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RESEARCH**

APPLICATION NUMBER:

761263Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

BLA 761263, 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.

Application Type	Original Biologics License Application
Application Number(s)	BLA 761263
Priority or Standard	Priority
Submit Date(s)	April 29, 2022
Received Date(s)	April 29, 2022
PDUFA Goal Date	December 29, 2022
Division/Office	Division of Hematologic Malignancies II/Office of Oncologic Diseases
Review Completion Date	December 22, 2022
Established Name	Mosunetuzumab
(Proposed) Trade Name	Lunsumio
Pharmacologic Class	CD20-directed CD3 T-cell engaging bispecific antibody
Applicant	Genentech, Inc.
Formulation(s)	Solution in a single-dose vial
Dosing Regimen	1 mg/1 mL, 30 mg/30 mL (1 mg/mL)
Applicant Proposed Indication(s)/Population(s)	Adult patients with relapsed or refractory follicular lymphoma after at least two prior systemic therapies
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	The treatment of adult patients with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy

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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
 DRM=Division of Risk Management

Glossary

AC	advisory committee
ADA	anti-drug antibody
ADME	absorption, distribution, metabolism, excretion
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CAR-T	chimeric antigen receptor-modified T-cell
CBER	Center for Biologics Evaluation and Research
CCOD	clinical cutoff date
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
CL	clearance
C _{max}	maximum drug concentration in serum
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CR	complete response
CRF	case report form
CRO	contract research organization
CRS	cytokine release syndrome
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DLBCL	diffuse large B-cell lymphoma
DMC	data monitoring committee
DOCR	duration of complete response
DOR	duration of response
DORC	duration of response in patients who achieved a complete response
ECG	electrocardiogram

eCTD	electronic common technical document
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-5L	Euro–Quality-of-Life-5D-5L
E-R	exposure-response
ETASU	elements to assure safe use
EZH2	enhancer of zeste homolog 2
FACT-Lym	Functional Assessment of Cancer Therapy- Lymphoma
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FL	follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
GCP	good clinical practice
G-CSF	granulocyte colony-stimulating factor
GLP	good laboratory practice
GRMP	good review management practice
HLH	hemophagocytic lymphohistiocytosis
HRQoL	health-related quality of life
ICH	International Conference on Harmonization
IND	Investigational New Drug
INV	investigator
IRF	Independent Review Facility
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
K-M	Kaplan-Meier
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NALT	new anti-lymphoma treatment
NCA	non-compartmental analysis
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NHL	non-Hodgkin lymphoma
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
ORR	objective response rate
OSE	Office of Surveillance and Epidemiology
OS	overall survival
OSI	Office of Scientific Investigation

PBPK	physiologically-based pharmacokinetics
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics or progressive disease
PFS	progression-free survival
PI	prescribing information
PI3K	phosphoinositide 3-kinase
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
POD24	progression of disease within 24 months
PopPK	population pharmacokinetics
PP	per protocol
PPI	patient package insert
PR	partial response
PRO	patient-reported outcomes
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	preferred term
QLQ-C30	Quality of Life Questionnaire-C30
RBC	red blood cell
REMS	risk evaluation and mitigation strategy
RO _{max}	maximum receptor occupancy
RP2D	recommended Phase II dose
R/R	relapsed/refractory
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCS	Summary of Clinical safety (Module 2.7.4)
SD	stable disease
SGE	special government employee
SMQ	standardized MedDRA query
SOC	standard of care or System Organ Class
TEAE	treatment emergent adverse event
TLS	tumor lysis syndrome
trFL	transformed follicular lymphoma
US	United States
WHO	World Health Organization

1 Executive Summary

1.1. Product Introduction

Product: Mosunetuzumab (LUNSUMIO)

Pharmacological Class: Bispecific CD20-directed CD3 T-cell engager.

Proposed Indication: Mosunetuzumab is a bispecific CD20-directed CD3 T-cell engager indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma after at least two prior systemic therapies.

Dosing regimen: The recommended dosage of mosunetuzumab is 1 mg on Cycle 1, Day 1; 2 mg on Cycle 1 Day 8; 60 mg on Cycle 1 Day 15 and Cycle 2 Day 1; and 30 mg on Cycle 3 Day 1 onward, administered every 3 weeks.

1.2. Conclusions on the Substantial Evidence of Effectiveness

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

Mosunetuzumab is a bispecific CD20-directed CD3 T-cell engager indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy.

This recommendation is based on the efficacy of mosunetuzumab from GO29781, an open-label, multicenter, multicohort study in 90 patients with relapsed or refractory follicular lymphoma (FL) who had received at least two prior therapies, including an anti-CD20 monoclonal antibody and an alkylating agent.

Patients received step-up doses of 1 mg on Cycle 1 Day 1 and 2 mg on Cycle 1 Day 8, followed by 60 mg on Cycle 1 Day 15, and 60 mg on Cycle 2 Day 1, then 30 mg every 3 weeks in subsequent cycles. A treatment cycle was 21 days. Mosunetuzumab was administered for 8 cycles unless patients experienced progressive disease or unacceptable toxicity. After 8 cycles, patients with a complete response discontinued therapy; patients with a partial response or stable disease continued treatment up to 17 cycles, unless patients experienced progressive disease or unacceptable toxicity.

In the 90 patients with relapsed or refractory FL enrolled in the GO29781 study, the median age was 60 years (range: 29 to 90 years), 33% were 65 years of age or older, 61% were male, 82%

were White, 9% were Asian, 4% were Black or African American, and 8% were Hispanic or Latino. A total of 77% of patients had Stage III-IV disease, 34% had bulky disease, and all patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The median number of prior therapies was 3 (range: 2 to 10), with 38% receiving 2 prior therapies, 31% receiving 3 prior therapies, and 31% receiving more than 3 prior therapies.

Efficacy was established on the basis of objective response rate (ORR) and duration of response (DOR) as assessed by an independent review facility (IRF) according to standard criteria for NHL (Cheson 2007). Among the 90 patients, the ORR per IRF was 80% (95% CI: 70, 88), with 60% achieving a complete response. With a median follow-up for DOR of 14.9 months, the estimated median DOR was 22.8 months (95% CI: 10, not reached). Of the 72 responders, 62% remained in response at 12 months and 57% at 18 months.

In this population, the overall response rate of 80%, with 60% achieving complete response, with durability and a tolerable safety profile constitutes a meaningful clinical benefit. To support accelerated approval, the efficacy data are considered in the context of available therapy for the patients with relapsed or refractory follicular lymphoma in the 3rd line setting and beyond. Available therapy includes anti-CD20 therapy (i.e., rituximab and obinutuzumab) as a single agent and in combination, bendamustine monotherapy and in combination, and immunotherapy combinations such as rituximab plus lenalidomide. In the 3rd line setting and beyond, the ORRs for these therapies, including single-agent and combinations, ranges from 57% to 80% with associated durability. In the 90 patients with FL treated with mosunetuzumab, all patients received prior anti-CD20 monoclonal antibody and an alkylating agent and the median number of prior therapies was 3. A total of 79% of patients were refractory to prior anti-CD20 monoclonal antibody therapy, 53% were refractory to both anti-CD20 monoclonal antibody and alkylator therapy, 9% received prior rituximab plus lenalidomide therapy, 21% received prior autologous stem cell transplant, and 3% received prior CAR T therapy. Given the prior therapies received, the overall response rate of 80% with associated durability for mosunetuzumab provides data to support a clinically meaningful benefit in the context of available therapy for patients with relapsed or refractory follicular lymphoma in the 3rd line setting and beyond.

Thus, the efficacy data for mosunetuzumab demonstrates substantial evidence of effectiveness in support of accelerated approval for the following indication:

- Treatment of adult patients with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

The benefit-risk assessment is favorable for mosunetuzumab, a bispecific CD20-directed CD3 T-cell engager indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy.

Efficacy:

Efficacy of mosunetuzumab is based on the results from GO29781, an open-label, multicenter, multicohort study in 90 patients with relapsed or refractory follicular lymphoma who had received at least two prior therapies, including an anti-CD20 monoclonal antibody and an alkylating agent.

Patients received step-up doses of 1 mg on Cycle 1 Day 1 and 2 mg on Cycle 1 Day 8, followed by 60 mg on Cycle 1 Day 15, and 60 mg on Cycle 2 Day 1, then 30 mg every 3 weeks in subsequent cycles. A treatment cycle was 21 days. Mosunetuzumab was administered for 8 cycles unless patients experienced progressive disease or unacceptable toxicity. After 8 cycles, patients with a complete response discontinued therapy; patients with a partial response or stable disease continued treatment up to 17 cycles, unless patients experienced progressive disease or unacceptable toxicity.

Efficacy was established on the basis of objective response rate (ORR) and duration of response (DOR) as assessed by an independent review facility (IRF) according to standard criteria for NHL (Cheson 2007). Among the 90 patients, the ORR per IRF was 80% (95% CI: 70, 88), with 60% achieving a complete response. With a median follow-up for DOR of 14.9 months, the estimated median DOR was 22.8 months (95% CI: 10, not reached). Of the 72 responders, 62% remained in response at 12 months and 57% at 18 months.

Safety:

The safety profile of mosunetuzumab was primarily supported by analysis of 218 patients with B-cell NHL that received the recommended dose and regimen (1/2/60/30 mg). The median duration of treatment was 8 cycles (range 1 to 17), with 52% exposed for at least 8 cycles. The most common adverse events ($\geq 20\%$) were cytokine release syndrome (39%), fatigue (36%), rash (34%), pyrexia (24%), and headache (21%). The most common Grade 3 to 4 laboratory abnormalities ($\geq 10\%$) were decreased lymphocyte count (92%), decreased phosphate (41%), increased glucose (40%), decreased neutrophil count (38%), increased uric acid (15%), decreased white blood cell count (22%), decreased hemoglobin

(19%), and decreased platelets (12%). Serious adverse events occurred in 52%, most often due to CRS (21%), pneumonia (5%), pyrexia (5%), sepsis (3%), and a 2% incidence each of tumor flare, urinary tract infection, pleural effusion, and renal insufficiency. Adverse events leading to treatment interruption occurred in 33%, most often due to neutropenia, infection, and CRS. Adverse events leading to treatment discontinuation occurred in 4%, most often due to CRS. Thus, the primary safety issues identified with mosunetuzumab include CRS, neurologic toxicity (including immune effector cell-associated neurotoxicity syndrome [ICANS]), infections, cytopenias, and tumor flare.

Benefit-Risk:

Mosunetuzumab has an overall favorable benefit-risk in patients with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy. In the 90 patients with relapsed or refractory FL enrolled in the GO29781 study, the median age was 60 years (range: 29 to 90 years), 33% were 65 years of age or older, 61% were male, 82% were White, 9% were Asian, 4% were Black or African American, and 8% were Hispanic or Latino. A total of 77% of patients had Stage III-IV disease, 34% had bulky disease, and all patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The median number of prior therapies was 3 (range: 2 to 10), with 38% receiving 2 prior therapies, 31% receiving 3 prior therapies, and 31% receiving more than 3 prior therapies.

In this population, the overall response rate of 80%, with 60% achieving complete response, with durability and a tolerable safety profile constitutes a meaningful clinical benefit and a favorable benefit-risk evaluation. To support accelerated approval, the efficacy data are considered in the context of available therapy for the patients with relapsed or refractory follicular lymphoma in the 3rd line setting and beyond. Available therapy includes anti-CD20 therapy (i.e., rituximab and obinutuzumab) as a single agent and in combination, bendamustine monotherapy and in combination, and immunotherapy combinations such as rituximab plus lenalidomide. In the 3rd line setting and beyond, the ORRs for these therapies, including single-agent and combinations, ranges from 57% to 80% with associated durability. In the 90 patients with FL, the median number of prior therapies was 3 and included an anti-CD20 monoclonal antibody and an alkylating agent. A total of 79% of patients were refractory to prior anti-CD20 monoclonal antibody therapy, 53% were refractory to both anti-CD20 monoclonal antibody and alkylator therapy, 9% received prior rituximab plus lenalidomide therapy, 21% received prior autologous stem cell transplant, and 3% received prior CAR T therapy. Therefore, the overall response of 80% with associated durability for mosunetuzumab provides data to support a clinically meaningful benefit in the context of available therapy for patients with relapsed or refractory follicular lymphoma in the 3rd line setting and beyond.

Thus, the benefit-risk of mosunetuzumab is deemed favorable to support accelerated approval for the following indication:

- Treatment of adult patients with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Follicular lymphoma (FL) is the second most common non-Hodgkin lymphoma. - Follicular lymphoma remains an incurable disease and relapse is nearly universal.	Follicular lymphoma is a serious and life-threatening disease.
Current Treatment Options	Treatment options for relapsed and refractory follicular lymphoma include anti-CD20 monoclonal antibodies, immunochemotherapy, an immunomodulatory agent, a PI3K inhibitor, an EZH2 inhibitor, and anti-CD19 CAR-T cell therapy.	New treatments are needed for patients with relapsed or refractory follicular lymphoma.
Benefit	- Study GO29781 was an open-label, multicenter, multi-cohort study that included 90 patients with relapsed or refractory follicular lymphoma who had received at least 2 prior systemic therapies. - Mosunetuzumab was administered as follows: 1 mg on Cycle 1 Day 1; 2 mg on Cycle 1 Day 8; 60 mg on Cycle 1 Day 15 and Cycle 2 Day 1; and 30 mg on Cycle 3 Day 1 onwards, administered every 3 weeks. - Objective response rate (ORR) per independent review facility in the 90 patients with relapsed and refractory follicular lymphoma was 80% (95% CI: 70%, 88%), with 60% achieving a complete response. - With a median follow-up for duration of response (DOR) of 14.9 months, the median DOR was 22.8 months (95% CI: 10, not reached).	Based on ORR with durability, mosunetuzumab has clinically meaningful activity in patients with relapsed or refractory follicular lymphoma who have received two or more lines of systemic therapy.
Risk and Risk Management	- Safety was evaluated in 218 patients treated at the recommended dose and regimen (1/2/60/30 mg). - The median duration of treatment was 8 cycles. - The most common adverse events (≥20%) were cytokine release syndrome, fatigue, rash, pyrexia, and headache.	The safety profile of mosunetuzumab is acceptable in the intended population. The USPI includes a boxed warning for CRS and warnings and precautions for neurologic toxicity, infections, cytopenias, tumor flare,

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The most common Grade 3 to 4 laboratory abnormalities ($\geq 10\%$) were decreased lymphocyte count, decreased phosphate, increased glucose, decreased neutrophil count, increased uric acid, decreased white blood cell count, decreased hemoglobin, and decreased platelets. • Fatal adverse events occurred in 2% of patients, primarily due to infection. • Serious adverse events occurred in 52% of patients and Grade 3-4 adverse events occurred in 66%. • The most common serious adverse events included cytokine release syndrome (CRS), pneumonia, fever, and sepsis. • Adverse events that led to treatment discontinuation occurred in 4% of patients, most often due to CRS. • The key safety concerns for mosunetuzumab are CRS, neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS), infections, cytopenias, and tumor flare.	and embryo-fetal toxicity. The USPI includes toxicity management for CRS, neurologic toxicity, infections, cytopenias, and other hematologic and non-hematologic toxicities. The safe use of mosunetuzumab can be managed through labeling and routine clinical care.

1.4. Patient Experience Data

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

☒	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
☒	Clinical outcome assessment (COA) data, such as	Section 8.1.2
☒	Patient reported outcome (PRO)	

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☐	Observer reported outcome (ObsRO)	
☐	Clinician reported outcome (ClinRO)	
☐	Performance outcome (PerfO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Section 2.1 Analysis of Condition]
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify)	
☐	Patient experience data that was not submitted in the application, but was considered in this review.	

X

Cross-Disciplinary Team Leader
 Nicholas Richardson, DO, MPH

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.

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Follicular lymphoma (FL) is the second most common non-Hodgkin lymphoma (NHL), accounting for an estimated 13,960 new cases diagnosed in the US in 2016 (Teras et al. 2016). In the US, FL is more frequently diagnosed in White (~92%) than in Black (~4%) or Asian/Pacific Islander (~4%) racial groups (Li et al. 2015; Blansky et al. 2020), while the incidence rates in men and women are similar. The incidence increases with age, and the median age of diagnosis of FL in the US is 63 years (SEER Cancer Statistics 2020).

FL tumor cells are malignant counterparts of normal germinal center B cells. In 85% of cases, cytogenetic analysis reveals the genetic hallmark of t(14;18)(q32;q21) genomic translocation, which results in the constitutive overexpression of the BCL-2 protein, a member of a family of proteins that regulates apoptosis. Almost all cases of FL carry additional genetic alterations (Hiddemann and Cheson 2014). The FL immunophenotype usually shows CD10+, CD20+, CD19+, CD22+ CD5- cells expressing surface immunoglobulin.

The high degree of mutational heterogeneity in FL is reflected in a highly variable clinical behavior, ranging from an extremely indolent course over decades to a clinically highly aggressive course with short DOR after treatment and recurrence of disease within 1-2 years after initial treatment (Freedman and Jacobsen 2020). Histologic transformation of FL from an indolent disease to the more aggressive DLBCL occurs with a risk of 2–3% per year, and is associated with more aggressive disease progression and poor survival outcome (Montoto and Fitzgibbon 2011; Link et al. 2013). Typically, the clinical course of FL is characterized by a series of remissions and relapses, with generally increasing refractoriness and decreasing duration of response to therapy. As the disease recurs, patients are treated with multiple lines of therapies during their lifetime. FL remains incurable, and a significant proportion of patients die from recurrent disease or treatment-related toxicity.

Patients with FL typically present with asymptomatic lymphadenopathy, however the majority of patients are diagnosed with advanced disease (Ann Arbor Stage III/IV), with up to 70% with bone marrow involvement (Freedman and Jacobsen 2020). The Follicular Lymphoma International Prognostic Index (FLIPI) is the most widely used prognostic scoring system to predict survival in newly diagnosed patients, though it may be prognostic at first relapse as well (Montoto et al. 2004).

