percentage change in integrated paraprotein from participants in study; (c) comparison between simulated and participant BRR stratified by doses and BL sBCMA levels. Ten VPops were fitted to the data, and then results aggregated to create each bar plot. BRR mean and 95% confidence interval (CI) of VPops are represented by bars and error bars colored by baseline sBCMA levels. BRR mean and two standard errors of observed participant data are shown in black dots and black error bars, respectively; 76 mg* corresponds to a dosing schedule that follows a priming regimen in the first week and 76 mg on day 8 and QW thereafter.
Source: Figure 3 and Figure 4 of the Applicant's QSP report

In addition, the Applicant also compared simulated sBCMA from one VPop (same VPop exhibited in Figure 61 to observed participant time-courses from study 1003 Cohort A IA. Particularly, the study 1001 and 1003 Cohort A IA sBCMA longitudinal participant data were set

aside for model validation and not used in the objective function for VPop construction. As shown in Figure 61, reasonable agreement between model results and participant data was observed, which supports the model's predictive power for variable outputs that were not used for calibration of VPops. Overall, these simulations illustrate that the QSP model captures dynamics and the best response of integrated paraproteins.

Figure 61: FDA – Comparison of VPOP simulated medians



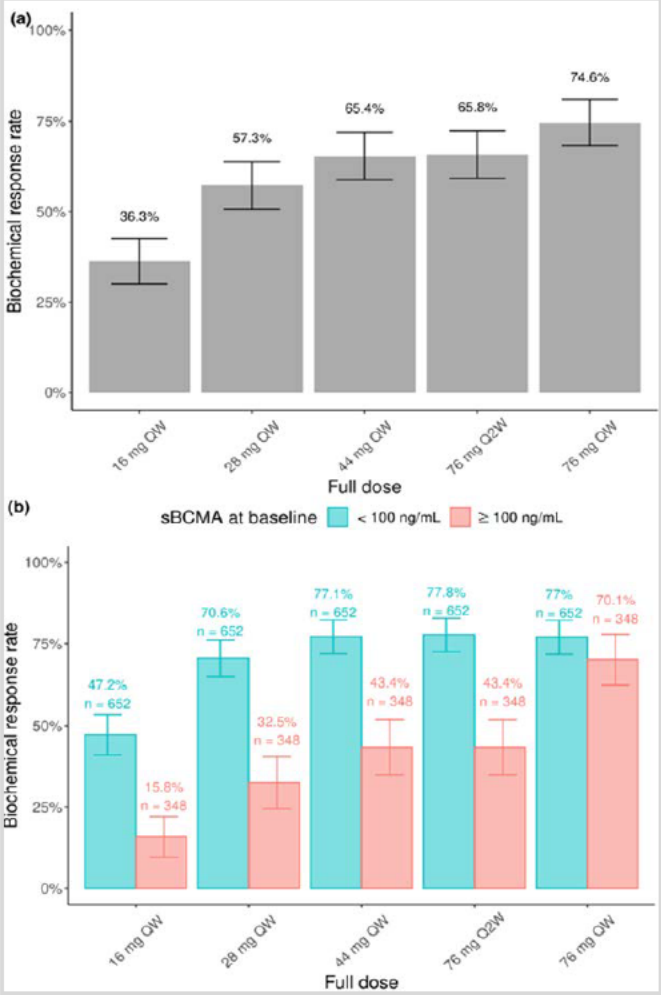
Comparison of VPop simulated medians for (a) free and (b) total sBCMA shown in solid black lines, with 95 longitudinal participant data from study 1003 Cohort A IA (n = 93) are summarized in medians and 2 standard errors, shown in black dots and error bars, respectively.
Source: Figure 5 of the Applicant's QSP report

2. Can the submitted QSP model simulations support the recommended dosing regimen of 76 mg QW SC with a priming regimen?

Yes. All 10 fitted VPops were used to compare different dosing regimens of interest by the Applicant and BRR was calculated and compared among different simulated regimens. Additionally, all simulations incorporated a conditional transition to Q2W after Cycle 6 for patients who have achieved IMWG response of PR or better with responses persisting for at least 2 months. Moreover, the effects of baseline sBCMA on drug efficacy were examined by stratifying virtual patients into two sub-cohorts by baseline sBCMA levels (high sBCMA if > 100 ng/mL from total analyte assay, otherwise low sBCMA). As shown in **Error! Reference source not found.**, simulated BRR for different efficacious doses and regimens in study 1001 were compared using virtual patients from 10 calibrated VPops. The highest response for the aggregated virtual cohorts is observed at 76 mg QW, with a 74.6% projected BRR (**Error! Reference source not found.** (a)). The next best performing doses were 76 mg Q2W and 44 mg QW, both with a simulated BRR of around 65%. Notably, when stratifying the VPops by high versus low levels of sBCMA at baseline (**Error! Reference source not found.** (b)), higher BRR was simulated in the virtual patients with lower baseline sBCMA levels across the explored doses. Specifically, virtual patients with low baseline sBCMA levels reached a maximum BRR of

around 77% with 44 mg QW, 76 mg QW, and 76 mg Q2W. In contrast, virtual patients with high baseline sBCMA levels have equivalent BRR of 43.4% between 44 mg QW and 76 mg Q2W and the maximum BRR of 70% is observed in the 76 mg QW regimen. Overall, through comparison of the same virtual patient cohorts, QSP simulated results support the recommended dosing regimen of 76 mg QW SC, which is expected to provide meaningful clinical benefit in the majority of RRMM patients, including those with high BL sBCMA levels.

Figure 62: FDA – BRR simulations for different dose QW or Q2W regimens across multiple VPops.

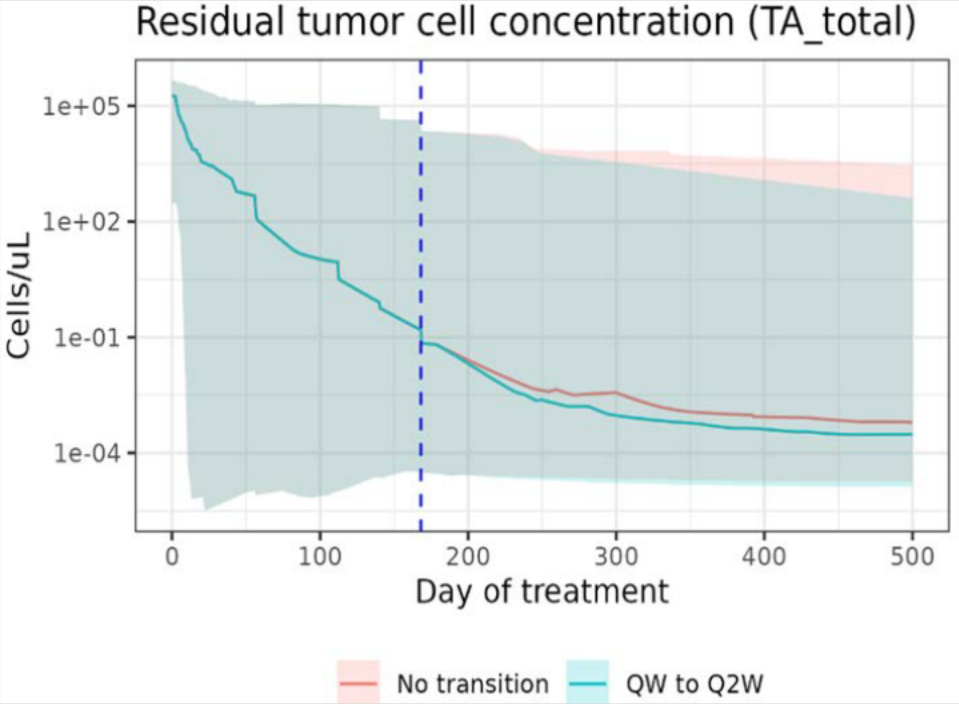


(a) Simulated BRR across doses for all ten aggregated VPops. Average BRR from ten VPops are shown by the grey bars with one standard error represented by the error bars. (b) Simulated BRR stratified by baseline sBCMA levels across doses for the same ten VPops. Averages and standard errors were appropriately weighted by cohort sizes before being aggregated. Doses are selected to correspond to efficacious dose range: 16 mg is the fixed dose equivalent of 215 mg/kg; 28 mg is the fixed dose equivalent of 360 mg/kg; 44mg is the fixed dose equivalent of 600 mg/kg; and 76 mg is the fixed dose equivalent of 1000 mg/kg.
Source: Figure 6 of the Applicant's QSP report

3. Can the submitted QSP model support a QW to Q2W dosing interval change after 6 Cycles with weekly dosing for participants with IMWG responses of partial response (PR) for at least 2 Cycles

Yes. Based on FDA's recommendations, to evaluate the effect of regimen transitioning from QW to Q2W after Cycle 6, the Applicant conducted the following simulations in responders who transitioned from QW to Q2W on or after Cycle 6 and in responders who did not switch dosing interval, respectively: a) simulate the residual tumor cell concentration vs. time profile; b) simulate Ab_BCMA dimmer concentration vs. time profile; c) simulate Ab_CD3 dimmer concentration vs. time profile; d) simulate the trimer concentration vs. time profile; e) simulate the T cell concentration vs. time profile; f) simulate sBCMA concentration vs. time profile. In the response to FDA's information request, as shown in Figure 63 (IR responses dated March 27th, 2023), simulated residual tumor cell concentration is reduced further in virtual responders transitioning from QW to Q2W (shown in a vertical, blue dashed line), however, the deviation may be clinically insignificant with substantial overlap in 90% prediction intervals.