Observation (watch-and-wait) is the standard practice for patients with advanced stage low

tumor burden FL. Guidelines recommend that treatment is only initiated upon occurrence of one or more of the modified GELF criteria (Brice et al. 1997; NCCN Guidelines v4.2021). For patients with FL for whom initiating systemic treatment is indicated, immunochemotherapy with an anti-CD20 monoclonal antibody (rituximab or obinutuzumab) and chemotherapy (bendamustine, CHOP or CVP), with or without extended maintenance dosing with rituximab or obinutuzumab monotherapy for up to 2 years is the standard of care for first-line treatment.

After initiating treatment, quality of response (e.g., achieving a CR, PCR-negative MRD in blood or bone marrow, or negative PET at end of treatment) is associated with improved OS (Bachy et al. 2010; Trotman et al 2018). A significantly higher risk of death is observed in patients with early progression of disease, specifically within 24 months of commencing first-line immunochemotherapy (Casulo et al. 2017; Seymour et al. 2019). Beyond the front-line setting, prognosis is influenced by several factors, including number of prior regimens, refractory status, and progressive decline of bone marrow reserve (Smith 2013). In patients with FL who progress from front-line therapies, the disease-free intervals and DOR become progressively shorter with increased refractoriness with each subsequent progression/relapse (Link et al. 2019; Rivas-Delgado et al. 2019). Patients who have received ≥ 2 prior therapies have a particularly poor prognosis, with a median PFS ranging from 1-1.1 years for third-line patients decreasing to 0.5 years for sixth-line patients with a corresponding median OS of 4.8-8.8 years and 1.9 years, respectively (Alperovich et al. 2016; Rivas-Delgado et al. 2019; Batlevi et al. 2020).

The FDA's Assessment:

The FDA agrees with the Applicant's position. Using data from the US Surveillance, Epidemiology, and End Results (SEER program), the age adjusted incidence rate based on 2015-2019 cases was 2.6 per 100000 men and women. Rates were higher in men (2.8) among all races than among women (2.4). Among men, rates were highest in Non-Hispanic Whites (3.2), followed by Hispanics (2.6), Non-Hispanic American/Indian Alaskan Natives (1.9), Non-Hispanic Asian/Pacific Islanders (1.7), and Non-Hispanic Blacks (1.3). Among women, rates were also highest among Non-Hispanic Whites (2.7), followed by Hispanics (2.4), Non-Hispanic American/Indian Alaskan Natives (1.8), Non-Hispanic Asian/Pacific Islanders (1.4), and Non-Hispanic Blacks (1.2).

2.2. Analysis of Current Treatment Options

The Applicant's Position:

Relapse to initial therapy for FL is almost inevitable. In the relapsed/refractory setting, treatment decisions take into consideration efficacy and DOR of prior therapy, stage of disease and tumor burden at relapse, the presence of symptoms, and the age and comorbidities of the patient.

For patients who require second-line therapy, there is no treatment considered standard of

care, and options vary widely. Rituximab as a single agent, bendamustine, obinutuzumab in combination with bendamustine followed by obinutuzumab monotherapy, lenalidomide plus a rituximab-product, and the radioimmunotherapy ⁹⁰Y-ibritumomab tiuxetan have all received regular full approval for the treatment of R/R FL in the US.

In the third-line setting, certain treatment options approved for first- and/or second-line FL are available treatment options. However, patients who have become refractory to anti-CD20-directed therapy or alkylating agents will unlikely derive treatment benefit by re-using these regimens. In later relapses, a non-chemotherapy approach is recommended. Agents under accelerated approval specifically for patients with relapsed or refractory FL after at least two prior therapies (and not considered to be available therapy because clinical benefit is yet to be confirmed) are the PI3K inhibitors idelalisib, copanlisib, and duvelisib, and the histone methyltransferase enhancer of zeste homolog 2 (EZH2) inhibitor tazemetostat, and the CD19-directed chimeric antigen receptor-modified T-cell (CAR-T) therapy axicabtagene ciloleucel (Yescarta®). Umbralisib, a dual PI3K delta and casein kinase 1 epsilon inhibitor, has received accelerated approval for the treatment of patients with R/R FL who have received at least three prior lines of systemic therapy.

Specific details of the indications, and the efficacy and safety data supporting FDA-approved drugs for patients with indications relevant to this FL application are listed in Table 1 below. Not included in the table are chemotherapeutic agents (e.g., chlorambucil, cyclophosphamide, vincristine, and doxorubicin) which are approved for use in the US to treat a broader spectrum of neoplastic diseases including malignant lymphomas.

In addition to approved therapies, there are chemotherapy agents or combinations that are used in the R/R setting, including some that are not FDA approved. Table 2 summarizes suggested treatment regimens for second-line and subsequent therapy, and third-line and subsequent therapy for the treatment of FL as described in the current National Comprehensive Cancer Network® Clinical Practice Guidelines in Oncology for B-cell Lymphomas (v4.2021).

Relapsed or refractory FL is a serious and life-threatening disease that remains incurable. Relapse is almost inevitable, and a significant proportion of patients die from recurrent disease or treatment-related toxicity. There is a high unmet need for patients with R/R FL who have received ≥ 2 prior therapies, particularly for patients who are R/R to different classes of agents and are left with limited treatment options that may have challenging safety profiles. New treatment options that will significantly extend duration of remission and that can overcome resistance to existing therapies, while providing acceptable safety and tolerability are needed.

Table 1: Applicant – Summary of Treatment Armamentarium Relevant to Relapsed or Refractory FL after Two or More Prior Therapies

Product (s) Name	Relevant Indication	Year of Approval And Type of Approval	Dosing/ Administration	Efficacy Information	Import
FDA Approved Treatments					
Rituximab	Single Agent: Relapsed or refractory, low grade or follicular, CD20-positive B-cell NHL	November 1997/ Full approval	375 mg/m ²	3 single arm studies: (n=296 R/R FL) -ORR: 36-57% -CR: 3-14%	Boxed mucoc Other: bowel hepatit
Obinutuzumab	In combination with bendamustine followed by obinutuzumab monotherapy for the treatment of patients with FL who relapsed after, or are refractory to, a rituximab-containing regimen	February 2016/ Full approval	1000 mg IV infusion of Days 1, 8, 15 of Cycle 1, 1000 mg on Day 1 of Cycles 2-6 or Cycles 2-8, and then 1000 mg every 2 months for up to 2 years	GADOLIN study: G-B arm (n=155), B arm (n=166) (R/R FL) -mPFS: G-B=not reached vs. B=13.8 months; HR=0.48 (95% CI: 0.34, 0.68) -ORR: G-B=78.7% vs. B=74.7% -CR: G-B=15.5% vs. B=18.7%	Boxed Other: reactio neutro
⁹⁰ Y-ibritumomab tiuxetan	relapsed or refractory, low-grade or follicular B-cell non-Hodgkin's lymphoma (NHL)	February 2002/ Full approval	See the package insert for details	IDEC 106-04 study: ibritumomab tiuxetan (n=64), rituximab (n=66) (R/R FL) -ORR: ibritumomab tiuxetan=83% vs. rituximab=55% -CR: ibritumomab tiuxetan=38% vs. rituximab=18% -mDOR: ibritumomab tiuxetan=14.3 months v.s. rituximab=11.5 months IDEC 106-06 (n=54 R/R FL): -ORR=74% -CR=15% -mDOR=6.4 months	Boxed cutane Other: extrava

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Product (s) Name	Relevant Indication	Year of Approval And Type of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Bendamustine	Indolent B-cell NHL that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.	November 2008/ Full approval	120 mg/m ² See the Package Insert for details	(n=100 rituximab-refractory iNHL) ORR: 74% CR: 13%	Myelosuppression, infections, infusion reactions and anaphylaxis, TLS, skin reactions, other malignancies, use in pregnancy
Lenalidomide	previously treated FL, in combination with a rituximab product	May 2019/ Full approval	20 mg PO QD on Days 1-21 of 28-day cycles	AUGMENT study: Len+R (n=178) vs Len+placebo (n=180) Median PFS (MZL and FL): Len+R: 39.4 months (95% CI: 22.9, NE); vs. Len+placebo: 14.1 months (95% CI: 11.4,); HR: 0.46 (95% CI: 0.34, 0.62) ORR in FL: Len+R =80% (95% CI: 73%, 86%) vs. Len+placebo=55% (95% CI: 47%, 64%) MAGNIFY study: ORR in FL =59% (95% CI: 51%, 66%)	Boxed warning: embryo-fetal toxicity, hematologic toxicity, venous and arterial thromboembolism Other: cardiac, secondary primary malignancies, hepatotoxicity, cutaneous reactions, TLS, tumor flare, impaired stem cell mobilization, hypersensitivity
Idelalisib	Relapsed follicular B-cell NHL (FL) in patients who have received at least two prior systemic therapies.	July 2014/ Accelerated approval based on ORR	150 mg PO BID	Study 101-09 (DELTA): (n=72 R/R FL) ORR: 54% (95% CI: 42%, 66%) CR: 8% PR: 46%	Boxed warning: hepatic, severe diarrhea, colitis, pneumonitis, intestinal perforation Other: severe cutaneous reactions, anaphylaxis, neutropenia, embryo-fetal toxicity
Copanlisib	Adult patients with relapsed FL who have received at least 2 prior systemic therapies	September 2017/ Accelerated approval based on ORR	60 mg IV on Days 1, 8, and 15 of a 28 day cycle on an intermittent schedule (3 weeks on and 1 week off)	CHRONOS-1 study: (n=104 relapsed FL) ORR: 59% (95% CI: 49%, 68%) CR: 14% PR: 44%	Infections, hyperglycemia, hypertension, non-infectious pneumonitis, neutropenia, cutaneous reactions, embryo-fetal toxicity

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Duvelisib	Adult patients with relapsed or refractory FL after at least 2 prior systemic therapies	September 2018/ Accelerated approval based on ORR	25 mg PO BID	DYNAMO study: (n=83 R/R FL) ORR: 42% (95% CI: 31%, 54%) CR: 1% PR: 41%	Boxed warning: infections, diarrhea or colitis, cutaneous reactions, pneumonitis Other: hepatotoxicity, neutropenia, embryo-fetal toxicity
Umbralisib	Relapsed or refractory FL who have received at least three prior lines of systemic therapy	2021/ Accelerated approval based on ORR	800 mg PO daily	Study UTX-TGR-205: (n=117 R/R FL) ORR: 43% (95% CI : 34%, 52%) CR: 3.4% PR: 39%	Infections, neutropenia, diarrhea or non-infectious colitis, hepatotoxicity, cutaneous reactions, allergic reactions, embryo-fetal toxicity
Tazemetostat	Adult patients with relapsed or refractory FL whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test Adult patients with relapsed or refractory FL who have no satisfactory alternative treatment options	June 2020/ Accelerated Approval based on ORR and DOR	800 mg PO BID	E7438-G000-101: EZH2 mutant FL (n=42) ORR: 69% (95% CI 53%, 82%) CR: 12% PR: 57% EZH2 wild-type FL (n=53) ORR: 34% (95% CI 22%, 48%) CR: 4% PR: 30%	Secondary malignancies, embryo-fetal toxicity
Axicabtagene ciloleucel	Adult patients with relapsed or refractory FL after two or more lines of systemic therapy	March 2021/ Accelerated approval based on ORR	2 x 10 ⁶ CAR-positive viable T-cells per kg of body weight, with a maximum of 2 x 10 ⁸ CAR-positive viable T-cells	ZUMA-5 study: (n=81 R/R FL) ORR: 91% (95% CI: 83%, 96%) CR: 60% PR: 31%	Boxed warning: cytokine release syndrome, neurologic toxicities Other: hypersensitivity reactions, infections, cytopenias, hypogammaglobulinemia, secondary malignancies, effects on ability to drive and use machines

B, bendamusine; CAR, chimeric antigen receptor-modified T-cell; CR, complete response; EZH2, enhancer of zeste homolog 2; FL, follicular lymphoma, G-B, obinutuzumab in combination with bendamustine; mDOR, median duration of response; NHL, non-Hodgkin’s lymphoma; ORR, objective response rate; PFS, progression-free survival; PR, partial response, TLS, tumor lysis syndrome.

Table 2: Applicant – Agents and Combination Regimens Recommended for Use in Patients with Relapsed and Refractory Follicular Lymphoma

Drug or Regimen
Second-line and subsequent therapy
Bendamustine ± obinutuzumab or rituximab ^a (not recommended if treated with prior bendamustine)
CHOP + obinutuzumab or rituximab ^a
CVP + obinutuzumab or rituximab ^a
Chlorambucil ± rituximab ^a
Cyclophosphamide ± rituximab ^a
⁹⁰ Y-Ibritumomab tiuxetan
Lenalidomide (if not a candidate for anti-CD20 monoclonal antibody therapy)
Lenalidomide ± rituximab ^a or obinutuzumab
Obinutuzumab
Rituximab ^a
Third-line and subsequent therapy
Idelalisib (relapsed/refractory FL after 2 prior therapies)
Copanlisib (relapsed/refractory FL after 2 prior therapies)
Duvelisib (relapsed/refractory FL after 2 prior therapies)
Umbralisib (relapsed/refractory FL after 3 prior therapies)
Tazemetostat (EZH2 mutation-positive relapsed/refractory FL after 2 prior therapies or EZH2 wild-type or unknown relapsed/refractory FL who have no satisfactory alternative treatment options)
Axicabtagene ciloleucel (after ≥2 lines of systemic therapy)

CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP, cyclophosphamide, doxorubicin, and prednisone.

^a FDA-approved biosimilar is an appropriate substitute for rituximab.

Source: Figure FOLL-B of NCCN Guidelines v4.2021.

The FDA’s Assessment:

In general, the FDA agrees with the Applicant’s position, but has provided additional information. Per the Federal Register, the indications in follicular lymphoma for duvelisib, idelalisib, and umbralisib were voluntarily withdrawn on 4/13/22, 5/26/22, and 5/31/22, respectively. Copanlisib remains under accelerated approval for the treatment of adult patients with relapsed follicular lymphoma who have received at least 2 prior systemic therapies. Tisagenlecleucel, a C19-directed genetically modified autologous T cell immunotherapy, also recently received accelerated approval on May 31, 2022, for adult patients with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant’s Position:

Mosunetuzumab is a new molecular entity and is not currently marketed in any country.

The Biologics License Application (BLA) 761263 is being submitted for accelerated approval of mosunetuzumab as a single agent for the indication of the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least two prior systemic therapies.

The FDA’s Assessment:

The FDA agrees with the Applicant’s position.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant’s Position:

For more detailed regulatory history, please see Module 1.6.3 Correspondence regarding meetings.

Table 3: Applicant – Regulatory History

Date	Event Summary
16 April 2015	IND 120651 for mosunetuzumab was activated and opened in the U.S. (b) (4) (b) (4) (protocol GO29781)
17 December 2018	Orphan Drug Designation was granted for treatment of FL
17 March 2020	Type B, End-of-Phase I meeting to discuss the proposed design of the Phase I Expansion Part of Study GO29781 to support accelerated approval of mosunetuzumab in the treatment of adult patients with relapsed or refractory FL who have received at least two prior systemic therapies
2 June 2020	Breakthrough Therapy Designation was granted for the treatment of adult patients with R/R FL who have received at least two prior systemic therapies
1 September 2020	Type B pre-Phase III/Multidisciplinary Breakthrough meeting to discuss the proposed development plan and registration strategy to support a future sBLA for mosunetuzumab in combination with lenalidomide indicated for the treatment of adult patients with previously treated FL, based on the planned BLA Phase III confirmatory study GO42909

BLA Multi-disciplinary Review and Evaluation {BLA 761263, Lunsumio (Mosunetuzumab)}

21 January 2021	Type B pre-BLA meeting to discuss the proposed content and format of the BLA for mosunetuzumab for the treatment of adult patients with R/R FL who have received at least two prior systemic therapies
22 July 2021	Type B Pre-BLA meeting to discuss and reach agreement on the acceptability of the results from the pivotal GO29781 study, to form the basis of a BLA to seek accelerated approval for mosunetuzumab for the treatment of adult patients with R/R FL who have received at least two prior systemic therapies
9 August 2021	BLA Part 1 of Rolling Submission, comprised of parts of Module 1, parts of Module 2, Module 3, and Module 4 components
7 September 2021	Informal Teleconference to continue the 22 July 2021 pre-BLA meeting question 2 discussion, regarding adequacy of study GO29781 duration of response (DOR) follow-up data for the planned September 10th BLA (rolling part 2 of 2)
30 September 2021	BLA Part 2 of Rolling Submission, comprising of parts of Module 3 components
6 December 2021	Type C Meeting (b) (4)

The FDA’s Assessment:

The FDA agrees with the Applicant’s position. The following additional interactions between the FDA and Applicant are noted:

10 March 2016	Type A meeting to discuss acceptability of amendment to assess Cycle 1 administration of BTCT4465A according to a double-step fractionated schedule and to assess safety, tolerability, pharmacokinetics, and preliminary efficacy of BTCT4465A in combination with atezolizumab in patients with relapsed/refractory B cell malignancies. Modification of safety management and mitigation plan for study GO29781 was also discussed.
7 May 2019	Type A meeting to discuss the analysis of all neurologic adverse events (NAEs) reported in Study GO29781, with additional analyses aimed at identifying events predictive of subsequent driving-impacting neurologic adverse events (DI-CCNAEs) and generating an individualized risk-based mitigation.
15 Jan 2020	Type A meeting to discuss patients treated with mosunetuzumab based on NAE reported in Study GO29781. (b) (4)

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

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4.1. Office of Scientific Investigations (OSI)

Clinical site inspections were requested for two clinical sites in the U.S. with the highest accrual for Study GO29781, along with inspection of the Applicant, Genentech, Inc. The clinical sites included 1) Site # 284510 – Washington University School of Medicine (Dr. Bartlett, MD; St. Louis, MO), which enrolled 40 patients and 2) Site 284773 – City of Hope (Dr. Budde, MD; Duarte, CA), which enrolled 66 patients. For both clinical sites inspections, no objectionable conditions or practices were identified, and no actions were indicated. Therefore, based on the clinical site inspections, the study data from the clinical sites were considered reliable. Additionally, the Applicant was inspected concerning its oversight of GO29781. Based on the inspection, no objectionable conditions or practices were identified, and no actions were indicated. Thus, the Applicant’s oversight of the clinical trial and the quality of conducting the study were determined to be adequate. The audited study data submitted to the Agency was deemed acceptable in support of the BLA application, in compliance with Good Clinical Practice.