Figure 63: FDA – Residual tumor cell concentration vs. time profile

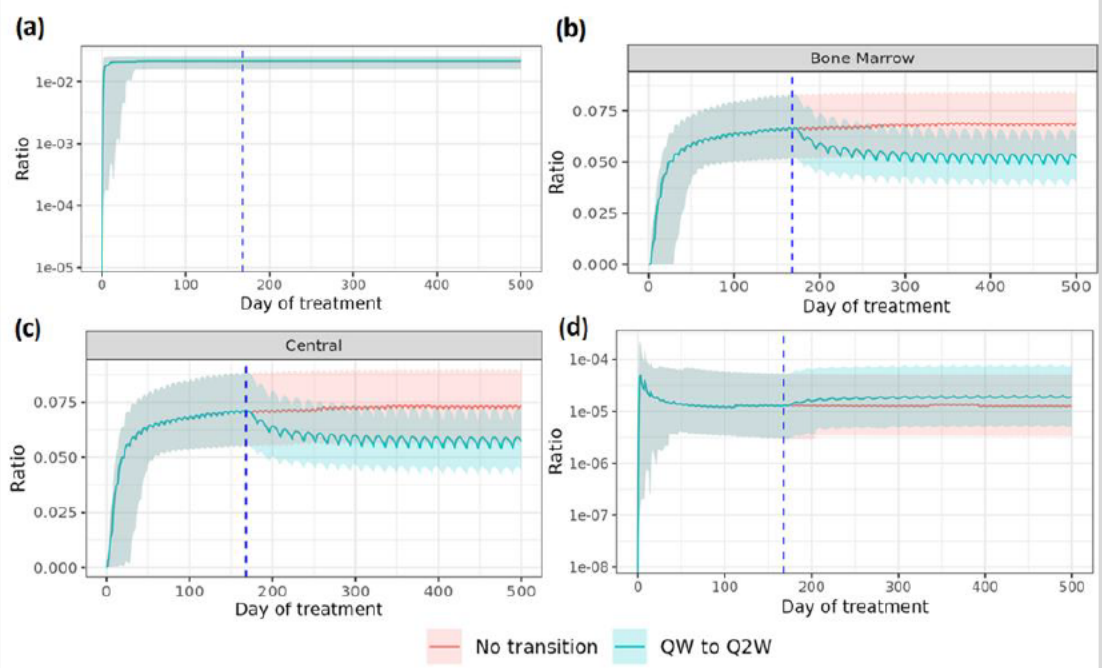


Virtual responders in the QW to Q2W regimen (shown in blue) show a slightly lower tumor burden after Cycle 6 compared to virtual responders in the QW regimen (shown in red, no transition).
Source: Figure 1 of the Applicant's IR Response dated March 27, 2023

Next, plots of drug-BCMA dimers (relative to tumor cell concentration), drug-CD3 dimers (relative to T cells) and drug-BCMA-CD3 trimers (relative to tumor cell concentration) were provided by the Applicant in Figure 64, respectively. As exhibited in Figure 64(a), normalized concentration of BCMA dimers is very similar between the two schedules (appears

overlapping). In comparison, normalized concentration of drug-CD3 dimers relative to T cells are fewer after Cycle 6 in the regimen with QW to Q2W transition (blue shade) than no transition (red shade) (Figure 64 (b and c)). A lower normalized concentration of drug-CD3 dimers relative to T cells can facilitate the formation of free CD3 with a BCMA dimer. Particularly, trimers relative to tumor cell concentration are slightly higher in the regimen with the QW to Q2W transition than no transition (Figure 64 (d)). This clear trend of higher levels of trimers in the QW to Q2W regimen compared to QW regimen supports the predicted slightly lower residual tumor cell concentration in the QSP model.

Figure 64: FDA – Plots of Drug-BCMA Dimers

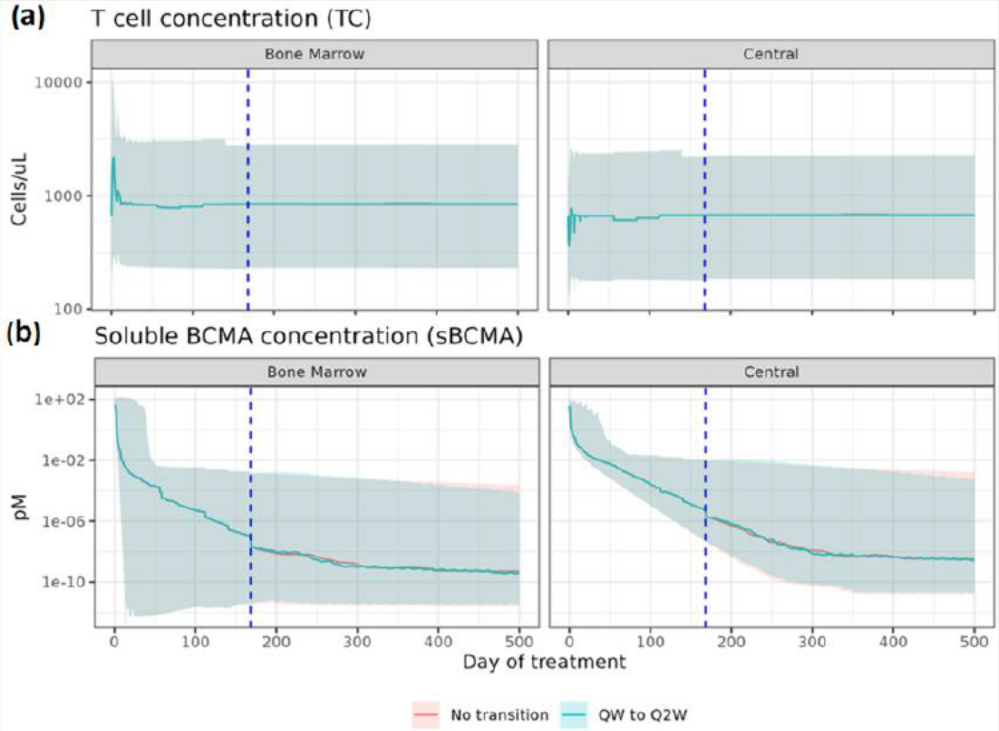


a) Ab-BCMA dimer concentration normalized by tumor cell concentration in no transition and QW-to-Q2W regimens; b and c, Ab-CD3 dimer concentration normalized by T cell concentration in no transition and QW-to-Q2W regimens; d, trimer concentration normalized by tumor cell concentration in no transition and QW-to-Q2W regimens

Source: Figures 1-3 of the Applicant's IR Response dated April 19th, 2023

Lastly, the Applicant provided plots of soluble BCMA (sBCMA) and T cell projected concentrations which were alike in the simulated regimens (Figure 65). As shown in the figure, T-cell reach a steady state quickly (Figure 65(a)) and sBCMA decreases for virtual responders that have declining residual tumor cells (Figure 65(b)). Overall, the Applicant's hypothesis and explanations regarding relative increase in average progressive disease among responders under constant QW versus QW to Q2W scenarios based on the above simulations seem to be reasonable. (b) (4)

Figure 65: FDA – T cell and sBCMA concentration vs. time profile.



No difference in simulated T cell concentrations (a) and soluble BCMA (b) between the two regimens
Source: Figure 4 of the Applicant's IR Response dated March 27th, 2023

In summary, the QSP model predictions showed slightly decrease in residual tumor concentration among responders under QW to Q2W versus constant QW scenarios with substantial overlap of the 90% prediction intervals of plotted biomarkers. Although the predicted differences might not be clinically relevant, the simulations suggest that the proposed switch to Q2W is as efficacious as a QW (no transition) regimen, supporting the recommended regimen and the reduction of the dosing interval to 76 mg Q2W after 24 weeks for participants who have achieved a response.

D. RISK ASSESSMENT

1. Model Risk Assessment

Table 87 showed the highlights of the regulatory impact of the Applicant's QSP model.

Table 87: FDA – Highlights of the regulatory impact of the QSP model

Impact on drug approval and/or labeling	Reviewer team's comments
Supportive evidence. Applicant states that this QSP model is proposed to explore, from a mechanistic perspective, the predicted efficacy at different dosing regimens in high and low baseline soluble sBCMA populations of simulated RRMM patients, as well as to evaluate the	Agree

maintenance of responses with and without transition from QW to Q2W after 24 weeks for participants with persistent responses. Applicant noted that QSP model provided supportive complementary evidence to clinical data and ER analysis for elranatamab dosing recommendation.	
Additional review team's modeling and simulation	
Clinical data are available to support the recommended dosing regimen elranatamab of 76 mg QW and the maintenance of responses with the proposed switch of dosing interval. Although the impact of the QSP modeling analysis is low on the drug's approval, the QSP analysis provided essential mechanistic rational to support the recommended dosing regimen i.e., a QW to Q2W dosing interval change at the maintaining stage. Review team has re-run the submitted model and assessed the dataset used to develop, refine, and validate the submitted QSP model. Information requests were issued to communicate Reviewer's concerns regarding model document/script deficiencies and model simulation hypothesis. Applicant was able to conduct additional simulation analysis to address Reviewer's concern. Review team conclude that the submitted QSP modeling provide insight on the mechanism of multiple myeloma and response to elranatamab treatment in adult patients. The QSP analysis can support the recommended dosing regimen and the proposed switch of dosing interval.	

Table 88: FDA – Summarized the overall model risk assessment of the Applicant's QSP modeling analysis.

Overall model risk assessment for patient population

	Description	Applicant's position	FDA Assessment
Model influence	Describe the model influence, i.e., what is the weight of model predictions in decision-making considering the totality of evidence	Low.	Low. Multiple sources of evidence, including Study 1003 efficacy and safety data, data from supportive studies including 1001 and 1009, exposure-efficacy, and exposure safety analyses support the recommended dosing regimen elranatamab of 76 mg QW. Similarly, multiple sources of evidence supported the maintenance of responses with the proposed switch of dosing interval. Dosing for participants with sustained responses was changed from QW to Q2W in Study 1003 Cohort A (n = 48), Study 1003 Cohort B (n = 14), and Study 1001 (n = 13). The data

			indicates continued benefit after switching to Q2W dosing and showed that the depth of response can continue to increase after the switch to Q2W dosing.
Decision consequence	Discuss your decision consequence based on all available evidence i.e., potential safety or efficacy risk to patients if an incorrect decision is made.	Low.	Low. The safety and efficacy of elranatamab treatment at the proposed dose are supported by clinical data and ER analysis.
Model Risk	Provide an assessment of overall risk of a wrong model prediction based on answers in 'Model influence' and 'Decision consequence'.	Low.	Low.

E. CONCLUSION

The submitted QSP model and analyses provide insight on the mechanism of multiple myeloma and response to elranatamab treatment in adult patients. The QSP analysis can provide supportive complementary evidence to clinical data and ER analysis for elranatamab dosing recommendation.

Specifically, the QSP model was able to describe the pharmacokinetic profiles of elranatamab and dynamics of biomarkers (i.e., integrated paraproteins, sBCMA) and biochemical response rate (BRR) after elranatamab treatment. Moreover, the QSP analysis was able to support the recommended dosing regimen of 76 mg QW SC with a priming regimen and a QW to Q2W dosing interval change after 6 Cycles with weekly dosing for participants with IMWG responses of ≥ partial response (PR) for at least 2 Cycles

19.4.6 Summary of Bioanalytical Method

Table 89: FDA – Bioanalytical Method Life Cycle Information: Elranatamab

Method Validation	Clinical Study	Bioanalytical Project (Report Date)	Method ID
C1079001 – Total PK (b) (4) RIQQ2 Original (05Nov2020) Amendment No. 1 (06Mar2023)	C1071001 C1071002 C1071003 C1071009	(b) (4) RJHR (27Sep2022) (b) (4) RSMY (15Nov2022) (b) (4) RSYC (03Nov2022) (b) (4) RVMQ (03Oct2022)	ICD 695
C1079002 – Free PK (b) (4) ROVV2 Amendment No. 1 (12Sep2022) Amendment No. 2 (23Feb2022)	C1071001 C1071002 C1071003 C1071009	(b) (4) RSYR (27Sep2022) (b) (4) RWKO (15Nov2022) (b) (4) RTJN (14Oct2022) (b) (4) RVMR (04Oct2022)	ICD 887

Table 90: FDA – Bioanalytical Method Life Cycle Information: Elranatamab Total PK (C1079001)

	Method Validation C1079001 ((b) (4) Project RIQQ2)	Study C1071001 ((b) (4) Project RJHR)	Study C1071002 ((b) (4) Project RSMY)
Analyte	Elranatamab (PF-06863135)	Elranatamab (PF-06863135)	Elranatamab (PF-06863135)
Validation type	Full validation	In-study	In-study
eCTD reference number	0002	0002	0002
Method ID	ICD 695 Version 1.00	ICD 695 Version 1.00	ICD 695 Version 1.00
Duration of time method	22Jan2018 - present	22Jan2018 - present	22Jan2018 - present
Bioanalytical site	(b) (4)		
Matrix	Human Serum		
Platform	Electrochemiluminescence (ECL)		
Format	A validated sandwich format using biotin-labeled mouse anti-hCD3 antibody to capture PF-06863135 and detected using ruthenium-labeled mouse anti-BCMA Combo C29 antibody, which binds to the PF-06863135 anti-BCMA arm.		
Stock reference, lot number, expiration date	Elranatamab (PF-06863135), Drug Product Lot 17-001511, current review date 31May2021	Elranatamab (PF-06863135) Drug Product Lot 17-001511, current review date 31May2021 Reference Standard Lot STL0006586-RS, current review date 30Nov2022	Elranatamab (PF-06863135) Drug Product Lot 17-001511, current review date 31May2021 Reference Standard Lot STL0006586-RS, current review date 30Nov2022
Calibration range from the lower limit of quantitation (LLOQ) to the upper limit of quantitation (ULOQ)	0.500 to 32.0 ng/mL	0.500 to 32.0 ng/mL	0.500 to 32.0 ng/mL
Matrix study population	Both normal healthy and multiple myeloma disease	Multiple myeloma	Multiple myeloma

Synopsis of amendment history	**Amendment No. 1**: Additional Long-term stability and	None	None

Table 91: FDA – Bioanalytical Method Life Cycle Information: Elranatamab Free PK (C1079002)

	Method Validation C1079002	**Study C1071001 ((b) (4) Project RSYR)**	**Study C1071002 ((b) (4) Project RWKO)**
Analyte	Elranatamab (PF-06863135)	Elranatamab (PF-06863135)	Elranatamab (PF-06863135)
Validation type	Full validation	In-study	In-study
eCTD reference number	0002	0002	0002
Method ID	ICD 887 Version 1.00	ICD 887 Version 1.00	ICD 887 Version 1.00
Duration of time method is in	02Apr2021 - present	02Apr2021 - present	02Apr2021 - present
Bioanalytical site	(b) (4)		
Matrix	Human Serum		
Platform	Electrochemiluminescence (ECL)		
Format	A validated sandwich format using biotin-labeled mouse anti-hCD3 antibody (binds to the anti-CD3 arm of PF-06863135) to capture free PF-06863135 and detected using ruthenium-labeled mouse anti-BCMA Combo C29 antibody (binds to the anti-BCMA arm of PF-		
Stock reference, lot number, expiration date	Elranatamab (PF-06863135) Drug Product Lot 17-001511, current review date 31M review date 30Nov2022	Elranatamab (PF-06863135) Drug Product Lot 17-001511, current review date 31May2021	Elranatamab (PF-06863135) Reference Standard Lot STL0006586-RS, current review date 30Nov2022
Calibration ranges from the lower limit of quantitation (LLOQ) to the upper limit of	50.0 to 6400 ng/mL	50.0 to 6400 ng/mL	50.0 to 6400 ng/mL
Matrix study population	Both normal healthy and multiple myeloma disease	Multiple myeloma	Multiple myeloma
Synopsis of amendment history	**Amendment No. 1**: Additional Specificity Evaluation of Free PF-06863135 in Normal Human Serum in the Presence of Anti-Drug Antibodies **Amendment No. 2**: Additional disease state selectivity, long-term stability, and parallelism.	None	None
	Study C1071003 ((b) (4) Project RTJN)	**Study C1071009 ((b) (4) Project RVMR)**	
Analyte	Elranatamab (PF-06863135)	Elranatamab (PF-06863135)	
Validation type	In-study	In-study	
eCTD reference number	0002	0002	
Method ID	ICD 887 Version 1.00	ICD 887 Version 1.00	
Duration of time method is in use	02Apr2021 - present	02Apr2021 - present	