4.2. Product Quality

Mosunetuzumab is bispecific CD20-directed CD3 T-cell engager. It is a humanized monoclonal anti-CD20xCD3 T-cell-dependent bispecific antibody of the immunoglobulin G1 (IgG1) isotype. Mosunetuzumab-axgb is produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology. The approximate molecular weight is 146 kDa.

Mosunetuzumab-axgb injection is a sterile, preservative-free, colorless solution for intravenous use.

Each single-dose vial contains a 1 mL solution of mosunetuzumab-axgb (1 mg), acetic acid (0.4 mg), histidine (1.6 mg), methionine (1.5 mg), polysorbate 20 (0.6 mg), sucrose (82.1 mg), and Water for Injection, USP. The pH is 5.8.

Each single-dose vial contains a 30 mL solution of mosunetuzumab-axgb (30 mg), acetic acid (12.8 mg), histidine (46.6 mg), methionine (44.8 mg), polysorbate 20 (18 mg), sucrose (2,462.4 mg), and Water for Injection, USP. The pH is 5.8.

The Office of Pharmaceutical Quality recommends approval of mosunetuzumab-axgb manufactured by Genentech, Inc. for human use under the conditions specified in the package insert. The data submitted support the conclusion that the manufacture of mosunetuzumab-axgb is well-controlled and leads to a product that is pure and potent.

4.3. Clinical Microbiology

The microbiology product quality and sterility assurance data are adequate to support approval.

4.4. Devices and Companion Diagnostic Issues

Not applicable

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Mosunetuzumab (RO7030816; also known as BTCT4465A) is a full-length, humanized immunoglobulin (Ig) G1 bispecific antibody, produced in Chinese hamster ovary (CHO) cells, and directed against CD20 and CD3. (b) (4)

(b) (4). The CD20 antigen is present on both healthy and malignant B-cells, and the CD3 receptor is expressed on the surface of T-cells. Mosunetuzumab promotes the T-cell dependent killing of B-cells through CD20 and therefore, is being developed for the treatment of patients with B-cell hematologic malignancies.

The proposed mechanism of action of mosunetuzumab was demonstrated with a variety of in vitro and in vivo pharmacology studies. A version of the antibody manufactured in (b) (4) was used in early nonclinical studies prior to the development of the CHO-manufactured clinical product. A bridging PK/PD study in transgenic mice showed that the exposure profile and effect on B-cell levels were comparable between the 2 versions of the antibodies. In vitro activity studies showed that binding to CD3 and CD20 (CD3 Kd =40 nM; CD20 Kd=68-83 nM), T-cell activation (EC50 = 128-149 ng/mL), B-cell killing (EC50 = 36-60 ng/mL) and cytokine induction (IL-2, IL-6, IFN γ , and TNF α) were also comparable between the antibodies. The cynomolgus monkey is a relevant species for toxicology studies based on mosunetuzumab binding to CD20 and CD3 in cynomolgus monkeys.

The Applicant conducted multiple single and repeat dose pilot toxicity studies to find a dose and dosing regimen that would minimize ADA formation and cytokine-release syndrome (CRS)-like toxicities. One such design was the step-up dosing approach which was used in the repeated-dose study. The GLP studies in cynomolgus monkeys included single-dose and repeated-dose 26-week toxicology studies, both via the intravenous route. In the single-dose study, mosunetuzumab was administered at 0.01, 0.1, or 1.0 mg/kg. Inflammatory responses were noted in animals (e.g., increased C-reactive protein (CRP) and fibrinogen, decreased

albumin, increased WBC differentials, and multi-organ infiltration) and are anticipated based on the mechanism of action that includes immune activation and cytokine release. Reductions in white blood cell counts and related pharmacodynamic effects on associated subpopulations were noted. Major toxicity findings included the following: clinical signs of emesis and decreased activity, transient increases in heart rate and body temperature with decreased blood pressure, increased CRP and bilirubin, decreased cholesterol and albumin levels, and microscopic findings. Microscopic findings were in the lymphoid system (decreased cellularity in the lymph nodes) and the central nervous system (CNS) that resolved, as well as inflammatory cell infiltrates in the vasculature, heart, liver, kidney, gastrointestinal tract, gall bladder, and lymphoid tissues. In the 26-week repeated-dose study, the animals were given 2 priming doses on dosing days 1 and 2 prior to weekly doses of 0.1 or 0.5 mg/kg for the rest of the dosing period. Two animals (one at 0.1 mg/kg and one at 0.5 mg/kg) were euthanized prematurely in moribund conditions due to immune suppression-mediated infection. Clinical signs included swelling, increased temperature, reduced movement, and emesis, which may be associated with mosunetuzumab-related cytokine release. Other findings in animals with unscheduled sacrifice were comparable to those in surviving animals and included the following: Reduced B-cells in the blood and lymphoid tissues, inflammatory signals such as increased monocyte, lymphocyte, eosinophil, and basophil counts in addition to increased globulin, CRP, and fibrinogen concentrations, and microscopic findings of inflammatory cell infiltration in multiple organs.

While no animal studies were conducted to assess the reproductive and developmental risks of mosunetuzumab, a weight of evidence (WoE)-based risk assessment report was submitted. The assessment is based on a variety of factors, including maternal and/or neonatal toxicities due to depletion of B-cells and cytokine release-related events. Based on the drug's mechanism of action and pharmacodynamic effects, mosunetuzumab may cause depletion of B-cells and impair infant immune response due to fetal exposure, increasing the risk of opportunistic infections. Risks associated with T-cell activation include cytokine release and associated inflammatory effects, which may adversely affect a pregnant woman, and maintenance of pregnancy. Adverse events that may occur in pregnant animals are those that have been described in general toxicology studies, e.g., diarrhea, cardiac events, acute phase protein reactions and inflammatory response, B-cell depletion, etc. The recommendation for using contraception in females of reproductive potential for 3 months after the last dose of the product, as reflected in the product label, is based on 5 half-lives of the product.

The nonclinical data of mosunetuzumab submitted to BLA 761263 are adequate to support the labeling and approval of mosunetuzumab for the proposed indication.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:

Not applicable.

5.3. Pharmacology

Primary pharmacology

The nonclinical studies were conducted using anti-CD20/CD3 T-cell-dependent bispecific (TDB) molecules manufactured in (b) (4) and CHO cells. The antibodies manufactured in CHO cells were used for clinical development.

Table 4: Characteristics of the three anti-CD20/CD3 TDB antibodies (excerpted from the Applicant's submission)

Anti-CD20/CD3 TDB Antibody	Description	Produced in	Fc Mutation/ Glycosylation
Mosunetuzumab (also referred to as BTCT4465A)	- Clinical candidate - Anti-CD20 half antibody: (b) (4) that binds to both human and cynomolgus monkey CD20 - Anti-CD3 half-antibody: (b) (4) (binds to both human and cynomolgus monkey CD3)	CHO	(b) (4)
(b) (4)	- Functionally equivalent to mosunetuzumab - Same amino acid sequence as mosunetuzumab but without the (b) (4) - Anti-CD20 half antibody: (b) (4) - Anti-CD3 half-antibody: (b) (4)	(b) (4)	None/None
(b) (4)	- Anti-CD20 half antibody: (b) (4) - Anti-CD3 half-antibody: (b) (4) - Also referred to as the proof-of-concept molecule	(b) (4)	None/None

CHO = Chinese hamster ovary; (b) (4) TDB = T-cell-dependent bispecific.
(b) (4)

- Mosunetuzumab (BTCT4465A CHO) was used in the GLP toxicology studies in cynomolgus monkeys. (b) (4)
- (b) (4) was used in pharmacology, pharmacokinetics, and pilot toxicology studies. (b) (4)

- (b) (4) was used in the initial proof-of-concept (POC) studies.

To help bridge the studies and confirm the comparable pharmacological activities for mosunetuzumab (BTCT4465A CHO) (b) (4) in vitro assays (Study 14-3525) were conducted with human peripheral blood mononuclear cells (PBMCs) isolated from healthy donors to compare the binding affinity of the two drug products to the targets, and their potency in B-cell killing, T-cell activation, and cytokine production. The binding affinities of mosunetuzumab (BTCT4465A CHO) (b) (4) to human CD20 and CD3 (Study 14-3525) were comparable as measured using a scatchard assay in human BJAB and Jurkat cells. Both products demonstrated similar potency in activating CD8+ T-cells and killing endogenous B-cells in vitro, using human PBMCs from three independent donors (Table 4). The levels of cytokine production (IL-2, IL-6, IFN- γ , and TNF- α) were comparable with (b) (4) CHO-derived BTCT4465A at pg/mL concentrations (Figure 1).

Table 5: In vitro binding and potency - mosunetuzumab (b) (4)

Molecule	Kd Average (nM)		CD8+ T-cell activation average (EC50 ng/mL)	Killing endogenous B-cells average (EC50 ng/mL)
	CD3	CD20		
BTCT4465A ((b) (4), CHO)	40	68	149	60
(b) (4)	40	83	128	36

EC50 = half-maximal effective concentration

Figure 1: In vitro cytokine production by mosunetuzumab and (b) (4) (excerpted from the Applicant’s submission)

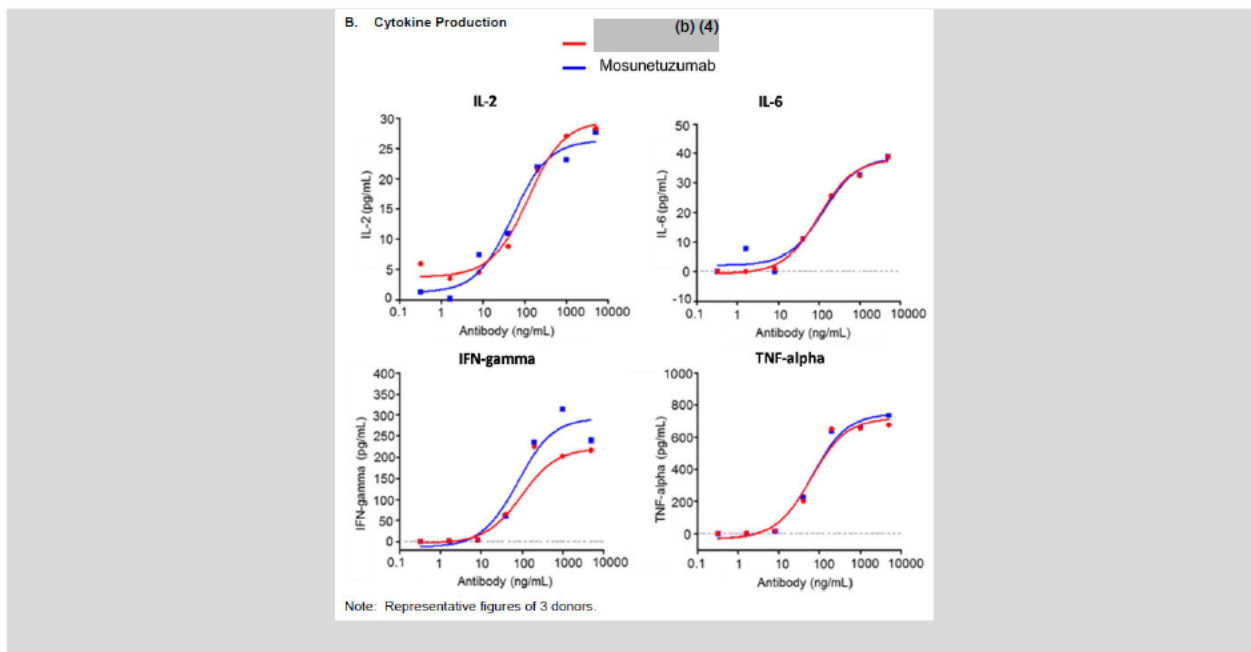


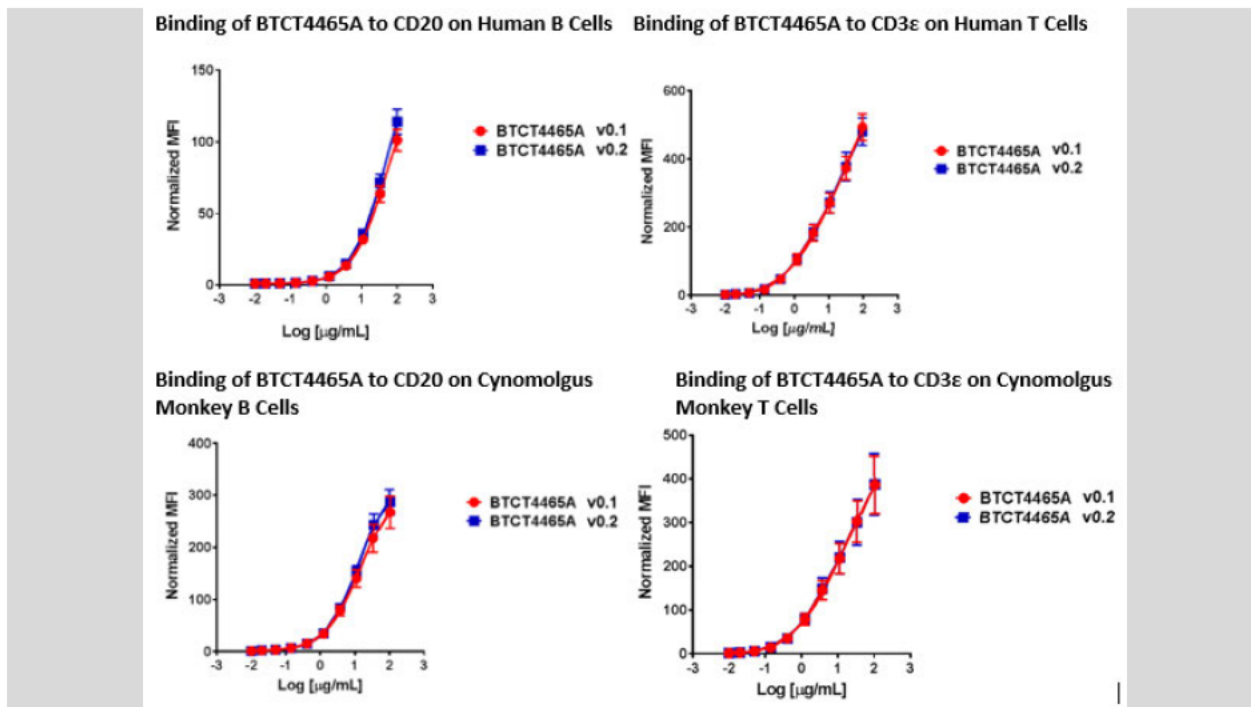
Table 6: Binding affinity of (b) (4) to CD3εγ and potency of (b) (4) in human and cynomolgus monkey PBMCs (excerpted from the Applicant’s submission)

	Binding affinity to CD3εγ antigens	EC ₉₀ for B cell-killing in PBMCs Avg (range)
Human	12.0 nM	0.42 (0.07–1.1; N=5)
Cynomolgus Monkeys	14.2 nM	0.05 (0.026, 0.078; N=2)

EC₉₀ = 90% maximal effective concentration; PBMCs = peripheral blood mononuclear cells.

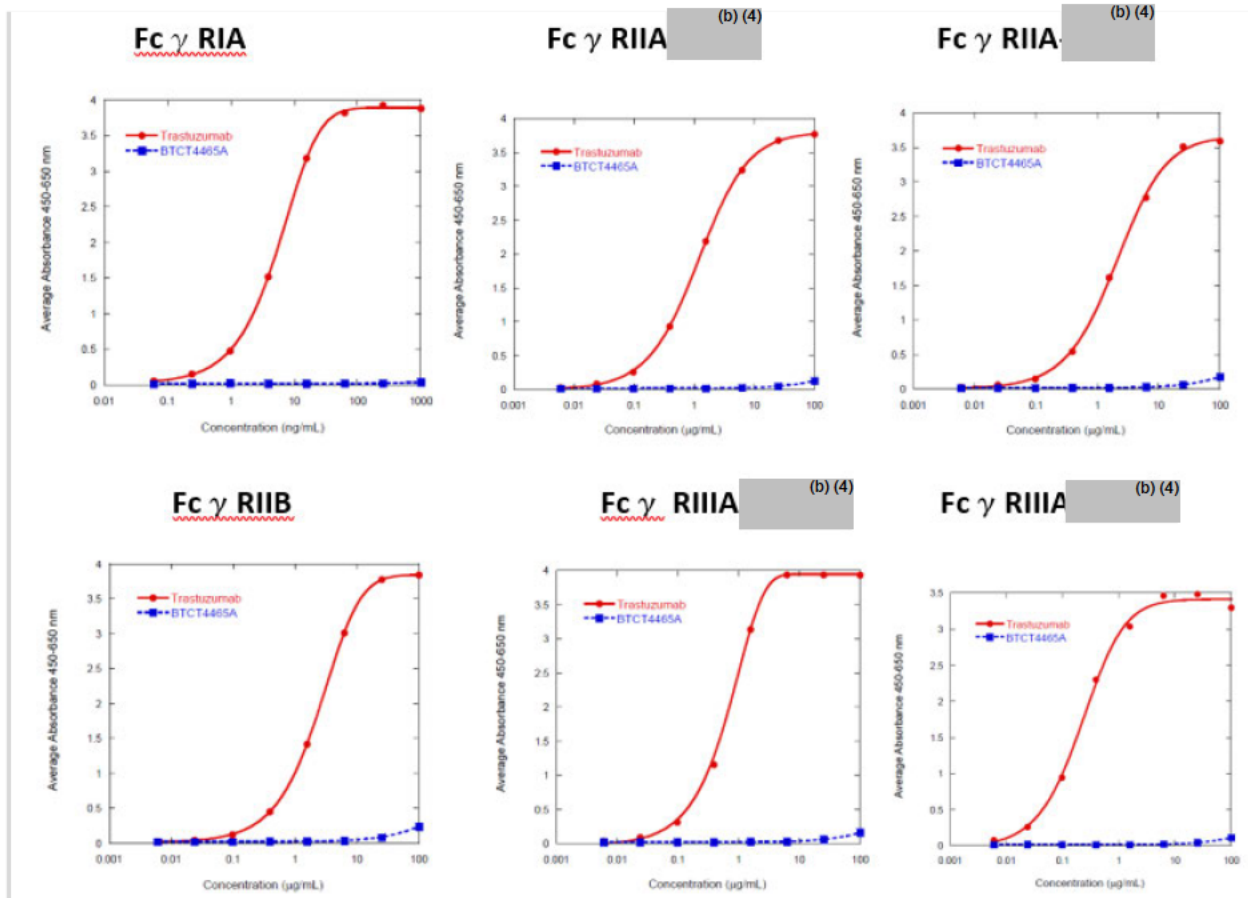
The binding of the mosunetuzumab v0.1-derived drug product (used for the investigational new drug (IND)-enabling pharmacology, pharmacokinetic, and toxicology studies, as well as for the ongoing Phase 1 study) and mosunetuzumab v0.2-derived drug product (an updated v0.2 drug substance manufacturing process) to CD3ε on T-cells and CD20 on B-cells in human and cynomolgus monkey PBMCs was assessed by flow cytometry (Study 17-2037). The two mosunetuzumab drug products demonstrated comparable binding to both CD20 and CD3ε on B-cells and T-cells in the human and cynomolgus monkey (Figure 2). Binding studies with (b) (4) and mosunetuzumab confirm the cynomolgus monkey as an appropriate non-human primate model for the nonclinical toxicology studies for BTCT4465A.