	Method Validation C1079002	Study C1071001 ((b) (4) Project RSYR)	Study C1071002 ((b) (4) Project RWKO)
Bioanalytical site	(b) (4)		
Matrix	Human Serum	Human Serum	
Platform	Electrochemiluminescence (ECL)	Electrochemiluminescence (ECL)	
Format	A validated sandwich format using biotin-labeled mouse anti-hCD3 antibody (binds to the anti-CD3 arm of PF-06863135) to capture free PF-06863135 and detected using ruthenium-labeled mouse anti-BCMA Combo C29 antibody (binds to the anti-BCMA arm of PF-06863135).		
Stock reference, lot number, expiration date	Elranatamab (PF-06863135) Reference Standard Lot STL0006586-RS,	Elranatamab (PF-06863135) Reference Standard Lot STL0006586-RS, current review date 30Nov2022	
Calibration ranges from the lower limit of quantitation (LLOQ) to the upper limit of quantitation (ULOQ)	50.0 to 6400 ng/mL	50.0 to 6400 ng/mL	
Matrix study population	Multiple myeloma	Multiple myeloma	

Table 92: FDA – Summary of Method Performance: Elranatamab Total and Free PK

Summary of Method Performance: Elranatamab Total PK	
Bioanalytical method validation report name, amendments and hyperlinks	(b) (4) RIQQ2 (05Nov2020) Original TITLE: THE VALIDATION OF AN ECL ASSAY FOR THE DETERMINATION OF TOTAL PF-06863135 (ANTI-BCMA-CD3 BISPECIFIC ANTIBODY) IN HUMAN SERUM SAMPLES (b) (4) RIQQ2 (06Mar2023) TITLE: THE VALIDATION OF AN ECL ASSAY FOR THE DETERMINATION OF TOTAL PF-06863135 (ANTI-BCMA-CD3 BISPECIFIC ANTIBODY) IN HUMAN SERUM SAMPLES
Method description	Samples containing PF-06863135 are incubated with 300 mM acetic acid (pH 3.0) to dissociate potential drug-target complexes. Dissociated samples are incubated with a neutralizing capture solution containing biotin-labeled mouse anti-hCD3 ID (binds to the PF 06863135 anti-CD3 arm), RN327 (anti-BCMA arm homodimer acting as a target blocker), and goat anti-hBCMA IgG polyclonal antibody (target blocker). PF-06863135 is captured via the biotin-labeled mouse anti-hCD3 ID, which then is bound to streptavidin-coated MSD Multi-Array™ plates. The bound PF-06863135 is detected with ruthenium-labeled mouse anti-BCMA Combo C29 anti-ID, which binds to the PF-06863135 anti-BCMA arm. Tripropylamine-containing buffer (MSD Read Buffer T) is added to the plate and, upon the application of an electrical charge, an electrochemiluminescent signal is produced. The resultant electrochemiluminescent signal is detected using an MSD instrument.
Materials used for standard calibration curve and concentration	Elranatamab (PF-06863135), Drug Product lot 17-001511, 2.00 mg/mL (C1079001 Validation, C1071001 and C1071002) Reference Standard Lot STL0006586-RS, 9.9 mg/mL (C1071001, C1071002, C1071003 and C1071009)
Validated assay range	0.500 to 32.0 ng/mL

Table 92: FDA – Summary of Method Performance: Elranatamab Total and Free PK

Material used for QCs and concentration	Elranatamab (PF-06863135), Drug Product lot 17-001511, 2.00 mg/mL (C1079001 Validation, C1071001 and C1071002) Reference Standard Lot STL0006586-RS, 9.9 mg/mL (C1071001, C1071002, C1071003 and C1071009)		
Minimum required dilutions (MRDs)	1:5		
Source and lot of reagents	The follow reagents were provided by Pfizer. **Drug:** PF-06863135 (Elranatamab), Drug Product Lot: 17-001511 and Reference Standard Lot: STL0006586-RS **Biotin-labeled Reagent** – Murine anti-hCD3 ID biotin, Lot: BB00707000-0877 **Ruthenium-labeled Reagent**– Mu anti-BCMA Combo C29 anti-ID ruthenium, Lot: BB00707000-0876 **Specific Block Reagent 1 –** Anti-BCMA (RN327), Lot: BB00708093-0339 **Specific Block Reagent 2 –** Goat anti-hBCMA Antibody, Lot: FQA061708A		
Regression model and weighting	4-Parameter Logistic Regression, 1/response^2 Weighting		
Validation parameters	**Method validation summary**		**Acceptability**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	Seven	Acceptable
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-0.819% to 2.69%	
	Cumulative precision (%CV) from LLOQ to ULOQ	≤4.61%	
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 5 QCs Inter-batch %CV Total Error (TE)	-5.56 to 4.69% ≤8.58% 8.73% to 11.0%	Acceptable
Performance of QCs during all validation runs	Cumulative accuracy (%bias) QCL, QCM, QCH	-6.13 to 5.67%	Acceptable
	Inter-batch %CV	≤8.53%	
Selectivity and matrix effect	**Healthy Normal Serum:** Unspiked: 10/10 (original lots), Acceptable LLOQ: 2/10 (original lots) LLOQ, Unacceptable ULOQ: 10/10 (original lots), Acceptable Re-evaluation: Unspiked: 20/20 (18 additional lots, 2 original lots), Acceptable LLOQ: 8/20 (18 additional lots, 2 original lots), Unacceptable Second Re-evaluation: Unspiked: 20/20 (20 additional lots), Acceptable LLOQ: 20/20 (20 additional lots), Acceptable. **Multiple Myeloma Serum:** Unspiked: 10/10 (original lots), Acceptable LLOQ: 3/10 (original lots), Unacceptable ULOQ: 9/10 (original lots), Acceptable Re-evaluation: Unspiked: 8/8 (original lots), Acceptable Unspiked: 12/12 (new lots), Acceptable LLOQ: 8/8 (original lots), Acceptable LLOQ: 11/12 (new lots), Acceptable		Acceptable

Table 92: FDA – Summary of Method Performance: Elranatamab Total and Free PK

Hemolysis effect	Unspiked: 6/6, Acceptable LLOQ: 6/6, Acceptable ULOQ 5/6, Acceptable			Acceptable
Lipemic effect	Unspiked: 6/6 (original lots), Acceptable LLOQ: 4/6 (original lots), Unacceptable ULOQ: 6/6 (original lots), Acceptable Re-evaluation Unspiked: 12/12 (6 original lots, 6 additional lots), Acceptable LLOQ: 11/12 (6 original lots, 6 additional lots), Acceptable			Acceptable
Dilution Linearity	**QCDIL (100,000 ng/mL)**	**Bias (%RE)**	**%CV**	Acceptable
	0-Fold (MRD)	>ULOQ	N/A	
	100-Fold	>ULOQ	N/A	
	4000-Fold	-6.99%	1.98%	
	6667-Fold	-2.38%	7.20%	
	66667-Fold	4.58%	5.20%	
Bench-top/process stability	18 hours at 22°C			Acceptable
Freeze-Thaw stability	6 F/T Cycles at -20°C 6 F/T Cycles at -80°C			Acceptable
Long-term storage stability	Long-term stability is currently established at 741 Days at -20°C and -70°C.			Acceptable
Parallelism	Parallelism was demonstrated in 6 individual subjects collected at or near Tmax (~Cmax) in disease populations from protocol C1071001.			Acceptable
Carryover	Not applicable			N/A
Specificity Evaluation(s)	**Target/Endogenous Interference** – hBCMA LLOQ: No interference spiked at 750 ng/mL ULOQ: No interference spiked at 500 ng/mL **Anti-drug Antibody (ADA) Interference** LLOQ: Specificity demonstrated in the presence of 1.0 µg/mL Anti-PF-06863135 Antibody ULOQ: Specificity demonstrated in the presence of 1.0 µg/mL Anti-PF-06863135 Antibody			Acceptable
Method performance in Study C1071001 ((b) (4) Project RJHR)				
Assay passing rate	96.7% (116/120) runs passed			Acceptable
Standard curve performance	Seven (7) standard calibrators from LLOQ to ULOQ • Cumulative bias (%RE) range: -0.2% to 1.1% (excluding anchor point) • Cumulative precision (%CV): ≤ 3.4% (excluding anchor point)			Acceptable
QC performance QC Samples (QCL, QCM and QCH)	• Cumulative bias (%RE) range: -5.6% to -1.3% • Cumulative precision (%CV): ≤ 8.7% • TE: ≤12.0%			Acceptable
Dilution QC performance	• Cumulative bias (%RE) range: -11.2% to 10.2% • Cumulative precision (%CV): 14.6%			Acceptable