Figure 2: Binding of mosunetuzumab to human and monkey CD3 and B-cells (excerpted from the Applicant’s submission)



The binding interactions of BTCT4465A with human Fc gamma receptors (Fc γ RIIA^{(b) (4)}, Fc γ RIIB, and Fc γ RIIIA^{(b) (4)}) were assessed in enzyme-linked immunosorbent assay (ELISA)-based ligand binding assays (Study 14-3202). Results showed that while trastuzumab positive control binds robustly to all Fc gamma receptors tested; mosunetuzumab shows minimal binding to each Fc gamma receptor tested.

Figure 3: Binding responses of BTCT4465A and Trastuzumab to FcγRs (excerpted from the Applicant's submission)



The following in vitro assays were performed to assess dependence of T-cell activation, and CD20+ target cell killing on Fc binding with (b) (4) (used in several POC studies), which binds to human CD3, but does not bind to cynomolgus monkey CD3 (Study 15-0391).

In vitro cell killing was assessed against the target B-cell line BJAB (a CD20-expressing cell) using normal human donor PBMCs as effector cells in the presence of (b) (4) (intact TDB; T-cell-dependent bispecific) antibody and a F(ab')₂ fragment (b) (4) lacking the Fc region. The potencies of cell killing of the F(ab')₂ fragment and intact TDB (T-cell-dependent bispecific) antibody were similar, suggesting anti-CD20/CD3 TDB-induced B-cell killing is not dependent on the Fc region (Figure 4A).

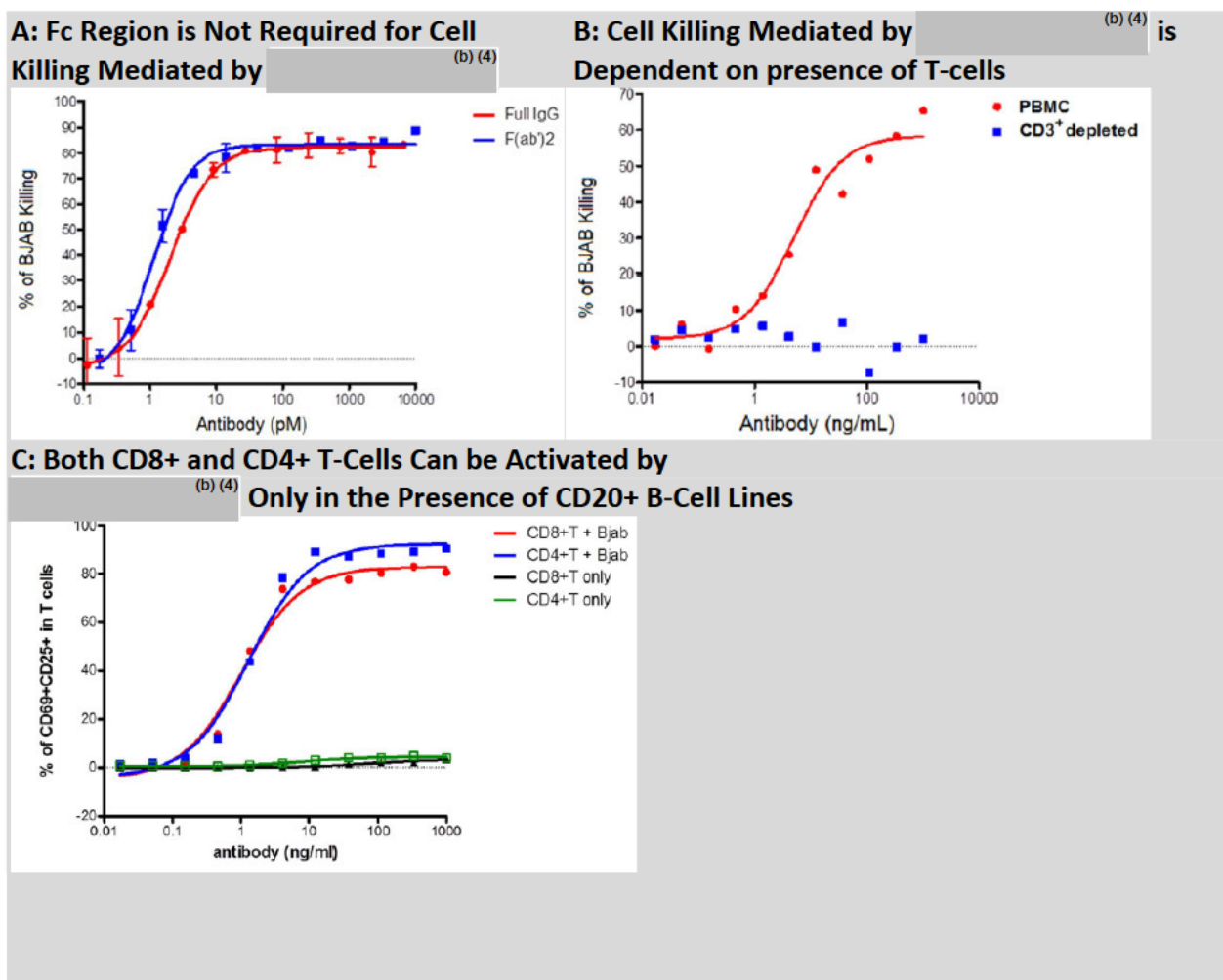
In vitro T-cell-dependent B-cell killing was demonstrated by incubating PBMCs isolated from healthy donor or PBMCs depleted of CD3+ T-cells with various concentrations of (b) (4) for 24 hours. (b) (4) treatment resulted in concentration-

dependent killing when incubated with CD3+ T-cells. However, depletion of CD3-expressing cells from PBMCs abolished the activity of (b) (4) indicating that T-cells are required for activity (Figure 4B).

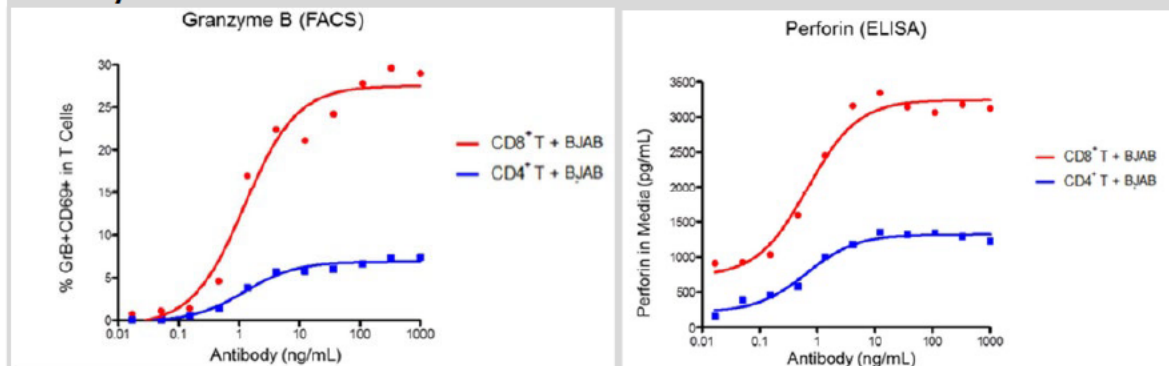
T-cell activation by the (b) (4) antibody was dependent on the presence of CD20+ target cells. BJAB cells and purified CD8+ T-cells or CD4+ T-cells were incubated with various concentrations of (b) (4) for 24 hours. The results show that T-cell activation marked as CD69+CD25+ was observed only in the presence of CD20+ target cells (Figure 4C).

BJAB cells and purified CD8+ T-cells or CD4+ T-cells were incubated with various concentrations of (b) (4) for 24 hours. Consistent with CD20 cell killing, (b) (4) treatment resulted in greater T-cell induction and higher levels of perforin release were detected with activated CD8+ T-cells than with CD4+ T-cells (Figure 4D).

Figure 4: T-cell Activation and CD20+ Target Cell Killing (excerpted from the Applicant's submission)



D: Both CD8+ and CD4+ T-Cells are Capable of Killing B-Cell Lines via Granzyme-Perforin Pathway



(b) (4) was tested in dose-response assays across a panel of seven B-lymphoma cell lines with various levels of surface CD20 expression and EC50 values ranged from 0.22 to 11 ng/mL in vitro (Figure 5). In addition, (b) (4) was also active in the killing of endogenous B-cells by endogenous T-cells in PBMCs prepared from healthy human donors with a mean EC50 for killing of < 3 ng/mL (Figure 6).

Figure 5: B-lymphoma cell killing

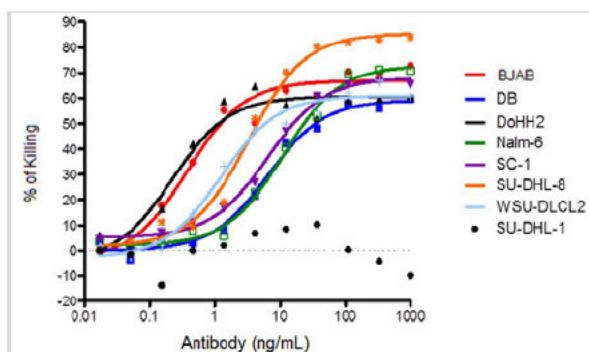
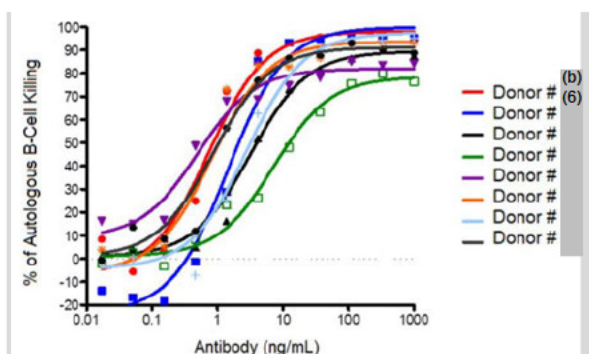


Figure 6: Killing of Endogenous B-cells from Healthy Donors



Comparative in vivo pharmacokinetic and pharmacodynamic activity of mosunetuzumab or (b) (4) was evaluated in human CD20/CD3ε double-transgenic B6N mice, in which

human CD20 and CD3ε are expressed on mouse B- and T-cells, respectively (Study 13-2919). Mice (n=12 per group) were given a single intravenous (IV) dose of 0.5 mg/kg BTCT4465A produced in either (b) (4) (Group 1) or CHO cells (Group 2). Serum samples were collected at 2, 8, and 24 hours after dosing and on Days 2 and 7, and assayed for BTCT4465A serum concentrations. Subsets of peripheral blood lymphocytes (helper T-cells [Th], cytotoxic T-cells [Tc], and B-cells) were collected and evaluated by flow cytometry for pharmacodynamic endpoints. Activation status of Th and Tc was evaluated by the early activation marker CD69, and B-cells were identified as CD45+ CD90.2+ CD19+ cells. In addition, at selected timepoints, spleen and lymph nodes were collected to evaluate pharmacodynamics by flow cytometry.

The group mean serum concentration-time profiles suggest that the pharmacokinetics in huCD20/huCD3 transgenic mice are similar for BTCT4465 produced in (b) (4) and in CHO cells after a single administration (Figure 7 and Table 7).

Figure 7: Group Mean Serum Concentrations (excerpted from the Applicant’s submission)

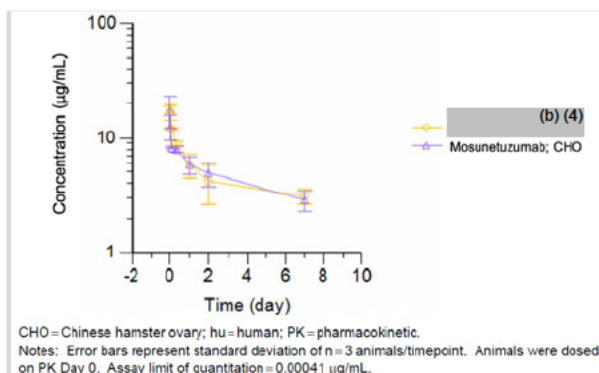


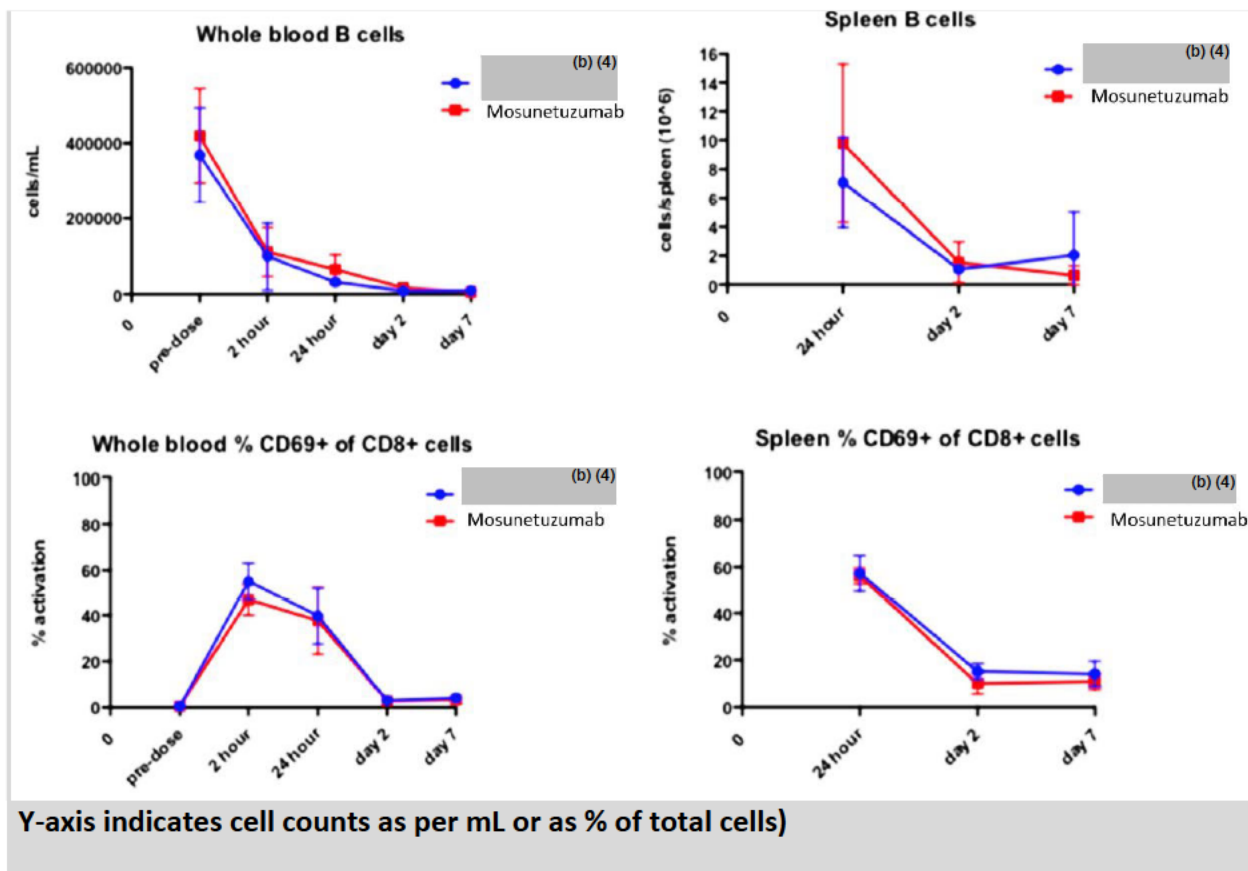
Table 7: Group Mean PK Parameters (excerpted from the Applicant’s submission)

Parameter (Unit)	Group 1, (b) (4) (0.5 mg/kg)	Group 2, Mosunetuzumab (0.5 mg/kg)
C _{max} (µg/mL)	18.0 ± 1.03	17.6 ± 3.20
AUC _{last} (day • µg/mL)	32.0 ± 2.80	32.3 ± 2.29
AUC _{inf} (day • µg/mL)	67.5	57.9
AUC % extrapolated (%)	52.6	44.2

AUC % extrapolated = percentage of AUC_{inf} predicted due to extrapolation from the last timepoint with measurable serum concentration to infinity; AUC_{inf} = area under the serum concentration-time curve extrapolated to infinity; AUC_{last} = area under the serum concentration-time curve from time = 0 to time of the last measurable concentration; CL = clearance; C_{max} = maximum observed serum concentration; hu = human; PK = pharmacokinetic; V_{ss} = volume of distribution at steady state.