Table 92: FDA – Summary of Method Performance: Elranatamab Total and Free PK

Method reproducibility	Incurred sample re-analysis was performed in ~10% (183/1839) of study samples, and 89.6% (164/183) were within ±30% difference. Since this is an on-going study, additional ISR may be assessed and reported in the final end of study bioanalytical report.	Acceptable
Study sample analysis/ stability	Long-term stability is currently established at 741 Days at -20°C and -70°C. Calibration standards, QCs and study samples were stored at -70°C and were all analyzed within the established long-term stability. Eleven (11) samples were analyzed outside of established 6 freeze/thaw stability cycles. Additional F/T stability will be evaluated to cover the freeze/thaw cycles.	Acceptable
Method performance in Study C1071002 ((b) (4) Project RSMY)		
Assay passing rate	66.7% (8/12) runs passed	Acceptable
Standard curve performance	Seven (7) standard calibrators from LLOQ to ULOQ • Cumulative bias (%RE) range: -1.6% to 1.5% (excluding anchor point) • Cumulative precision (%CV): ≤ 4.0% (excluding anchor point)	Acceptable
QC performance QC Samples (QCL, QCM and QCH)	• Cumulative bias (%RE) range: -3.9% to -0.6% • Cumulative Precision (%CV): ≤ 6.4% • TE: ≤10.0%	Acceptable
Dilution QC performance	• Cumulative bias (%RE) range: -0.8% to 5.1% • Cumulative precision (%CV): ≤7.1%	Acceptable
Method reproducibility	Incurred sample re-analysis was performed in 21.7% (23/106) of study samples, and 91.3% (21/23) of the samples were within ±30% difference. Since this is an on-going study, additional ISR may be assessed and reported in the final end of study bioanalytical report.	Acceptable
Study sample analysis/ stability	Long-term stability is currently established at 741 Days at -20°C and -70°C. Calibration standards, QCs and study samples were stored at -70°C and were all analyzed within the established long-term stability.	Acceptable
Method performance in Study C1071003 ((b) (4) Project RSYC)		
Assay passing rate	84.9% (102/119) runs passed	Acceptable
Standard curve performance	Seven (7) standard calibrators from LLOQ to ULOQ • Cumulative bias (%RE) range: -1.7% to 3.0% (excluding anchor point) • Cumulative precision (%CV): ≤ 5.5% (excluding anchor point)	Acceptable
QC performance QC Samples (QCL, QCM and QCH)	• Cumulative bias (%RE) range: -5.2% to -2.8% • Cumulative precision (%CV): ≤ 12.0% • TE: ≤14.8%	Acceptable
Dilution QC performance	• Cumulative bias (%RE) range: -4.9% to 8.5% • Cumulative precision (%CV): ≤13.5%	Acceptable
Method reproducibility	Incurred sample re-analysis was performed in 5.15% (104/2019) of study samples, and 83.7% (87/104) of the samples were within ±30% difference. Since this is an on-going study, additional ISR may be assessed and reported in the final end of study bioanalytical report.	Acceptable
Study sample analysis/ stability	Long-term stability is currently established at 741 Days at -20°C and -70°C. Calibration standards, QCs and study samples were stored at -70°C and were all analyzed within the established long-term stability. Three (3) samples were analyzed outside of established 6 freeze/thaw stability cycles. Additional F/T stability will be evaluated to cover the freeze/thaw cycles.	Acceptable

Table 92: FDA – Summary of Method Performance: Elranatamab Total and Free PK

Method performance in Study C1071009 ((b) (4) Project RVMQ)		
Assay passing rate	100% (18/18) runs passed	Acceptable
Standard curve performance	Seven (7) standard calibrators from LLOQ to ULOQ • Cumulative bias (%RE) range: -3.8% to 5.6% (excluding anchor point) • Cumulative precision (%CV): ≤ 8.4% (excluding anchor point)	Acceptable
QC performance QC Samples (QCL, QCM and QCH)	• Cumulative bias (%RE) range: -12.6% to -7.6% • Cumulative precision (%CV): ≤ 10.9% • TE: ≤19.6	Acceptable
Dilution QC performance	• Cumulative bias (%RE): -6.2% to 3.6% • Cumulative precision (%CV): 7.1%	Acceptable
Method reproducibility	Currently there is no reportable ISR data for study C1071009. Since this study is still on-going, ISR will be assessed and reported in the final end of study bioanalytical report.	Acceptable
Study sample analysis/ stability	Long-term stability is currently established at 741 Days at -20°C and -70°C. Calibration standards, QCs and study samples were stored at -70°C and were all analyzed within the established long-term stability.	Acceptable

Summary of Method Performance: Elranatamab Free PK	
Bioanalytical method validation report name, amendments and hyperlinks	(b) (4) ROVV2 (12Sep2022) TITLE: THE VALIDATION OF AN ELECTROCHEMILUMINESCENT METHOD FOR DETERMINATION OF FREE PF-06863135 IN HUMAN SERUM (b) (4) ROVV2 (23Feb2023) TITLE: THE VALIDATION OF AN ELECTROCHEMILUMINESCENT METHOD FOR DETERMINATION OF FREE PF-06863135 IN HUMAN SERUM
Method description	Samples containing PF-06863135 are incubated with biotin-labeled Mu anti-hCD3 ID (binds to the anti-CD3 arm of PF-06863135). PF-06863135 is captured via the biotin-labeled mouse anti-hCD3 which binds to blocked streptavidin-coated Multi-Array TM plates. The bound PF-06863135 is detected with ruthenium-labeled Mu anti-BCMA Combo C29 anti-ID (binds to the anti-BCMA arm of PF-06863135). Tripropylamine (TPA, MSD GOLD Read Buffer) is added to the plate, and upon application of an electrical charge, an electrochemiluminescent signal is produced and detected with the MSD instrument.
Materials used for standard calibration curve and concentration	Elranatamab (PF-06863135), Drug Product lot 17-001511, 2.00 mg/mL (C1079002 Validation and C1071001) Reference Standard Lot STL0006586-RS, 9.9 mg/mL (C1079001 Validation, C1071002, C1071003 and C1071009)
Validated assay range	50.0 to 6400 ng/mL
Material used for QCs and concentration	Elranatamab (PF-06863135), Drug Product lot 17-001511, 2.00 mg/mL (C1079002 Validation and C1071001) Reference Standard Lot STL0006586-RS, 9.9 mg/mL (C1079001 Validation, C1071002, C1071003 and C1071009)

Table 92: FDA – Summary of Method Performance: Elranatamab Total and Free PK

Minimum required dilutions (MRDs)	1:50		
Source and lot of reagents	The follow reagents were provided by Pfizer. **Drug:** PF-06863135 (Elranatamab), Drug Product Lot: 17-001511 and Reference Standard Lot: STL0006586-RS **Biotin-labeled Reagent** – Murine anti-hCD3 ID biotin, Lot: BB00711491-0124 **Ruthenium-labeled Reagent** – Mu anti-BCMA Combo C29 anti-ID ruthenium, Lot: BB00711491-0125		
Regression model and weighting	five-parameter logistic (5PL), weighted 1/response²		
Validation parameters	**Method validation summary**		**Acceptability**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	Nine	Acceptable
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-9.8% to 9.5%	
	Cumulative precision (%CV) from LLOQ to ULOQ	≤5.0%	
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 7 QCs Inter-batch %CV Total Error (TE)	0.6% to 17.7% ≤10.1% ≤22.2%	Acceptable
Performance of QCs during all validation runs	Cumulative accuracy (%bias) and precision in QCL, QCM, QCH	**Accuracy:** 0.3% to 13.1% RE **Precision:** ≤12.2 % CV	Acceptable
Selectivity and matrix effect	**Healthy Normal Serum:** Unspiked: 10/10 sources (100%) were BLQ LLOQ: 9/10 sources (90.0%) Back-up LLOQ: 9/10 sources (90.0%) Re-evaluation ULOQ: 10/10 sources (100%) Backup ULOQ: 9/10 sources (90.0%) Upon original assessment, aberrant data was collected for the spike controls in Run 14ROVV2. Therefore, samples were repeated at n = 2 in Run 21ROVV2. The mean result for the two replicates were utilized to make outcome observation. **Commercial Multiple Myeloma Serum:** Unspiked: 10/10 sources (100%) were BLQ LLOQ: 3/10 sources (30.0%) Back-up LLOQ: 4/10 sources (40.0%) Back-up ULOQ: 7/10 sources (70.0%) ULOQ: 7/10 sources (70.0%) Due to elevated levels of endogenous sBCMA in multiple myeloma patient population and the nature of the free elranatamab PK assay to only measure free (unbound sBCMA) elranatamab, a matrix effect was observed in 7 out 10 and 3 out of 10 individual multiple myeloma samples tested at the LLOQ and ULOQ levels, respectively.		Acceptable Acceptable Acceptable

Table 92: FDA – Summary of Method Performance: Elranatamab Total and Free PK

<table>
<tr><td>Additional Selectivity and matrix effects</td><td colspan="3">C1071003 Multiple Myeloma Baseline Study Samples:
Unspiked: 10/10 sources (100%) were BLQ
LLOQ: 1/10 sources (10.0%)
ULOQ:1/10 sources (10.0%)

Repeated:
Unspiked: 20/20 sources (100%) were BLQ
LLOQ: 2/20 sources (10.0%)
ULOQ: 3/20 sources (15.0%)

Additional disease state selectivity assessments were conducted for the Free PK method in multiple myeloma patient samples from clinical study C1071003. Based on the Free PK assay format and goal to only measure free unbound drug, BCMA is expected to interfere in the assay. Additional selectivity assessments demonstrated the assay is performing as expected and detecting only free unbound elranatamab drug concentrations.</td><td>Acceptable</td></tr>
<tr><td>Hemolysis effect</td><td colspan="3">High Hemolysis Level Tested (5%)
Unspiked: BLQ
QCLLOQ: -11.8 %RE
Backup QCULOQ: 9.5 %RE
QCULOQ: 8.7 %RE

Re-evaluation
QCLLOQ Backup: 8.8 %RE
Upon initial assessment in Run 22ROVV2, the non-hemolyzed spike control for the back-up LLOQ level quantitated beyond the ± 25.0% limit of acceptability. Therefore, this level was re-prepared, and samples evaluated in Run 28ROVV2.</td><td>Acceptable

Acceptable</td></tr>
<tr><td>Lipemic effect</td><td colspan="3">High Lipemic Level Tested (400 mg/dL intralipid)
Unspiked: BLQ
QCLLOQ: -21.4 %RE
Back-up QCLLOQ: -4.9 %RE
Back-up QCULOQ: -3.6 %RE
QCULOQ: 10.2 %RE</td><td>Acceptable</td></tr>
<tr><td>Dilution Linearity and hook effect</td><td>QCDIL (100,000 ng/mL)</td><td>Bias (%RE)</td><td>%CV</td><td>Acceptable</td></tr>
<tr><td></td><td>0-Fold (MRD)</td><td>>ULOQ</td><td>N/A</td><td></td></tr>
<tr><td></td><td>10-Fold</td><td>>ULOQ</td><td>N/A</td><td></td></tr>
<tr><td></td><td>20-Fold</td><td>9.1%</td><td>8.3%</td><td></td></tr>
<tr><td></td><td>160-Fold</td><td>18.1%</td><td>2.8%</td><td></td></tr>
<tr><td></td><td>800-Fold</td><td>6.4%</td><td>2.1%</td><td></td></tr>
</table>

Table 92: FDA – Summary of Method Performance: Elranatamab Total and Free PK

Specificity Evaluation(s)	**Target/Endogenous Interference –** sBCMA Unspiked: BLQ LLOQ: No interference spiked <50 ng/mL Back-up ULOQ: No interference spiked <50 ng/mL Back-up QCULOQ: No interference spiked up to 50 ng/mL QCULOQ: No interference spiked up to 100 ng/mL **Anti-drug Antibody (ADA) Interference -** (anti-BCMA combo C29-03 anti-ID) Unspiked: > 1.00 µg/mL LLOQ: > 1.00 µg/mL ULOQ: > 1.00 µg/mL **Anti-drug Antibody (ADA) Interference -** (anti-human CD3 anti-ID) Unspiked: > 1.00 µg/mL LLOQ: > 1.00 µg/mL ULOQ: > 1.00 µg/mL	Acceptable Acceptable Acceptable
Bench-top/process stability	27 hours at room temperature	Acceptable
Freeze-Thaw stability	6 F/T Cycles at -20°C 6 F/T Cycles at -70°C	Acceptable
Long-term storage stability	Long-term stability is currently established at 365 Days at -20°C and 672 Days at -70°C. Additional stability is ongoing and will be reported in an amendment to the validation.	Acceptable
Parallelism	Parallelism was demonstrated in 6 individual subjects collected at or near Tmax (~Cmax) in disease populations from protocol C1071001.	Acceptable
Carryover	Not applicable	N/A
	Method performance in Study C1071001 ((b) (4) Project RSYR)	
Assay passing rate	92.3% (84/91) runs passed	Acceptable
Standard curve performance	Nine (9) standard calibrators from LLOQ to ULOQ • Cumulative bias (%RE) range: -5.8% to 10.6% • Cumulative precision (%CV): ≤ 4.9%	Acceptable
QC performance QC Samples (QCL, QCM and QCH)	• Cumulative bias (%RE) range: -6.3% to 11.9% • Cumulative precision (%CV): ≤ 7.9% • TE: ≤16.0%	Acceptable
Dilution QC performance	• Cumulative bias (%RE): 4.1% • Cumulative precision (%CV): 8.1%	Acceptable
Method reproducibility	Incurred sample re-analysis was performed in 9.5% (174/1841) of study samples, and 90.2% (157/174) of the samples were within ±30% difference. Since this is an on-going study, additional ISR may be assessed and reported in the final end of study bioanalytical report.	Acceptable
Study sample analysis/ stability	Long-term stability is currently established at 365 Days at -20°C and 672 Days at -70°C. Calibration standards, QCs and study samples were stored at -70°C and were all analyzed within the established long-term stability. Four (4) samples were analyzed outside of established 6 freeze/thaw stability cycles. Additional F/T stability will be evaluated to cover the freeze/thaw cycles.	Acceptable

Table 92: FDA – Summary of Method Performance: Elranatamab Total and Free PK

Method performance in Study C1071002 ((b) (4) Project RWKO)		
Assay passing rate	100% (7/7) runs passed	
Standard curve performance	Nine (9) standard calibrators from LLOQ to ULOQ • Cumulative bias (%RE) range: -5.5% to 11.2% • Cumulative precision (%CV): ≤ 5.3%	Acceptable
QC performance QC Samples (QCL, QCM and QCH)	• Cumulative bias (%RE) range: -10.2% to 6.8% • Cumulative precision (%CV): ≤ 9.5%	Acceptable
Dilution QC performance	• Cumulative bias (%RE): -3.2% • Cumulative precision (%CV): 6.7%	Acceptable
Method reproducibility	Incurred sample re-analysis was performed in 20.8% (22/106) of study samples, and 100% (22/22) of the samples were within ±30% difference. Since this is an on-going study, additional ISR may be assessed and reported in the final end of study bioanalytical report.	Acceptable
Study sample analysis/ stability	Long-term stability is currently established at 365 Days at -20°C and 672 Days at -70°C. Calibration standards and QCs were stored at -70°C and were analyzed within the established long-term stability. Study samples were stored at -70°C and were analyzed within current established stability.	Acceptable
Method performance in Study C1071003 ((b) (4) Project RTJN)		
Assay passing rate	94.5% (86/91) runs passed	
Standard curve performance	Nine (9) standard calibrators from LLOQ to ULOQ • Cumulative bias (%RE) range: -5.3% to 10.3% • Cumulative precision (%CV): ≤ 4.6%	Acceptable
QC performance QC Samples (QCL, QCM and QCH)	• Cumulative bias (%RE) range: -7.5% to 10.1% • Cumulative precision (%CV): ≤ 9.3%	Acceptable
Dilution QC performance	• Cumulative bias (%RE): 0.6% • Cumulative precision (%CV): 10.9%	Acceptable
Method reproducibility	Incurred sample re-analysis was performed in 6.2% (125/2027) of study samples, and 84.8% (106/125) of the samples were within ±30% difference. Since this is an on-going study, additional ISR may be assessed and reported in the final end of study bioanalytical report.	Acceptable
Study sample analysis/ stability	Long-term stability is currently established at 365 Days at -20°C and 672 Days at -70°C. Calibration standards, QCs and study samples were stored at -70°C and were all analyzed within the established long-term stability.	Acceptable
Method performance in Study C1071009 ((b) (4) Project RVMR)		
Assay passing rate	100% (15/15) runs passed	Acceptable
Standard curve performance	Nine (9) standard calibrators from LLOQ to ULOQ • Cumulative bias (%RE) range: -6.4% to 10.3% (excluding anchor points) • Cumulative precision (%CV): ≤ 5.2% (excluding anchor points)	Acceptable
QC performance QC Samples (QCL, QCM and QCH)	• Cumulative bias (%RE) range: -8.8% to 7.8% • Cumulative precision (%CV): ≤ 8.5%	Acceptable
Dilution QC performance	• Cumulative bias (%RE): -5.3% • Cumulative precision (%CV): 7.7%	Acceptable