The pharmacodynamic endpoints show no differences in B-cell absolute counts or T-cell activation (CD69%) of Th and Tc cells in whole blood, spleen and inguinal lymph nodes between mosunetuzumab or (b) (4) after a single administration (Figure 8).

Figure 8: Comparison of Biological Activity of (b) (4) and Mosunetuzumab in Human CD20/CD3 Double-Transgenic Mice (excerpted from the Applicant’s submission).



Secondary Pharmacology

The Applicant’s Position:

No secondary pharmacology studies have been conducted.

The FDA’s Assessment:

The FDA concurs with the Applicant.

Safety Pharmacology

The Applicant’s Position:

Safety pharmacology evaluation was incorporated into single- and repeat-dose toxicity studies. Cardiovascular safety pharmacology findings included dose-dependent and reversible hypotension at 1 mg/kg IV, and tachycardia and increased core body temperature at

≥ 0.1 mg/kg IV. With the exception of decreased RR, PR, and QT intervals due to increased heart rate, no quantitative or qualitative changes in electrocardiography were present. These findings are consistent with cytokine release and associated acute protein reactions. CNS findings were limited to one incidence of convulsion in one animal at high exposure multiples (refer to Section 5.5.1). There were no drug-related effects on respiratory endpoints.

The FDA's Assessment:

The FDA's assessment of safety pharmacology was made during the review of the GLP single-dose and repeat-dose studies in monkeys and is summarized in Section 5.5.1.

5.4. ADME/PK

The Applicant's Position:

In huCD20/CD3 transgenic mice, after a single IV dose, mosunetuzumab and (b) (4), a functionally equivalent antibody used in early nonclinical studies, demonstrated similar PK profiles and comparable B-cell killing in blood and tissues. In cynomolgus monkeys, after a single IV dose, mosunetuzumab exhibited dose-proportional exposure and rapid clearance (CL) at dose levels between 0.01 and 1 mg/kg. The dose proportionality at these doses was likely due to a large component of target-mediated CL. Following repeat IV dosing in cynomolgus monkeys, (b) (4) showed dose-dependent PK with higher exposure in later cycles, likely due to B-cell depletion and T cells returning to baseline after initial activation and expansion, leading to an eventual reduction of target-mediated CL.

The FDA's Assessment:

The FDA generally concurs with the Applicant's position.

The Applicant conducted multiple single and repeat dose pilot studies to find a dose and dosing regimen that would minimize ADA formation and cytokine-release syndrome (CRS)-like toxicities.

Table 8: Summary table of in vivo toxicology studies (excerpted from the Applicant's submission)

Molecule/ Reference	Treatment Duration/ Type of Study	GLP Status	Dose (mg/kg/day)	MTD or NOAEL
mosunetuzumab/ (b) (4)	Single-dose/ Pivotal	GLP	0, 0.01, 0.1, 1 (IV); 1 (SC)	MTD = 1 mg/kg IV; NOAEL = 0.1 mg/kg IV or 1 mg/kg SC
	Single-dose/ CNS Investigative	Non-GLP	1 (IV)	MTD = 1 mg/kg IV
	Single-dose/ CNS Investigative	Non-GLP	1 (IV)	MTD = 1 mg/kg IV
	4-week/ Dose range-finding	Non-GLP	0, 0.01, 0.1, 1 (IV)	MTD = 1 mg/kg IV
	4-week/ Mitigation of toxicity with SC dosing and pretreatment with RTX and Dex	Non-GLP	1 (IV or SC)	MTD = 1 mg/kg IV
	4-week/ Evaluation of brain MRI	Non-GLP	1 (IV)	MTD = 1 mg/kg IV
mosunetuzumab/ (b) (4)	4-week/ Evaluation of step- dosing	Non-GLP	0.2/0.8/0.3 ^a 0.2/0.8/1 ^a 0.2/0.8/3 ^a (IV)	MTD = 0.2/0.8/0.3 mg/kg IV
mosunetuzumab/ (b) (4)	26-week/ Pivotal chronic toxicity	GLP	0/0/0 ^b 0.2/0.8/0.1 ^b 0.2/0.8/0.5 ^b (IV)	MTD < 0.2/0.8/0.1 mg/kg IV due to secondary infection

Type of Study	Major Findings
Single-dose comparative PK/B-cell depletion study of CHO-derived and (b) (4) derived versions of mosunetuzumab (BTCT4465A) in humanized	Mice (single dose) Comparable PK profiles between the 2 versions of the drug product. Summary of toxicokinetic parameters for BTCT4465A manufacturing variants in mouse serum (Group 1= (b) (4) antibody; Group 2= CHO-produced antibody. Excerpted from the Applicant's submission)

Type of Study	Major Findings																																														
CD20/CD3 transgenic mice (study 13-2919)	<table border="1"> <thead> <tr> <th>Parameter (Unit)</th> <th>Group 1 Anti-CD20/CD3 TDB antibody (0.5 mg/kg)</th> <th>Group 2 BTCT4465A (0.5 mg/kg)</th> </tr> </thead> <tbody> <tr> <td>C_{max} (µg/mL)</td> <td>18.0 ± 1.03</td> <td>17.6 ± 3.20</td> </tr> <tr> <td>AUC_{last} (days • µg/mL)</td> <td>32.0 ± 2.80</td> <td>32.3 ± 2.29</td> </tr> <tr> <td>AUC_{inf} (days • µg/mL)</td> <td>67.5</td> <td>57.9</td> </tr> <tr> <td>AUC % extrapolated (%)</td> <td>52.6</td> <td>44.2</td> </tr> </tbody> </table>	Parameter (Unit)	Group 1 Anti-CD20/CD3 TDB antibody (0.5 mg/kg)	Group 2 BTCT4465A (0.5 mg/kg)	C _{max} (µg/mL)	18.0 ± 1.03	17.6 ± 3.20	AUC _{last} (days • µg/mL)	32.0 ± 2.80	32.3 ± 2.29	AUC _{inf} (days • µg/mL)	67.5	57.9	AUC % extrapolated (%)	52.6	44.2																															
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GLP single-dose Tox/PK/PD study of mosunetuzumab in cynomolgus monkeys (study 14-1246)	Monkeys (single-dose) • C_{max} increased dose-proportionately. • AUC increased less than dose-proportionately from 0.01 to 0.1 mg/kg, but more than dose-proportionately from 0.1 to 1.0 mg/kg. Summary of toxicokinetic parameters in single-dose monkey study (excerpted from the Applicant's submission) <table border="1"> <thead> <tr> <th>Route</th> <th>Dose (mg/kg)</th> <th>Sex</th> <th>C_{max} (µg/mL)</th> <th>AUC₍₀₋₇₎ (µg•Day/mL)</th> <th>AUC_(0-t) (µg•Day/mL)</th> </tr> </thead> <tbody> <tr> <td rowspan="9">IV Infusion</td> <td rowspan="3">0.01</td> <td>Female</td> <td>0.160 ± 0.0268</td> <td>0.396 ± 0.0238</td> <td>0.438 ± 0.0911</td> </tr> <tr> <td>Male</td> <td>0.169 ± 0.0236</td> <td>0.374 ± 0.0420</td> <td>0.402 ± 0.0809</td> </tr> <tr> <td>Combined</td> <td>0.165 ± 0.0243</td> <td>0.385 ± 0.0342</td> <td>0.420 ± 0.0834</td> </tr> <tr> <td rowspan="3">0.1</td> <td>Female</td> <td>1.64 ± 0.108</td> <td>2.68 ± 0.689</td> <td>3.01 ± 0.880</td> </tr> <tr> <td>Male</td> <td>1.60 ± 0.261</td> <td>2.36 ± 0.427</td> <td>2.37 ± 0.428</td> </tr> <tr> <td>Combined</td> <td>1.62 ± 0.189</td> <td>2.52 ± 0.566</td> <td>2.69 ± 0.734</td> </tr> <tr> <td rowspan="3">1</td> <td>Female</td> <td>17.7 ± 2.19</td> <td>33.0 ± 3.20</td> <td>42.7 ± 11.8</td> </tr> <tr> <td>Male</td> <td>18.0 ± 1.55</td> <td>31.2 ± 4.60</td> <td>38.0 ± 17.3</td> </tr> <tr> <td>Combined</td> <td>17.8 ± 1.83</td> <td>32.1 ± 3.92</td> <td>40.4 ± 14.4</td> </tr> </tbody> </table>	Route	Dose (mg/kg)	Sex	C _{max} (µg/mL)	AUC ₍₀₋₇₎ (µg•Day/mL)	AUC _(0-t) (µg•Day/mL)	IV Infusion	0.01	Female	0.160 ± 0.0268	0.396 ± 0.0238	0.438 ± 0.0911	Male	0.169 ± 0.0236	0.374 ± 0.0420	0.402 ± 0.0809	Combined	0.165 ± 0.0243	0.385 ± 0.0342	0.420 ± 0.0834	0.1	Female	1.64 ± 0.108	2.68 ± 0.689	3.01 ± 0.880	Male	1.60 ± 0.261	2.36 ± 0.427	2.37 ± 0.428	Combined	1.62 ± 0.189	2.52 ± 0.566	2.69 ± 0.734	1	Female	17.7 ± 2.19	33.0 ± 3.20	42.7 ± 11.8	Male	18.0 ± 1.55	31.2 ± 4.60	38.0 ± 17.3	Combined	17.8 ± 1.83	32.1 ± 3.92	40.4 ± 14.4
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26-week repeat-dose toxicity study in cynomolgus monkeys (study 8348466)	Monkeys (repeat-dose): • After study Day 7, C_{max} and AUC increased greater than dose-proportionately. • At low dose (LD), ADAs were detected in 5 out of 8 animals (63%) on TK Days 28 and 84, in 3 out of 7 animals (43%) on TK Days 133 and 182. • The lower exposures on TK Days 175-182 (AUC of 10.7 mcg/mL*d) compared to TK Days 0-3 (AUC of 30.8 mcg/mL*d) may be due to the ADAs. • At high dose (HD), ADAs were detected in 4 out of 8 animals (50%) on TK Day 28, in 1 out of 8 animals (13%) on TK Days 84 and 133, and in 1 out of 7 animals (14%) on TK Day 182.																																														

Type of Study	Major Findings							
	Summary of toxicokinetic parameters in repeat-dose monkey study (excerpted from the Applicant's submission)							
	Dose Level [Study Day 1] (mg/kg)	Dose Level [Study Day 2] (mg/kg)	Dose Level [Study Days 7 to 182] (mg/kg)	Interval	C _{max} (µg/mL)		AUC (day*µg/mL)	
					M/F	M+F	M/F	M+F
	0.2	0.8	0.1	TK Day 0-1	3.93/2.63	3.28	2.47/1.75	2.11
				TK Day 0-3	23.6/21.6	22.6	32.9/28.7	30.8
				TK Day 175-182	2.33/2.65	2.57	9.75/11.0	10.7
				TK Day 182-185	2.14/2.44	2.37	5.00/5.31	5.23
	0.2	0.8	0.5	TK Day 0-1	3.93/3.73	3.83	2.77/2.69	2.73
				TK Day 0-3	23.0/21.4	22.2	32.9/30.7	31.8
				TK Day 175-182	16.9/17.4	17.1	80.0/90.8	84.6
				TK Day 182-185	17.5/18.8	18.0	39.9/41.8	40.7

5.5. Toxicology

5.5.1. General Toxicology

The Applicant's Position:

Mosunetuzumab has been evaluated in single-dose and repeat-dose toxicology studies up to 26 weeks in cynomolgus monkeys following IV administration. Key mosunetuzumab-related toxicities included post-dose CRS-like toxicities that were primarily limited to the first dose, reversible findings of vascular/perivascular inflammatory cell infiltrates, and increased susceptibility to infection following chronic dosing due to sustained B-cell depletion. All of the findings were considered pharmacologically-mediated effects.

The most consistent findings were CRS-like toxicities following IV administration. They were primarily limited to the first dose and included tachycardia, fever, and acute phase reactions at ≥ 0.1 mg/kg, clinical signs (e.g., emesis, hypoactivity) at ≥ 0.2 mg/kg, and hypotension and evidence of minimal hepatocellular cell injury at 1 mg/kg. Microscopic findings of vascular/perivascular inflammatory cell infiltrates were present primarily within the brain, with decreased incidence in spinal cord and sciatic nerve in single and repeat-dose studies, and were also present infrequently in other organs in the 26-week toxicity study. In the brain, the findings were accompanied with local microglial reaction; however, no neuronal degeneration was observed. These findings were reversible and were considered secondary to cytokine/chemokine-induced up-regulation of chemokine receptors and adhesion molecules in the vessels of the brain and immune cell activation, margination, and transmigration. In-life neurologic abnormalities were limited to one incidence of convulsion in one animal on Day 8 following a total of 2 mg/kg dose, corresponding to C_{max} and AUC_{Day0-7} values approximately 50-fold and 20-fold, respectively, higher than those in patients exposed to mosunetuzumab during the first two weeks of dosing (1 mg on Day 1 and 2 mg on Day 8) in Study GO29781. The

CNS microscopic lesions in this animal were more extensive than those identified in the remaining animals and were considered causal for the convulsion. Following chronic dosing, mosunetuzumab was associated with microscopic evidence of upper urinary tract and/or enteric infection, which resulted in moribundity and early euthanasia in two animals. The increased susceptibility to infection was considered to be secondary to prolonged B-cell depletion, a pharmacologic effect of mosunetuzumab. With the exception of the above findings, no other toxicities were observed following 26 weeks of mosunetuzumab administration at the highest dose tested, corresponding to approximately 5-fold multiples relative to the steady-state exposure (AUC) in human at the recommended clinical dose of 1/2/60/30 mg.

The FDA's Assessment:

The GLP-compliant single-dose toxicity (IV/SC) and 26-week repeat-dose toxicity (IV) studies in cynomolgus monkeys were reviewed and we generally agree with the adverse findings described by the Applicant. Detailed reviews of the 26-week study and the summary of the single-dose toxicity study are included.

Study title/ Study number: BTCT4465A: 26 Week Multiple Dose Intravenous (Infusion) Administration Toxicity and Toxicokinetic Study in the Cynomolgus Monkey

Key Study Findings

- Two animals (one at 0.1 mg/kg and one at 0.5 mg/kg) were euthanized prematurely in moribund conditions due to immune suppression/enteric infection.
- Clinical signs including red/swollen face, swollen eyes, warm to touch, subdued, and emesis occurred mostly during the step dosing phase, consistent with BTCT4465A-related cytokine release.
- Consistent with BTCT4465A pharmacological activity, markedly reduced B lymphocytes in the blood and lymphoid tissues, transient cytokine release and T-cell activation, and associated transient decrease in circulating T-cells and natural killer cells were observed at both dose levels tested.
- Clinical pathology showed increased indicators of inflammation (monocyte, lymphocyte, eosinophil, and basophil counts and globulin, CRP and fibrinogen concentrations).
- BTCT4465A-induced toxicity was observed within the systemic vasculature (vascular/perivascular inflammatory cell infiltration) in multiple tissues (brain, heart, liver, kidney, gastrointestinal tract, gall bladder), lymphoid tissues (decreased germinal centers/follicles/GALT), bone marrow (increased cellularity consistent with inflammation), kidney (inflammatory infiltration/tubular basophilia, likely related to ascending urinary tract infection), and pancreas (decreased exocrine granulation) in animals administered 0.1 or 0.5 mg/kg.

GLP compliance: Yes

BLA Multi-disciplinary Review and Evaluation {BLA 761263, Lunsumio (Mosunetuzumab)}

Methods	
Dose and frequency of dosing:	Step Dosing on Study Days 1 and 2, and then weekly dosing (Study Days 8 to 183): Low dose (LD): 0, 0.2 mg/kg (D1), 0.8 mg/kg (D2) and then 0.1 mg/kg weekly High dose (HD): 0, 0.2 mg/kg (D1), 0.8 mg/kg (D2) and then 0.5 mg/kg weekly
Route of administration:	60-minute intravenous infusion
Formulation/Vehicle:	(b) (4) histidine, (b) (4) sucrose, 0.06% (w/v) polysorbate 20, (b) (4) Methionine, pH 5.8.
Species/Strain:	Monkey/cynomolgus
Number/Sex/Group:	4/sex/group (Control, LD, HD)
Age:	Males: 297 to 333 weeks old Females: 246 to 396 weeks old
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters		Major findings		
Mortality				
Animal#	Sex	Dose (mg/kg/week)	Day of Death	Cause of death (COD) Pathologist's findings
P0104	Male	LD (0.1)	96	Moribund Sacrifice Cause of death: Immune suppression/urinary and enteric infection. Clinical signs: Body weight decrease (-26% over Study Days 1 to 95), dehydration, soft feces, thin appearance, skin tenting, subdued and sluggish behavior. Microscopic findings: inflammation (vascular/perivascular inflammatory cell infiltration in multiple organs) immunosuppression within the spleen and lymph nodes consistent with BTCT4465A-related pharmacologic activity of B-cell depletion; inflammation in the duodenum/ileum/jejunum was suggestive of enteric infection and considered secondary to generalized immunosuppression.