Table 92: FDA – Summary of Method Performance: Elranatamab Total and Free PK

Method reproducibility	Incurred sample re-analysis was performed in 7.4% (25/339) of study samples, and 100% (25/25) of the samples were within ±30% difference. Since this is an on-going study, additional ISR may be assessed and reported in the final end of study bioanalytical report.	Acceptable
Study sample analysis/ stability	Long-term stability is currently established at 365 Days at -20°C and 672 Days at -70°C. Calibration standards, QCs and study samples were stored at -70°C and were all analyzed within the established long-term stability.	Acceptable

Source: Applicant's response to IR on 3/10/ 2023

19.5 Study C1071003 (MAGNETISSM-3) Eligibility Criteria

The full eligibility criteria from Study C1071003 (MAGNETISSM-3) protocol amendment 9 are as follows:

Inclusion Criteria

1. Male or female participants age ≥18 years.
2. Willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.
3. Prior diagnosis of MM as defined according to IMWG criteria (Rajkumar et al, 2014)
4. Measurable disease based on IMWG criteria as defined by at least 1 of the following:
   a) Serum M-protein ≥0.5 g/dL by SPEP;
   b) Urinary M-protein excretion ≥200 mg/24 hours by UPEP;
   c) Serum immunoglobulin FLC ≥10 mg/dL (≥100 mg/L) AND abnormal serum immunoglobulin kappa to lambda FLC ratio (<0.26 or >1.65).
5. Refractory to at least one IMiD*.
6. Refractory to at least one PI*.
7. Refractory to at least one atni-CD38 antibody*.
8. Relapsed or refractory last anti-MM regimen.
9. Cohort A: No prior BCMA-directed therapy. Cohort B: Has received prior BCMA-directed ADC or BCMA-directed CAR T-cell therapy, either approved or investigational.
10. ECOG ≤2.
11. LVEF ≥40% as determined by MUGA or ECHO.
12. Adequate hepatic function characterized by the following:
    a) Total bilirubin ≤2x ULN (≤3x ULN if documented Gilbert's Syndrome);
    b) AST ≤2.5x ULN; and
    c) ALT ≤2.5x ULN.
13. Adequate renal function defined by an estimated creatinine clearance ≥30 mL/min (according to the Cockcroft Gault formula, by 24-hour urine collection for creatinine clearance, or according to local institutional standard method).
14. Adequate bone marrow function characterized by the following:
    a) ANC ≥1.0 x 10^9/L(use of GCSF is permitted if at least 7 days prior to planned start of dosing);
    b) Platelets ≥25 x 10^9/L (transfusion support is permitted if completed at least 7 days prior to planned start of dosing);
    c) Hemoglobin ≥8 g/dL (transfusion support is permitted if completed at least 7 days prior to planned start of dosing).
15. Resolved acute effects of any prior therapy to baseline severity or CTCAE Grade ≤1.
16. Capable of giving signed informed consent.

***** Refractory is defined as having disease progression while on therapy or within 60 days of the last dose in any line, regardless of response

Exclusion Criteria: Participants are excluded if any of the following apply:

1. Smoldering MM.
2. Active plasma cell leukemia.
3. Amyloidosis.
4. POEMS Syndrome.
5. Stem cell transplant within 12 weeks prior to enrollment or active GVHD.
6. Impaired cardiovascular function or clinically significant cardiovascular diseases, defined as any of the following within 6 months prior to enrollment:
   a) Acute myocardial infarction or acute coronary syndromes;
   b) Clinically significant cardiac arrhythmias;
   c) Thromboembolic or cerebrovascular events;
   d) Prolonged QT syndrome (or triplicate average QTcF >470 msec at screening).
7. Ongoing Grade ≥2 peripheral sensory or motor neuropathy.
8. History of any grade peripheral sensory or motor neuropathy with prior BCMA-directed therapy (Cohort B).
9. History of GBS or GBS variants, or history of any Grade ≥3 peripheral motor polyneuropathy.
10. Active HBV, HCV, SARS-CoV2, HIV, or any active, uncontrolled bacterial, fungal or viral infection. Active infections must be resolved at least 14 days prior to enrollment.
11. Any other active malignancy within 3 years prior to enrollment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma *in situ*.
12. Other surgical (including major surgery within 14 days prior to enrollment), medical or psychiatric conditions including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the Investigator's judgment, make the participant inappropriate for the study.
13. Previous treatment with an anti-BCMA bispecific antibody.
14. Previous administration with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).
15. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the Investigator, and their respective family members.
16. Known or suspected hypersensitivity to the study intervention or any of its excipients.
17. Live attenuated vaccine must not be administered within 4 weeks of the first dose of study intervention.

Source: Protocol C1071003 Amendment 9, pp. 49-52, copied with minor modifications to formatting and removal of cross references to attachments and other sections of the protocol.

19.6 FDA Grouped Terms

Table 93 lists the grouped preferred terms utilized in the FDA's safety analyses.

Table 93: FDA – Grouped Preferred Terms

FDA Grouped Term (GT)	Preferred Terms
Abdominal pain (GT)	Abdominal discomfort Abdominal pain Abdominal pain lower Abdominal pain upper
Acute kidney injury (GT)	Acute kidney injury Acute renal injury Acute renal failure Renal failure
Cardiac arrhythmia (GT)	Atrial fibrillation Bradycardia Sinus bradycardia Sinus tachycardia Tachycardia Ventricular extrasystoles Ventricular tachycardia
Cardiac failure (GT)	Cardiac failure acute Cardiac failure congestive Cardiopulmonary failure
Congestion (GT)	Nasal congestion Respiratory tract congestion Sinus congestion
Cough (GT)	Cough Productive cough Upper-airway cough syndrome
COVID-19 (GT)	COVID-19 Post-acute COVID-19 syndrome Suspected COVID-19
Dyspnea (GT)	Dyspnea Dyspnea exertional
Edema (GT)	Edema Edema peripheral Eye edema Fluid retention

	Lip edema Localized edema Periorbital edema Peripheral swelling
Encephalopathy (GT)	Agitation Altered state of consciousness Cognitive disorder Confusional state Delirium Depressed level of consciousness Disorientation Hallucination Lethargy Memory impairment Mental status changes Metabolic encephalopathy Somnolence Toxic encephalopathy
Fatigue (GT)	Asthenia Fatigue Malaise
Hemorrhage (GT)	Anal hemorrhage Conjunctival hemorrhage Diarrhea hemorrhagic Ear hemorrhage Epistaxis Hemarthrosis Hematoma Hematoma muscle Hematuria Hemorrhoidal hemorrhage Intestinal hemorrhage Rectal hemorrhage Subdural hematoma Upper gastrointestinal hemorrhage Vascular access site hemorrhage
Injection site reaction (GT)	Injection site dryness Injection site erythema Injection site hemorrhage Injection site induration Injection site inflammation Injection site pain

	Injection site pruritis Injection site rash Injection site reaction Injection site urticaria
Motor dysfunction (GT)	Ataxia Balance disorder Gait disturbance Motor dysfunction Muscle contracture Muscle spasms Muscular Weakness Peripheral motor neuropathy Peroneal Nerve Palsy Tremor
Musculoskeletal pain (GT)	Arthralgia Arthropathy Back pain Flank pain Musculoskeletal chest pain Musculoskeletal pain Myalgia Neck pain Pain in extremity
Pneumonia (GT)*	COVID-19 Pneumonia Lower respiratory tract infection Lower respiratory tract infection viral Pneumocystis jirovecii pneumonia Pneumonia Pneumonia adenoviral Pneumonia bacterial Pneumonia cytomegaloviral Pneumonia fungal Pneumonia influenzal Pneumonia pseudomonal Pneumonia viral
Rash (GT)	Erythema Palmar-plantar erythrodysesthesia syndrome Rash Rash erythematous Rash macular Rash maculo-papular Rash pustular Symmetrical drug-related interiginous and flexural exanthema

Sensory neuropathy (GT)	Burning sensation Dysaesthesia Hypoaesthesia Neuropathy peripheral Paraesthesia Parosmia Peripheral sensorimotor neuropathy Peripheral sensory neuropathy Polyneuropathy Sensory loss
Sepsis (GT)	Bacteremia Device related bacteremia Device related sepsis Escherichia bacteremia Escherichia sepsis Klebsiella sepsis Pseudomonal sepsis Sepsis Septic shock Staphylococcal bacteremia Staphylococcal sepsis Streptococcal sepsis Urosepsis
Skin Exfoliation (GT)	Dermatitis exfoliative Dermatitis exfoliative generalized Skin exfoliation
Thrombosis (GT)	Deep vein thrombosis Mesenteric artery thrombosis Peripheral arterial occlusive disease Pulmonary embolism Superficial vein thrombosis Thrombosis
Transaminase elevation (GT)	Alanine aminotransferase increased Aspartate aminotransferase increased
Upper respiratory tract infection (GT)	Acute sinusitis Bronchitis Bronchitis viral Chronic sinusitis Influenza-like illness Nasopharyngitis Pharyngitis Respiratory tract infection viral Rhinitis

	Rhinovirus infection Sinusitis Sinusitis bacterial Upper respiratory tract infection Viral upper respiratory tract infection
Urinary tract infection (GT)	Cystitis Escherichia urinary tract infection Urinary tract infection Urinary tract infection bacterial Urinary tract infection enterococcal

Source: FDA Analysis

19.7 Additional FDA Safety Analyses

The FDA's Assessment:

In the March 29, 2023 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. The Applicant provided a response on April 4, 2023. Overall, the median duration of CRS was 2 days regardless of whether tocilizumab was administered. The median time to next elranatamab dose was 5 days regardless of whether tocilizumab was administered. A slightly higher percentage of patients with CRS who received tocilizumab experienced a dose interruption of elranatamab compared to patients with CRS who did not receive tocilizumab, but the overall incidence of dose interruptions due to CRS was low. 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. (b) (4)

BLA 761345				

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Daniela Torres, PhD	DHOT	Sections: 5	Select one: ☑ Authored ☐ Approved
	Signature: Daniela Torres -S Digitally signed by Daniela Torres -S Date: 2023.07 07 08.57.24 -04'00'			
Nonclinical Team Leader	Brenda Gehrke, PhD	DHOT	Sections: 5	Select one: ☑ Authored ☑ Approved
	Signature: Brenda Gehrke -S Digitally signed by Brenda Gehrke -S Date: 2023.07.07 09.25.51 -04'00'			
Nonclinical Team Deputy Division Director	Haleh Saber, PhD, MS	DHOT	Sections: 5, 14	Select one: ☐ Authored ☑ Approved
	Signature: Haleh Saber -S Digitally signed by Haleh Saber -S Date: 2023 07.25 13:46:33 -04'00'			
Clinical Pharmacology Reviewer	Yue Xiang, PharmD	OCP/DCPI	Sections: 6, 19.4	Select one: ☑ Authored ☐ Approved
	Signature: Yue Xiang -S Digitally signed by Yue Xiang -S Date: 2023.07.21 14:25:27 -04'00'			
Clinical Pharmacology Team Leader	Xiling Jiang, PhD	OCP/DCPI	Sections: 6, 19.4	Select one: ☑ Authored ☑ Approved
	Signature: Xiling Jiang -S Digitally signed by Xiling Jiang -S Date: 2023 07.21 14:20:14 -04'00'			
Clinical Pharmacology Division Director	Brian Booth, PhD	OCP/DCPI	Sections: 6, 15, 19.4	Select one: ☐ Authored ☑ Approved
	Signature: Brian P. Booth -S Digitally signed by Brian P. Booth -S Date: 2023.07.26 13:11:14 -04'00'			
Pharmacometrics Reviewer	Hongshan Li, PhD	OCP/DPM	Sections: 6, 19.4	Select one: ☑ Authored ☐ Approved
	Signature: Hongshan Li -S Digitally signed by Hongshan Li -S Date: 2023.07 26 14:15:32 -04'00'			
Pharmacometrics Associate Director	Jiang Liu, PhD	OCP/DPM	Sections: 6, 19.4	Select one: ☑ Authored ☑ Approved
	Signature: Jiang Liu -S Digitally signed by Jiang Liu -S Date: 2023.07.26 14:08:35 -04'00'			

Genomics	Youssef Roman, PharmD, PhD	OCP/DTPM	Sections: 19.4.3	**Select one:** ☑ Authored ☐ Approved
	Signature: Joseph M. Roman -S Digitally signed by Joseph M. Roman -S Date: 2023.07.21 14:36:10 -04'00'			
Genomics Team Leader	Jeffrey Kraft, PhD	OCP/DTPM	Sections: 19.4.3	**Select one:** ☑ Authored ☑ Approved
	Signature: Jeffrey B. Kraft Jr -S Digitally signed by Jeffrey B. Kraft Jr -S Date: 2023 07.26 18:06:48 -04'00'			
Associate Director for Labeling	Elizabeth Everhart, MSN, RN, ACNP	OOD	Sections: 11	**Select one:** ☑ Authored ☐ Approved
	Signature: Elizabeth E. Everhart -S Digitally signed by Elizabeth E. Everhart -S Date: 2023.07.24 12:08:53 -04'00'			
Clinical Reviewer	Rachel Ershler, MD, MHS	OOD/DHM II	Sections: All	**Select one:** ☑ Authored ☐ Approved
	Signature: Rachel E. Ershler -S Digitally signed by Rachel E. Ershler -S Date: 2023.07.25 12:28:41 -04'00'			
Clinical Team Leader	Bindu Kanapuru, MD	OOD/DHM II	Sections: All	**Select one:** ☐ Authored ☑ Approved
	Signature: Bindu Kanapuru -S Digitally signed by Bindu Kanapuru -S Date: 2023.07.27 14:49:56 -04'00'			

Statistical Reviewer	Jing Zhang, PhD	OB/DBIX	Sections: 7, 8	**Select one:** ☑ Authored ☐ Approved
	Signature: Jing Zhang -S Digitally signed by Jing Zhang -S Date: 2023 07.24 17:02:10 -04'00'			
Statistical Team Leader	Qing Xu, PhD	OB/DBIX	Sections: 7, 8	**Select one:** ☑ Authored ☑ Approved
	Signature: Qing Xu -S Digitally signed by Qing Xu -S Date: 2023.07.24 17 19 37 -04'00'			
Supervisory Mathematical Statistician	Lisa Rodriguez, PhD	OB/DBIX	Sections: All	**Select one:** ☐ Authored ☑ Approved
	Signature: Lisa R. Rodriguez -S Digitally signed by Lisa R. Rodriguez -S Date: 2023.07.21 09:39:19 -04'00'			
Cross-Disciplinary Team Leader (CDTL)	Bindu Kanapuru, MD	OOD/DHM II	Sections: All	**Select one:** ☑ Authored ☑ Approved
	Signature: Bindu Kanapuru -S Digitally signed by Bindu Kanapuru -S Date: 2023.07.27 14 50 47 -04'00'			
Division Director (Clinical)	Nicole Gormley, MD	OOD/DHM II	Sections: All	**Select one:** ☐ Authored ☑ Approved
	Signature: Nicole J. Gormley -S Digitally signed by Nicole J. Gormley -S Date: 2023.07.26 10:30:00 -04'00'			

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/s/

RACHEL E ERSHLER
08/14/2023 10:00:38 AM

MARC R THEORET
08/14/2023 10:47:39 AM
My signature indicates that I have considered the FDA assessments and recommendations included in this Review in determining the regulatory action.