P0503	Female	HD (0.5)	158	Moribund Sacrifice Cause of death: Immune suppression/enteric infection. Clinical signs: Body weight decrease (-14% over Study Days 1 to 158), diarrhea, thin appearance, and skin tenting. Microscopic findings: immunosuppression in the spleen and lymph nodes consistent with BTCT4465A-related pharmacologic activity of B-cell depletion; inflammation in the ileum/jejunum/cecum/colon (inflammatory cell infiltration) was suggestive of enteric infection and considered secondary to generalized immunosuppression.																																		
Clinical Signs	Clinical observations for terminal euthanasia animals included liquid feces, skin tenting, and semi-closed eyes. Step dosing: Red face/swollen eyes, warm to touch, raised hair, not eating in females, subdued/sluggish behavior, nasal discharge and emesis in males and females were noted mostly on Study Day 1 (0.2 mg/kg) or 2 (0.8 mg/kg). Weekly Dosing: Swollen eyelids and salivation occurred in one female at 0.5 mg/kg on Study Day 8.																																					
Body Weights	Body weight loss was noted in one female (-5.6%) at 0.1 mg/kg and 3 females (-5.6 to -16%) at 0.5 mg/kg.																																					
Food Consumption	Poor food consumption was noted on Study Days 2 and 3 for all test article-dosed animals and on Days 12 and 13 for females at 0.5 mg/kg.																																					
Ophthalmoscopy	Unremarkable																																					
Neurological Examinations	Unremarkable																																					
Body Temperature	Unremarkable																																					
Hematology	Step Dosing Phase: ↓reticulocytes (RET), ↓neutrophils (Neu), ↓lymphocytes (Lym), ↓monocytes (Mono), ↓white blood cells (WBC), and ↑fibrinogen (FIBRIN). These changes were noted on Study Day 2. Weekly Dosing Phase – Day 186 % Differences in Hematology Parameters Compared to Control <table border="1"> <thead> <tr> <th rowspan="2">Dose (mg/kg/dose)</th> <th colspan="2">0.1</th> <th colspan="2">0.5</th> </tr> <tr> <th>M</th> <th>F</th> <th>M</th> <th>F</th> </tr> </thead> <tbody> <tr> <td>RET%</td> <td>↓41</td> <td>↑59</td> <td>0</td> <td>↓41</td> </tr> <tr> <td>RBC10¹²/L</td> <td>↑2</td> <td>↓9</td> <td>↓1</td> <td>↓7</td> </tr> <tr> <td>HGB (g/dL)</td> <td>↓8</td> <td>↓6</td> <td>↓9</td> <td>↓5</td> </tr> <tr> <td>PCV%</td> <td>↓7</td> <td>↓3</td> <td>↓7</td> <td>↓1</td> </tr> <tr> <td>MONO</td> <td>↑15</td> <td>↑104</td> <td>↓9</td> <td>↑42</td> </tr> </tbody> </table>				Dose (mg/kg/dose)	0.1		0.5		M	F	M	F	RET%	↓41	↑59	0	↓41	RBC10 ¹² /L	↑2	↓9	↓1	↓7	HGB (g/dL)	↓8	↓6	↓9	↓5	PCV%	↓7	↓3	↓7	↓1	MONO	↑15	↑104	↓9	↑42
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Clinical Chemistry	Step Dosing Phase: ↑alanine aminotransferase (ALT), ↑aspartate aminotransferase (AST) and/or total bilirubin (BIL) concentrations, ↑C reactive protein (CRP), ↑APTT and PT, ↓protein parameters (albumin concentration, accompanied by decreased total protein concentration), and ↑blood urea nitrogen (BUN). These changes were noted on Study Day 2. Weekly Dosing Phase – Day 186 % Differences in Clinical Chemistry Parameters Compared to Control <table border="1"> <thead> <tr> <th rowspan="2">Dose (mg/kg/dose)</th> <th colspan="2">0.1</th> <th colspan="2">0.5</th> </tr> <tr> <th>M</th> <th>F</th> <th>M</th> <th>F</th> </tr> </thead> <tbody> <tr> <td>AST IU/L</td> <td>↓44</td> <td>↓2</td> <td>↓31</td> <td>↓25</td> </tr> <tr> <td>ALT IU/L</td> <td>↓62</td> <td>↓22</td> <td>↓54</td> <td>↓38</td> </tr> <tr> <td>ALP IU/L</td> <td>↑42</td> <td>↑40</td> <td>↑81</td> <td>↑46</td> </tr> <tr> <td>GGT IU/L</td> <td>↓20</td> <td>↓10</td> <td>↓22</td> <td>↓16</td> </tr> <tr> <td>CRP mg/L</td> <td>↓47</td> <td>↓22</td> <td>↑1249</td> <td>↑67</td> </tr> <tr> <td>ALB\GLB RATIO</td> <td>0</td> <td>↓9</td> <td>↓11</td> <td>↑6</td> </tr> <tr> <td>BUN mg/dL</td> <td>↑16</td> <td>↑9</td> <td>↑8</td> <td>↑1</td> </tr> <tr> <td>NA mmol/L</td> <td>↓2</td> <td>↑1</td> <td>↓2</td> <td>↑1</td> </tr> <tr> <td>K mmol/L</td> <td>↓6</td> <td>↑1</td> <td>↓0</td> <td>↑7</td> </tr> <tr> <td>CL mmol/L</td> <td>↑1</td> <td>↓3</td> <td>↓1</td> <td>↓1</td> </tr> <tr> <td>TCO2 mmol/L</td> <td>↑3</td> <td>↓6</td> <td>↓3</td> <td>↓12</td> </tr> </tbody> </table>	Dose (mg/kg/dose)	0.1		0.5		M	F	M	F	AST IU/L	↓44	↓2	↓31	↓25	ALT IU/L	↓62	↓22	↓54	↓38	ALP IU/L	↑42	↑40	↑81	↑46	GGT IU/L	↓20	↓10	↓22	↓16	CRP mg/L	↓47	↓22	↑1249	↑67	ALB\GLB RATIO	0	↓9	↓11	↑6	BUN mg/dL	↑16	↑9	↑8	↑1	NA mmol/L	↓2	↑1	↓2	↑1	K mmol/L	↓6	↑1	↓0	↑7	CL mmol/L	↑1	↓3	↓1	↓1	TCO2 mmol/L	↑3	↓6	↓3	↓12
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Urinalysis	Unremarkable																																																																
Immunotoxicology	B-Cell Activating Factor (BAFF) Analysis: Serum concentrations of BAFF were elevated (> 5 times) in animals administered 0.2/0.8/0.1 and 0.2/0.8/0.5 mg/kg when compared with pre-treatment and control animal results. Highest concentrations were observed post-dose on Study Days 8 and 29 and appeared less elevated as the study progressed. Cytokines: Mild to marked transient increases in serum concentrations of cytokines including IFNγ, TNFα, IL-17A, IL-2, MCP-1, IL-5, IL-6, MIP-1β, IL-10 and CXCL8/IL-8 were observed after the first dose (0.2 mg/kg), peaking at 2 to 6 hours. Minimal to mild increases or no changes were present following the second dose (0.8 mg/kg) on Study Day 2 or subsequent doses.																																																																

Immunophenotyping	Changes in lymphocyte populations were measured in the blood, spleen, and lymph node. Sustained B-cell depletion in the blood and lymphoid tissues, T-cell activation, and associated transient decreases in circulating T-cells and natural killer cells were observed at 0.1 and 0.5 mg/kg dose levels.
Gross Pathology	Macroscopic findings included red cecum (1 animal at 0.5 mg/kg), small spleen (2 animals at 0.5 mg/kg), small adrenal (1 animal each at 0.2 and 0.5 mg/kg), and dark pancreas (2 animals at 0.5 mg/kg).
Organ Weights	Reduced adrenal weights in males at 0.1 and 0.5 mg/kg and spleen weights in females at 0.5 mg/kg were observed.

Histopathology findings Day 183 (Terminal Sacrifice)							
Weekly Dose (mg/kg)	0 (Control)		0.1		0.5		
Number of Animals:	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	
Brain-Vascular/perivascular inflammatory cell infiltration	Minimal	0	0	0	1	3	3
Liver-Vascular/perivascular inflammatory cell infiltration	Minimal	0	0	0	1	1	0
Kidney Inflammatory cell infiltration	Minimal	1	2	2	3	2	1
	Slight	0	0	1	0	1	0
	Moderate	0	1	0	0	1	0
Kidney Basophilia, tubular	Minimal	0	1	1	1	0	0
	Slight	0	0	0	0	1	0
Vascular/perivascular inflammatory cell infiltration	Minimal	0	0	0	1	0	0
Stomach-Vascular/perivascular inflammatory cell infiltration	Minimal	0	0	0	0	1	0
Duodenum-Vascular/perivascular inflammatory cell infiltration	Minimal	0	0	0	0	1	0
Jejunum-Vascular/perivascular inflammatory cell infiltration	Minimal	0	0	0	0	1	0
Rectum-Vascular/perivascular inflammatory cell infiltration	Minimal	0	0	0	0	1	0

Cecum-Vascular/perivascular inflammatory cell infiltration	Minimal	0	0	0	0	1	0
Heart-Vascular/perivascular inflammatory cell infiltration	Minimal	0	0	0	0	1	0
Gall bladder-Vascular/perivascular inflammatory cell infiltration	Minimal	0	0	0	0	1	0
Spleen							
Germinal centers, decreased	Marked	0	0	1	1	1	1
	Severe	0	0	0	2	3	2
Follicles, decreased	Marked	0	0	1	3	1	1
	Severe	0	0	0	0	3	1
Germinal centers, increased	Slight	0	0	2	0	0	0
Follicles, increased	Slight	0	0	1	0	0	0
	Moderate	0	0	1	0	0	0
Mesenteric Lymph Node							
Germinal centers, cortex, decreased	Moderate	0	0	1	0	1	1
	Marked	0	0	0	1	1	1
	Severe	0	0	0	2	2	1
Follicles, cortex, decreased	Minimal	0	0	0	0	0	1
	Moderate	0	0	1	0	1	0
	Marked	0	0	0	3	1	1
	Severe	0	0	0	0	2	1
Germinal centers, cortex, increased	Slight	0	0	1	0	0	0
Follicles, cortex, increased	Slight	0	0	1	0	0	0
Mandibular Lymph Node							
Follicles, cortex, decreased	Minimal	0	0	0	0	0	1
	Slight	0	0	0	2	0	1
	Moderate	0	0	1	0	0	0
	Marked	0	0	0	0	3	1
	Severe	0	0	0	0	1	0
Germinal centers, cortex, decreased	Slight	0	0	0	2	0	0
	Moderate	0	0	1	0	0	1

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	Marked	0	0	0	0	1	0
	Severe	0	0	0	0	3	2
Germinal centers, cortex, increased							
	Minimal	0	0	1	0	0	0
	Slight	0	0	1	0	0	0
Follicles, cortex, increased							
	Minimal	0	0	1	0	0	0
	Slight	0	0	1	0	0	0
Axillary Lymph Node							
Germinal centers, cortex, decreased							
	Slight	0	0	0	0	0	1
	Moderate	0	0	0	1	0	0
	Marked	0	0	1	2	4	1
	Severe	0	0	0	0	0	1
Follicles, cortex, decreased							
	Moderate	0	0	0	1	0	0
	Marked	0	0	1	2	4	1
	Severe	0	0	0	0	0	1
Germinal centers, cortex, increased							
	Minimal	0	0	1	0	0	0
Follicles, cortex, increased							
	Minimal	0	0	1	0	0	0
Popliteal Lymph Node							
Germinal centers, cortex, decreased							
	Slight	0	0	1	0	0	0
	Marked	0	0	0	2	4	1
	Severe	0	0	0	1	0	1
Follicles, cortex, decreased							
	Marked	0	0	0	3	4	1
	Severe	0	0	0	0	0	1
Germinal centers, cortex, increased							
	Minimal	0	0	1	0	0	0
	Slight	0	0	1	0	0	0
Follicles, cortex, increased							
	Minimal	0	0	1	0	0	0
	Slight	0	0	1	0	0	0
Sciatic Nerve-Eosinophilic infiltration							
	Minimal	0	0	0	1	0	1
Adrenal-Vacuolation, cortex, decreased							
	Minimal	0	0	2	1	2	1
Pancreas-Exocrine cell granulation, decreased							
	Minimal	0	0	1	1	2	2
Ileum-Gut associated lymphoid tissue (GALT), decreased							
	Slight	0	0	1	0	0	0

	Moderate	0	0	0	3	4	2
	Femur + marrow-Cellularity, marrow, increased						
	Minimal	0	0	0	1	0	1
	Slight	0	0	0	2	1	0
	Moderate	0	0	0	0	2	0
	Sternum + marrow-Cellularity, marrow, increased						
	Minimal	0	0	0	3	1	1
Toxicokinetics	The toxicokinetics information was presented and discussed in the pharmacokinetics section.						
Anti-Drug Antibodies	ADAs were detected in 5 out of 8 Group 2 (0.1 mg/kg) animals and in 4 out of 8 Group 3 (0.5 mg/kg) animals administered BTCT4465A. Exposure appeared to be lower in animals that were ADA-positive in Group 2 (0.1 mg/kg), but exposure was not consistently impacted in ADA-positive animals in Group 3 (0.5 mg/kg).						

General toxicology; additional studies

Study title/number: A Single Dose Toxicokinetic, Pharmacodynamic, and Toxicology Study of BTCT4465A via Intravenous Infusion or Subcutaneous Administration in Cynomolgus Monkeys with a 7-week Recovery Period/14-1246

A GLP-compliant single-dose toxicology study of BTCT4465A in monkeys was conducted with IV infusion or subcutaneous (SC) injection once followed by a 7-week recovery period. Monkeys were dosed with BTCT4465A at 0 (IV/SC), 0.01 (IV), 0.1(IV), or 1 mg/kg (IV/SC). Necropsy procedures were performed on Day 8 (terminal; 3M/3F), Day 22 (first recovery necropsy; 2 M/2F per dose except 1M/2F at 1 mg/kg IV) and Day 57 (second recovery necropsy; 2M/2F each control and HD). The Day 22 necropsy was performed on animals instrumented with a telemetry device for collection of cardiovascular and body temperature data. Clinical signs included emesis, decreased activity/hunched posture and mucoid feces on Day 1 post-dose at 1 mg/kg IV.

The cardiovascular and body temperature safety assessment on telemetered animals revealed transient and dose-dependent increases in heart rate and body temperature at 0.1 mg/kg IV and 1 mg/kg (IV or SC) and decreased blood pressure at 1 mg/kg IV on Day 1. Heart rate increases (RR interval decreases) at these dose levels had correlating decreases in PR and QT intervals (1 mg/kg IV and SC, only), but there was no effect on QTca. Cardiovascular findings resolved by Day 7.

Changes in hematology parameters at ≥ 0.01 mg/kg included decreased white blood cells associated with decreased lymphocytes and decreased monocytes and basophils. Changes in coagulation parameters included increased fibrinogen at ≥ 0.1 mg/kg and prolongation of the

prothrombin time and activated partial thromboplastin time at 1 mg/kg. Changes in clinical chemistry parameters, included increased CRP at ≥ 0.01 mg/kg, increased bilirubin and decreased cholesterol and albumin (with associated decreases in total protein, albumin to globulin ratio and calcium) at ≥ 0.1 mg/kg, and increased urea nitrogen and creatinine, and decreased sodium and chloride at 1 mg/kg. Clinical pathology changes tended to recover by Day 8 through Day 22 or Day 57.

BTCT4465A-related microscopic findings were observed in tissues including the lymphoid system (spleen, thymus, lymph nodes and/or gut associated lymphoid tissue [GALT]), liver, heart, and central nervous system (CNS) at ≥ 0.01 mg/kg IV and 1 mg/kg SC. In the spleen, increased lymphocyte cellularity within the periarteriolar sheaths (PALS) and increased phagocytic cells within the red pulp correlated with increased spleen weights. In the thymus, decreased lymphocyte cellularity was noted that correlated with decreased thymus weights. In GALT, decreased number and size of follicular germinal centers, and decreased number and size of lymphoid follicles in the lymph nodes were observed at 1 mg/kg IV and SC. Findings in the liver included with hypertrophy/hyperplasia of sinusoidal Kupffer cells at ≥ 0.1 mg/kg IV. These findings were noted during the recovery necropsies with lower incidence on Day 22 in the spleen, lymph nodes and liver and limited to 0.1 and 1 mg/kg (IV and SC), and on Day 57 in the spleen and lymph nodes at 1 mg/kg IV. In CNS tissues, perivascular (generally) infiltrates of eosinophils with associated microgliosis were observed in the brain and/or spinal cord and/or spinal nerve roots at 1 mg/kg IV and SC. These changes were not associated with clinical observations. No CNS findings were noted on Days 22 or 57.

BTCT4465A induced pharmacodynamic effects of rapid and sustained B-cell depletion in blood and lymphoid tissues, increases in serum BAFF levels, dose-dependent reductions in T lymphocyte populations (total, T-helper, and T-cytotoxic) and NK cells, T-cell activation associated T-cell redistribution (total, Th and Tc lymphocytes), and cytokine/chemokine increases (IL-1RA, IL-2, IL-5, IL-6, IL-13, IL-17, G-CSF, TNF- α , and IFN- γ) in all groups (≥ 0.01 mg/kg) at the 2 hours post-dose time point. These changes trended toward recovery by Day 8 through Day 57.

5.5.2. Genetic Toxicology

The Applicant's Position:

In accordance with the current ICH guidance (ICH S6(R1) 2011), genotoxicity studies have not been conducted with mosunetuzumab because the potential of biotechnology products, in particular high molecular weight monoclonal antibodies, to elicit DNA damage in somatic or germ cells via electrophilic reactions is unlikely.

The FDA's Assessment:

The FDA concurs with the Applicant.

5.5.3. Carcinogenicity

The Applicant's Position:

No carcinogenicity studies have been conducted with mosunetuzumab and are not planned for the intended oncology indication, as per Guidance for Industry S6R1.

The FDA's Assessment:

The FDA concurs with the Applicant.

5.5.4. Reproductive and Developmental Toxicology

The Applicant's Position:

Male and female reproductive assessments were conducted as a part of the 26-week chronic toxicity study in sexually mature cynomolgus monkeys (Study 16-1815). Evaluation included organ weights, and macroscopic and microscopic evaluation of male and female reproductive organs (including qualitative spermatogenesis progression for males and general phases of menstrual cycles for females). There were no mosunetuzumab-related effects identified in the male or female reproductive assessment.

A weight of evidence (WOE)-based risk assessment for potential developmental effects was conducted. Based on low placental transfer of antibodies during the first trimester, the mechanism of action and available data of mosunetuzumab, and the data from other approved anti-CD20 antibodies developed by the Applicant (e.g., rituximab [Rituxan® USPI], obinutuzumab [Gazyva® USPI], ocrelizumab [Ocrevus® USPI]), the risk for teratogenicity is low. Studies with mosunetuzumab in non-pregnant animals have demonstrated that prolonged B-cell depletion in the dam can lead to increased risk of opportunistic infection, which may result in fetal loss, as shown with ocrelizumab [Ocrevus® USPI]). Transient CRS associated with mosunetuzumab administration may also be harmful to pregnancy.

A briefing book, including the WOE-based risk assessment and a request to waive a non-human primate embryo-fetal and prenatal/postnatal development study, was submitted to the FDA (dated 3 April 2018; Reference ID: 4277993). In a written communication from the FDA dated 14 June 2018, the Agency agreed to the waiver request. During the End-of-Phase-I Type B meeting on 18 March, 2020, the Agency recommended to remove the list of products for which the Sponsor does not have the right-to-reference, and considered other components used in the WOE-based risk assessment reasonable for submission. The updated risk assessment document is included in Module 4 (Assessment of Developmental Effects).

The FDA's Assessment:

To address the potential effects of mosunetuzumab on embryo-fetal development, the Applicant submitted an assessment for reproductive and developmental risk using a weight-of-evidence (WOE) approach and with the recommendation in the ICH S6(R1) guideline. The relevant information is summarized below and supports that the main reproductive risk for mosunetuzumab is B-cell depletion in neonates and includes information from other products that the Applicant (Genentech, Inc.) owns or have the right of reference to.

The WOE risk assessment includes the following information; references cited were provided by the Applicant:

1. Maternal and/or neonatal toxicities have been observed with the FDA approved anti-CD20 antibodies, including rituximab, obinutuzumab and ocrelizumab.
  - a. Obinutuzumab crosses the blood-placental barrier and it is secreted in the milk of pregnant monkeys. There was complete depletion of B lymphocytes in infants, and higher prenatal loss in treatment groups compared to controls but within the range of historical control data.
2. Based on its mechanism of action and pharmacodynamic effects seen in animals, mosunetuzumab may cause depletion of B-cells and impair the immune response after birth due to fetal exposure to mosunetuzumab. Impaired immune response may likely be associated with opportunistic infections. Secondary infections due to B-cell depletion and associated mortality/early euthanasia were observed in cynomolgus monkeys following prolonged treatment with mosunetuzumab in the 26-week toxicity study.
3. Mosunetuzumab-related toxicities including vomiting, diarrhea, hypoactivity/hunched posture, hypotension, tachycardia, fever, acute phase protein reactions, leukocyte margination, in cynomolgus monkeys may pose a risk to the maintenance of pregnancy.

5.5.5. Other Toxicology Studies

The Applicant's Position:

An in vitro assay was performed in human PBMCs to assess cytokine release and T cell activation induced by mosunetuzumab. The results (EC₂₀ values) were used to inform the starting dose in the first in human study. Additionally, the same assay was used to evaluate the potential impact of (b) (4) a product-related variant that may be formed at low levels in the production of mosunetuzumab, on the activities of mosunetuzumab. The results were used to support the proposed control strategy (b) (4) for the commercial material. A tissue cross-reactivity study could not be conducted due to poor analytical sensitivity and specificity of mosunetuzumab as an IHC reagent.

The FDA's Assessment:

BTCT4465A induces B-cell killing, T-cell activation, and cytokine production in human PBMCs from healthy donors in a concentration-dependent manner (Study: 14-3526). Low levels of (b) (4) (b) (4) spiked in BTCT4465A had minimal impact on BTCT4456A-induced, target cell-dependent T-cell activation and cytokine release in whole PBMCs, and did not appear to inhibit BTCT4456A-induced B-cell killing.

The Agency concurs with the Applicant that BTCT4465A exhibited both poor analytical sensitivity and specificity as an IHC reagent and thus, tissue cross-reactivity in human and cynomolgus monkey tissue panels was not determined (Study: 14-2073).

X

X

Non-Clinical Reviewer

Non-Clinical Team Leader

Simon Williams, PhD

Brenda Gehrke, PhD

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

Mosunetuzumab is an anti-CD20/CD3 T-cell-dependent bispecific (TDB) antibody targeting both CD3 (on the surface of T cells) and CD20 (on the surface of B cells). The Applicant is seeking approval of mosunetuzumab for the treatment of patients with relapsed or refractory (R/R) follicular lymphoma (FL) who have received at least two prior systemic therapies. The proposed dosing regimen is shown in Table 9 below (hereafter referred to as 1/2/60/30 mg). The proposed treatment duration is 8 cycles initially; if patients received PR or SD, continue treatment for up to 1 year (17 cycles).

Table 9: Recommended Dose and Schedule (21-Day Treatment Cycles)

Day of Treatment	Dose

60

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

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.

Cycle 1	Day 1	1 mg
	Day 8	2 mg
	Day 15	60 mg
Cycle 2	Day 1	60 mg
Cycles 3+	Day 1	30 mg

The primary efficacy and safety evidence supporting the proposed dosage regimen results from the pivotal B11 expansion cohort in Study GO29781, an ongoing first-in-human, multicenter, open-label, Phase I/II dose escalation and expansion study demonstrating an objective response rate (ORR) of 80% and a complete response rate (CR) of 60%, as well as an overall acceptable safety profile.

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

Recommendations

The Office of Clinical Pharmacology has reviewed the information submitted in BLA761263. This BLA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below in Table 10.

Table 10: Key Clinical Pharmacology Review Issues and Recommendations by FDA

Review Issue	Recommendations and Comments
Pivotal and Supportive evidence of effectiveness	The primary evidence of effectiveness comes from the pivotal B11 FL RP2D cohort in study GO29781. The proposed dosage regimen (1/2/60/30 mg) is supported by an ORR of 80% and CR of 60% in patients with relapsed or refractory FL.
General dosing instructions	The proposed dosage regimen (1/2/60/30 mg) is selected with the following rationale: • The step-up doses (1 mg and 2 mg) are clinically active doses that help mitigate CRS risk in later cycles. • No exposure response trends were observed for safety endpoints except for Grade ≥ 2 CRS, at the proposed dose of 1/2/60/30 mg, the observed Grade ≥ 2 CRS and the Exposure-Response model predicted that the probability for Grade ≥ 2 CRS over the first two cycles is relatively low. • There were positive exposure response relationships for

	efficacy endpoints, such as CR, ORR and PFS. • Tumor size continued to decrease after shifting from loading dose (60 mg) to base dose (30 mg). The treatment duration is supported by observed efficacy data showing that: • Majority of CR (50 out of 54 cases) were achieved within 8 cycles of treatment. • Patients who received PR or SD after 8 cycles of treatment benefited (deepened response from PR to CR, or received late PR/CR) from continued treatment beyond 8 cycles.
Dosage recommendations for restarting therapy after dose delay	The proposed dosage recommendation for restarting therapy after dose delay is to mitigate CRS risk and is supported by: • Observed clinical data showing that CRS was mitigated. • PopPK simulations showing that mosunetuzumab concentrations were maintained approximately at or above concentration levels achieved with 2 mg prior to administration of the 60 mg loading dose, consistent with the proposed dosing regimen (1/2/60/30 mg) and the associated CRS mitigation strategy.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dosage adjustment is needed in patient subgroups. The effect of severe renal impairment to end-stage renal disease (CLcr < 30 mL/min) and moderate to severe hepatic impairment (total bilirubin > 3 to 10x ULN, any AST) is unknown.
Drug-drug interactions	Mosunetuzumab administration resulted in transient release of cytokines, which may suppress CYP450 enzymes and cause drug-drug interactions. Increased exposure of CYP450 substrates is more likely to occur after the first dose of mosunetuzumab on Cycle 1 Day 1 and up to 14 days after the second loading dose on Cycle 2 Day 1 and during and after CRS. Monitor for toxicity or concentrations 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.
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:

The evaluation of the clinical pharmacology of mosunetuzumab to support this BLA application was based on clinical data from the IV monotherapy cohorts of Study GO29781, including the fixed dosing group (Group A; 0.05-2.8 mg IV q3w) and the Cycle 1 step-up dosing group (Group B; 0.4/1/2.8-1/2/60 mg IV q3w) in patients with R/R NHL.

- Characterization of mosunetuzumab clinical serum PK, including assessment of distribution and elimination characteristics, dose linearity characterization, source of PK variability, and individual-level covariates for mosunetuzumab in patients with NHL, are provided.
- The integrated E-R analyses, combined with the observed clinical efficacy and safety data, provide strong support for the RP2D/intended registration dose and schedule for mosunetuzumab in patients with R/R FL.

See Section 6.3.1 for details.

The Applicant’s Position:

Collectively, the PK and E-R analyses support the intended registration dose and schedule for mosunetuzumab in patients with R/R FL and support a positive benefit-risk profile.

The FDA’s Assessment:

The mosunetuzumab clinical pharmacology program included data from two groups (Group A and Group B) in study GO29781 (Table 11, Table 12).

Table 11: Group A Dose Escalation, Q3W fixed dosing, Mosunetuzumab IV Monotherapy in Patients with R/R B-Cell NHL (N=33)

Cohort	Number of Patients	Dose (D1 of each 21-day cycle)
A1	N=1	0.05 mg
A2	N=1	0.2 mg
A3	N=3	0.4 mg
A4	N=4	0.8 mg
A5	N=6	1.6 mg
A6	N=7	1.2 mg
A7	N=3	2.0 mg
A8	N=8	2.8 mg

Table 12: Group B Dose Escalation and Expansion, Step-up dosing, Mosunetuzumab IV Monotherapy in Patients with R/R B-Cell NHL (N=414)

Cohort	Number of Patients	Dose		
		C1D1	C1D8	C1D15
B1	N=6	0.4 mg	1 mg	2.8 mg
B2	N=17	0.8 mg	2 mg	4.2 mg
B3	N=1	1 mg	1 mg	3 mg
B4	N=6	1 mg	2 mg	6 mg
B5	N=29	0.8 mg	2 mg	6 mg
B6	N=5	1 mg	2 mg	9 mg
B7	N=77, including N=46 FL $\geq$ 2 prior therapies	1 mg	2 mg	13.5 mg
B8	N=10	1 mg	2 mg	20 mg
B9	N=25	1 mg	2 mg	27 mg
B10	N=17	1 mg	2 mg	40.5 mg
B11 ^a	N=3, escalation phase N=218, expansion phase ^b	1 mg	2 mg	60 mg

^aDosing regimen in B11 cohort is the intended registration dose and schedule, 1 mg on C1D1, 2 mg on C1D8, 60 mg on C1D15 and C2D1, 30 mg on D1 of subsequent cycles.

^bB11 expansion phase included R/R FL patients (N=90), R/R DLBCL/trFL patients (N=88), R/R MCL patients (N=25), R/R Richter's patients (N=14) and other (N=1).

The results from these groups and cohorts generally provide adequate characterization of mosunetuzumab PK properties.

Absorption: The drug product is administered intravenously; no food effect is expected.

Distribution: The mean (CV%) volume of distribution of mosunetuzumab-axgb is 5.49 L (31%).

Elimination: The steady-state mean (CV%) terminal elimination half-life of mosunetuzumab-axgb is 16.1 (17.3%) days. The geometric mean (CV%) clearance at baseline and at steady state are 1.08 L/day (63%) and 0.584 L/day (18%), respectively.

Dose proportionality: Mosunetuzumab exposures increase in an approximately dose-proportional manner in the dose range studied (0.2–60 mg).

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

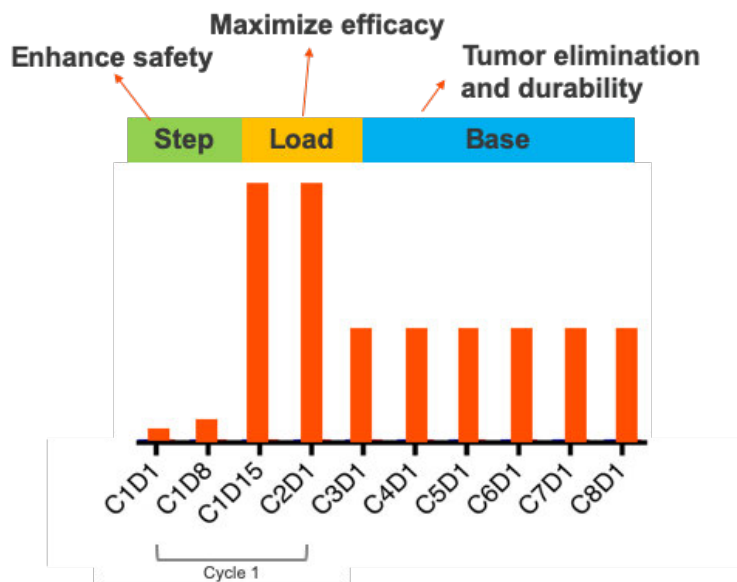
Data:

The intended registration dose and schedule of mosunetuzumab is administered using the Cycle 1 step-up regimen (i.e., 1 mg and 2 mg on Cycle 1 Day 1 and 8, respectively, as the “step doses”, followed by two “loading doses” of 60 mg on Cycle 1 Day 15 and Cycle 2 Day 1, and then maintained at the “base dose” of 30 mg for the remaining Cycles 3–8; treatment continues for 17 cycles [approximately 1 year] if CR is not achieved by Cycle 8), hereafter referred to as 1/2/60/30 mg.

A schematic of the intended registration dose and schedule is shown in Figure 9.

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Figure 9: Applicant – Conceptual Illustration of the Intended Registration Dose and Schedule* for Mosunetuzumab in R/R FL



*With the option to dose up to 17 cycles if complete response is not achieved by Cycle 8.

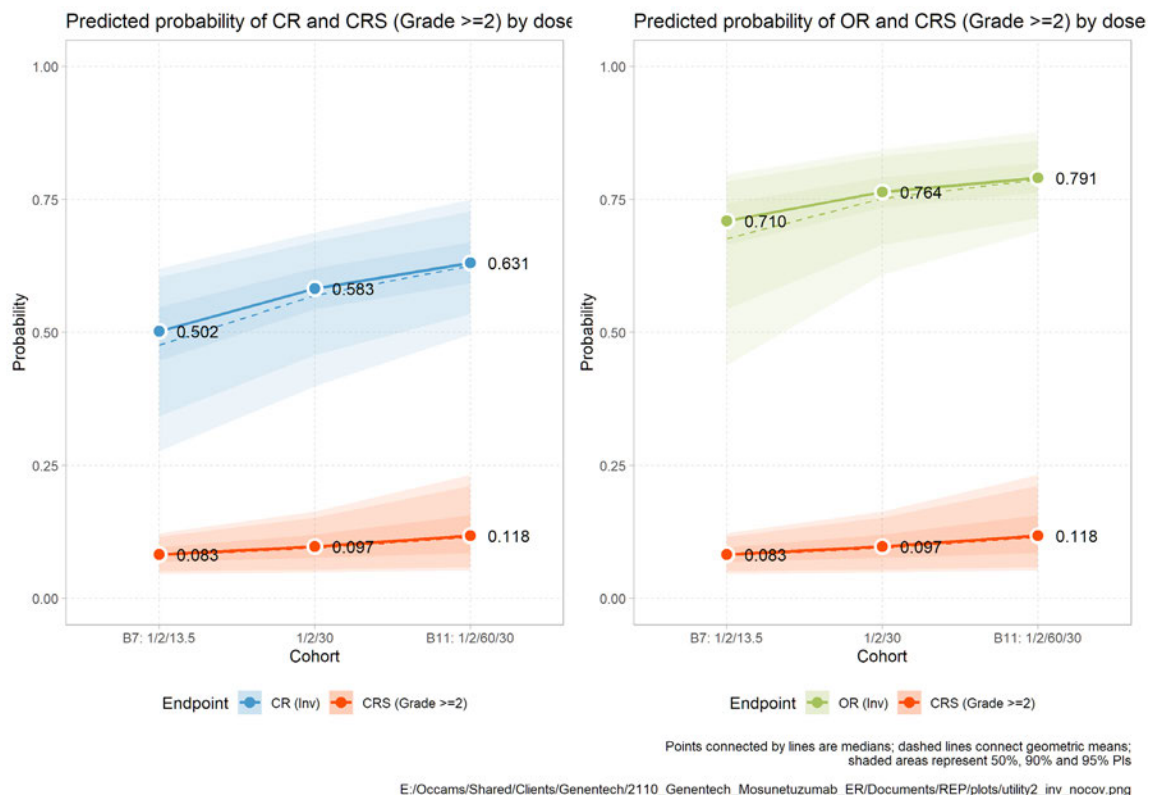
The rationale for the intended registration dose and schedule of 1/2/60/30 mg is summarized below:

- “Step Doses” of 1 mg and 2 mg on Cycle 1 Day 1 and 8 are pharmacodynamically and clinically active and well tolerated doses shown to mitigate the maximum receptor occupancy (RO_{max})-dependency of the acute CRS.
- “Loading Doses” of 60 mg on Cycle 1 Day 15 and Cycle 2 Day 1 are predicted to achieve maximal clinical response (i.e., CRR and ORR) by exposure-response analyses in the proposed patient population.
- “Base Doses” of 30 mg on Day 1 in each cycle in Cycles 3 and beyond are expected to achieve maximal and durable clinical response following the initial tumor debulking after the first 2 cycles based on the totality of data.

The model-predictions based on integrated ER analyses of efficacy and safety for Study GO29781 including patients with R/R FL indicate a broad therapeutic window of mosunetuzumab with minimal/low exposure-dependency for the overall safety risk using the Cycle 1 step-up dosing regimen. The integrated ER analyses, combined with the observed clinical efficacy and safety data, provide strong support for the RP2D/intended registration dose and schedule of 1/2/60/30 mg to achieve a favorable clinical benefit-risk profile in patients with R/R FL, with high clinical response rate (model-predicted probability for CRR and ORR of approximately 63% and 79%, respectively) and low (<12%) probability of a patient experiencing

Grade ≥ 2 CRS that is manageable and primarily confined to Cycle 1 (Figure 10). Overall occurrence of Grade ≥ 3 CRS observed at the clinical dose was low ($<3\%$) in patients in the B11 RP2D cohort. The RP2D/intended registration dose and schedule of 1/2/60/30 mg is expected to achieve PK exposures that maximize clinical efficacy for the majority of the patient population with manageable safety profiles.

Figure 10: Applicant – Integrated Understanding of Mosunetuzumab Clinical Dose-Response Relationships Predicted by Modeling for CR, OR and Grade ≥ 2 CRS



CR= complete response; CRS= cytokine release syndrome; Inv= investigator; OR= objective response.

Note: base models (i.e., without covariates) used for predication.

Filled circles represent the model-predicted probability of response (blue for CR, green for OR, red for of Grade ≥ 2 CRS) at selective dose levels; Points connected by solid lines are medians; dashed lines connect geometric means; shaded areas represent 50%, 90%, and 95% confidence intervals.

For the 1/2/60/30 mg dose regimen, the modelling predicts 1) a median CRR of 63.1% (95% prediction interval = 49.7–75.0%), 2) a median ORR of 79.1% (69.1–87.7%), and 3) a median Grade ≥ 2 CRS rate of 11.8% (5.27–23.2%). For the 1/2/30 mg dose regimen, the modelling predicts 1) a median CRR of 58.3% (95% prediction interval = 39.90–68.8%), 2) a median ORR of 76.4% (60.9–84.4%), and 3) a median Grade ≥ 2 CRS rate of 9.75% (4.90–16.3%). For the 1/2/13.5 mg dose regimen, the modelling predicts 1) a median CRR of 50.2% (95% prediction interval = 27.7–62.0%), 2) a median ORR of 71.0% (43.9–79.8%), and 3) a median Grade ≥ 2 CRS rate of 8.27% (4.60–12.3%).

The Applicant's Position:

The totality of data including the pharmacological expectation, the integrated E-R analyses for efficacy and safety, and the observed clinical efficacy and safety, consistently support the rationale for selection of the 1/2/60/30 mg as the intended registration dose and schedule of mosunetuzumab in patients with R/R FL ≥ 2 prior therapies.

The FDA’s Assessment:

FDA agrees with the Applicant’s position that the proposed dosing regimen of mosunetuzumab for the general patient population (1/2/60/30 mg) is acceptable. The dose selection is based on the following rationale:

- Priming dosing regimen
  - 1) The priming doses 1 mg and 2 mg are clinically active doses. In patients with FL who received ≥ 2 prior therapies, the minimum efficacious dose is 1.2 mg, as shown in Table 13.

Table 13: Efficacy (by IRF) by Dose Cohort in FL Patients with ≥ 2 Prior Therapies

Cohort	Dose Level (mg)	Total (N)	CR (N)	OR (N)
A2	0.2	1	0	0
A5	1.6	1	0	1
A6	1.2	2	1	1
A8	2.8	3	1	1
B1	0.4/1/2.8	1	0	0
B2	0.8/2/4.2	3	2	3
B4	1.0/2/6	1	1	1
B5	0.8/2/6	9	4	7
B6	1.0/2/9	2	1	2
B7	1/2/13.5	46	21	31
B11	1/2/60/30	90	54	72

IRF= Independent Review Facility

Source: Reviewer’s analysis based on Exposure Response Efficacy dataset ereff.xpt (ereff_21OCT2021.csv)

- 2) Cytokine release syndrome (CRS) mainly occurred following the first 3 doses in Cycle 1. The majority of CRS occurred after the first loading dose (60 mg) on C1D15, and the CRS risk in subsequent cycles was mitigated. Similar trends were observed in the overall safety population (referred to as B11 RP2D cohort) and patients with FL (referred to as B11 FL RP2D cohort) receiving the proposed mosunetuzumab dosage of 1/2/60/30 mg. See Table 14-Table 15 and Figure 11-Figure 12.

Table 14: FDA CRS Events by Dose Cycles in B11 RP2D Cohort (N=218)

B11 RP2D cohort (Safety Population, n=218)	

CRS by ASTCT	C1D1-D7 (N=218)	C1D8-14 (N=207)	C1D15+ (N=201)	C2 (N=198)	C3+ (N=167)
	Step-Up 1 (1 mg)	Step-Up 2 (2 mg)	Loading Dose 1 (60 mg)	Loading Dose 2 (60 mg)	Base Dose (30 mg)
Any Grade	33 (15.1%)	10 (4.8%)	67 (33.3%)	9 (4.5%)	2 (1.2%)
Grade 1	24 (11.0%)	7 (3.4%)	38 (18.9%)	8 (4.0%)	2 (1.2%)
Grade 2	9 (4.1%)	3 (1.4%)	24 (11.9%)	0	0
Grade 3	0	0	4 (2.0%)	1 (0.5%)	0
Grade 4	0	0	1 (0.5%)	0	0

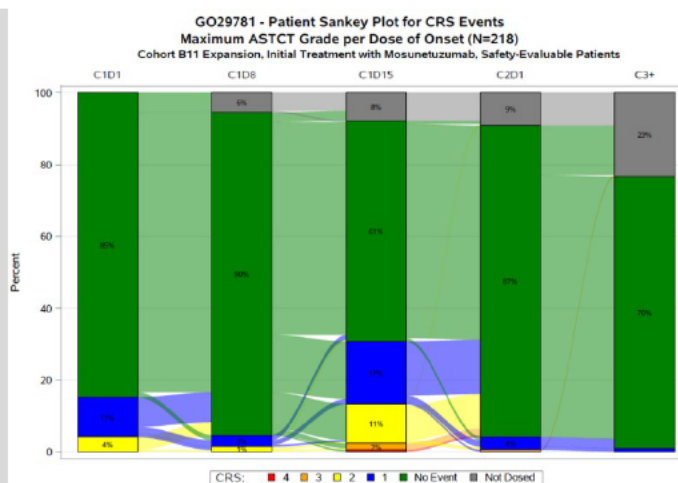
Source: summary of clinical safety support data page 17-18.

Table 15: FDA CRS Events by Dose Cycles in B11 FL RP2D Cohort (N=90)

Safety Population (B11 FL RP2D Cohort, n=90)					
CRS by ASTCT	C1D1-D7 (N=90)	C1D8-14 (N=89)	C1D15+ (N=88)	C2 (N=87)	C3+ (N=83)
	Step-Up 1 (1 mg)	Step-Up 2 (2 mg)	Loading Dose 1 (60 mg)	Loading Dose 2 (60 mg)	Base Dose (30 mg)
Any Grade	21 (23.3%)	5 (5.6%)	32 (36.4%)	9 (10.3%)	2 (2.4%)
Grade 1	17 (18.9%)	4 (4.5%)	18 (20.5%)	8 (9.2%)	2 (2.4%)
Grade 2	4 (4.4%)	1 (1.1%)	13 (14.8%)	0	0
Grade 3	0	0	0	1 (1.1%)	0
Grade 4	0	0	1 (1.1%)	0	0

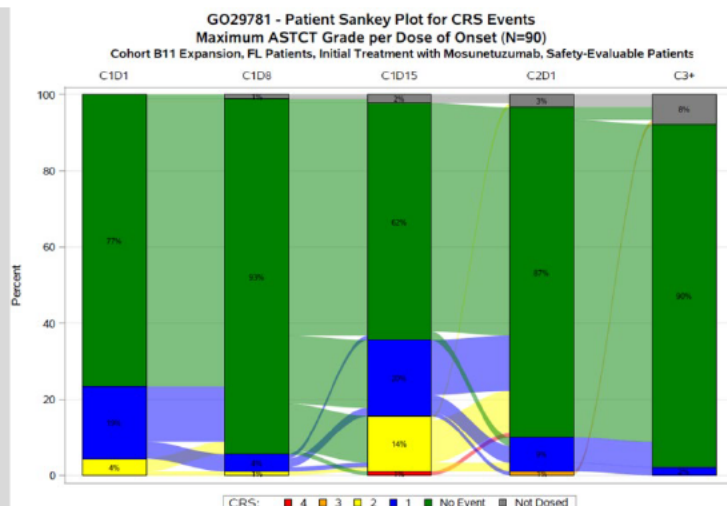
Source: summary of clinical safety support data page 18-19.

Figure 11: Sankey Plot for CRS Event by Dose Cycles in B11 RP2D Cohort (N=218)



Source: Response to FDA information request received on 06/28/2022.

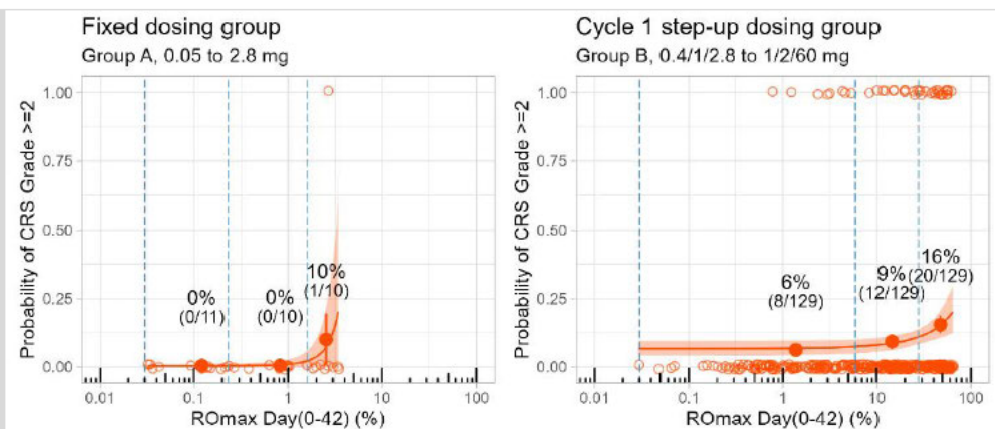
Figure 12: Sankey Plot for CRS Event by Dose Cycles in B11 FL RP2D Cohort (N=90)



Source: Response to FDA information request received on 06/28/2022.

- 3) Positive E-R relationship for Grade ≥ 2 CRS was observed by dosing regimen, as shown in Figure 13. The implementation of step-up dosing strategy in group B allowed continued dose escalation to higher dose levels in Group B to the dose of 1/2/60/30 mg with tolerable safety profile. MTD was not reached.

Figure 13: Exposure-Response for Occurrence of Grade ≥ 2 CRS by Dosing Regimens (by ASTCT Grading)



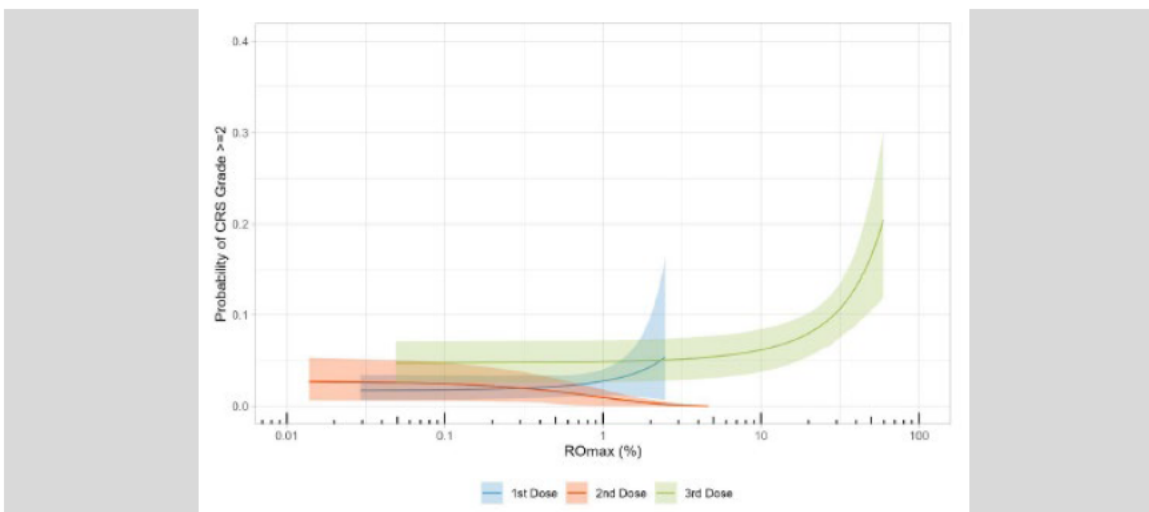
Note: R0max Day(0-42) (%), model-predicted maximum CD20 receptor occupancy (RO%) over 0-42 days post-dose.

Source: Figure 14 in summary of clinical pharmacology.

Additional E-R analyses for Grade ≥ 2 CRS following each dose in Cycle 1 revealed that the E-R relationship changes with repeat dosing, see Figure 14. There was a slight trend following C1D1 dose (1st dose), and no trend following C1D8 dose (2nd dose), after the

third dose on C1D15, the curve remained relatively flat and start to emerge at ROmax% (median 31.1, range: 0.0482 to 64.3) achieved with the proposed dose and schedule of 1/2/60/30 mg.

Figure 14: Overlay of Cycle-1 Exposure-Response Curves Between Dosing Windows for Occurrence of Grade ≥ 2 CRS Following Cycle 1 Step-Up Dosing Regimen (by ASTCT Grading)



Source: Figure 16 in summary of clinical pharmacology.

Of note, exploratory covariates analysis showed that histology and age are significant covariates of occurrence of Grade ≥ 2 CRS; patients with histologies other than DLBCL, transformed follicular lymphoma (trFL), or FL, and patients ≤ 64 years old, are predicted to have a higher probability of Grade > 2 CRS. See details in Section 20.4.5.

- **Loading doses and base doses**

- 1) Positive Exposure-Response relationships were observed for efficacy endpoints, such as CR, OR, and PFS.
  - 2) No Exposure-Response Trends were observed for safety endpoints, higher mosunetuzumab exposure up to the proposed dose of 1/2/60/30 mg did not lead to earlier onset time or higher incidence of any Grade ≥ 1 AEs, any Grade ≥ 3 AEs, Grade ≥ 3 Neutropenia, Grade ≥ 3 Infections and infestations or any Grade Neurological AEs.
  - 3) Tumor size continued to decrease after shifting from loading dose to base dose.
- See details on Exposure-Response relationships in section 20.4.5.

- **Treatment duration**

- 1) Majority of CRs (50 out of 54 cases) were achieved within 8 cycles of treatment based on the IRF assessment. Median duration of CR has not been reached.
- 2) Only 16 out of 90 efficacy evaluable patients received more than 8 cycles of treatment.

Based on the IRF assessment, 5 patients had a late initial response or deepening of a response with additional treatment cycles. These included: 3 patients who had a deepening of response from PR to CR, 1 patient who had an initial PR after 13 cycles of treatment and 1 patient who had an initial CR after 13 cycles of treatment. Despite the small sample size, available clinical data provided supportive evidence that patients who receive PR or SD after 8 cycles of treatment may benefit from continued treatment beyond 8 cycles.

6.2.2.2. Therapeutic Individualization

Data:

The mosunetuzumab population PK (PopPK) analysis dataset included data from 439 PK-evaluable patients from Study G029781 who received mosunetuzumab by IV administration. Body weight, tumor burden, albumin, previous anti-CD20 drug concentrations, and sex were found to be statistically significant covariates on mosunetuzumab PK with marginal impact on drug exposure. None of these covariates resulted in more than 20% change in mosunetuzumab exposure (area under the concentration–time curve from time 0 to 42 days, AUC_{0-42}), when evaluated at extreme values compared to the typical patients. Neither patient age, renal impairment status, hepatic impairment status, drug material used, histology (i.e., FL vs. DLBCL vs. other), nor race (Asian vs. non-Asian) were identified as covariates influencing mosunetuzumab PK. Effects of covariates of special interest (body weight, age, gender, race, hepatic function and renal function, NHL histology) on mosunetuzumab PK were summarized below:

Body Weight

The body weight effect on mosunetuzumab exposure was relatively small compared to the overall inter-individual variability of the population and was not clinically relevant. There does not appear to be an impact of body size on efficacy of mosunetuzumab.

Age

Age had no statistically significant impact on the mosunetuzumab PK parameters. The age effect on mosunetuzumab exposure was relatively small compared to the overall inter-individual variability of the population and was not clinically relevant. There were no differences in safety and efficacy of mosunetuzumab observed by age subgroup.

Gender

The mosunetuzumab AUC_{0-42} for a typical female patient (weighing 78 kg) is approximately 6% higher than a typical male patient and not considered clinically meaningful. There were no differences in safety and efficacy of mosunetuzumab observed by gender subgroup.

Race

Race (Asian vs. non-Asian) had no statistically significant impact on the mosunetuzumab PK

parameters. The race effect on mosunetuzumab exposure was relatively small compared to the overall inter-individual variability of the population and was not clinically relevant. There were no differences in efficacy of mosunetuzumab observed by race subgroup.

Hepatic Impairment

None of the lab values tested (i.e., AST, ALT, total bilirubin) was a statistically significant covariate on mosunetuzumab PK. Hepatic function category had no apparent effect on model predicted mosunetuzumab PK exposure. The limited data indicated that mosunetuzumab exposures in patients with mild hepatic impairment were not meaningfully different compared to those with normal hepatic function. The number of patients with moderate hepatic impairment is limited (n=2) and no patients with severe hepatic impairment have been studied. No dose recommendation can be made for mosunetuzumab in patients with moderate or severe hepatic impairment.

Renal Impairment

CrCL was not a statistically significant covariate on mosunetuzumab PK. Renal function category had no apparent effect on model predicted mosunetuzumab PK exposure. However, the number of patients with severe renal impairment is limited (n=1) and no patients on dialysis have been studied, and a recommended dose for mosunetuzumab has not been determined for these patients.

NHL histology

NHL histology (DLBCL, FL, and others) had no statistically significant impact on the mosunetuzumab PK parameters. Mosunetuzumab PK exposure (AUC_{0-42}) is comparable across NHL histology groups.

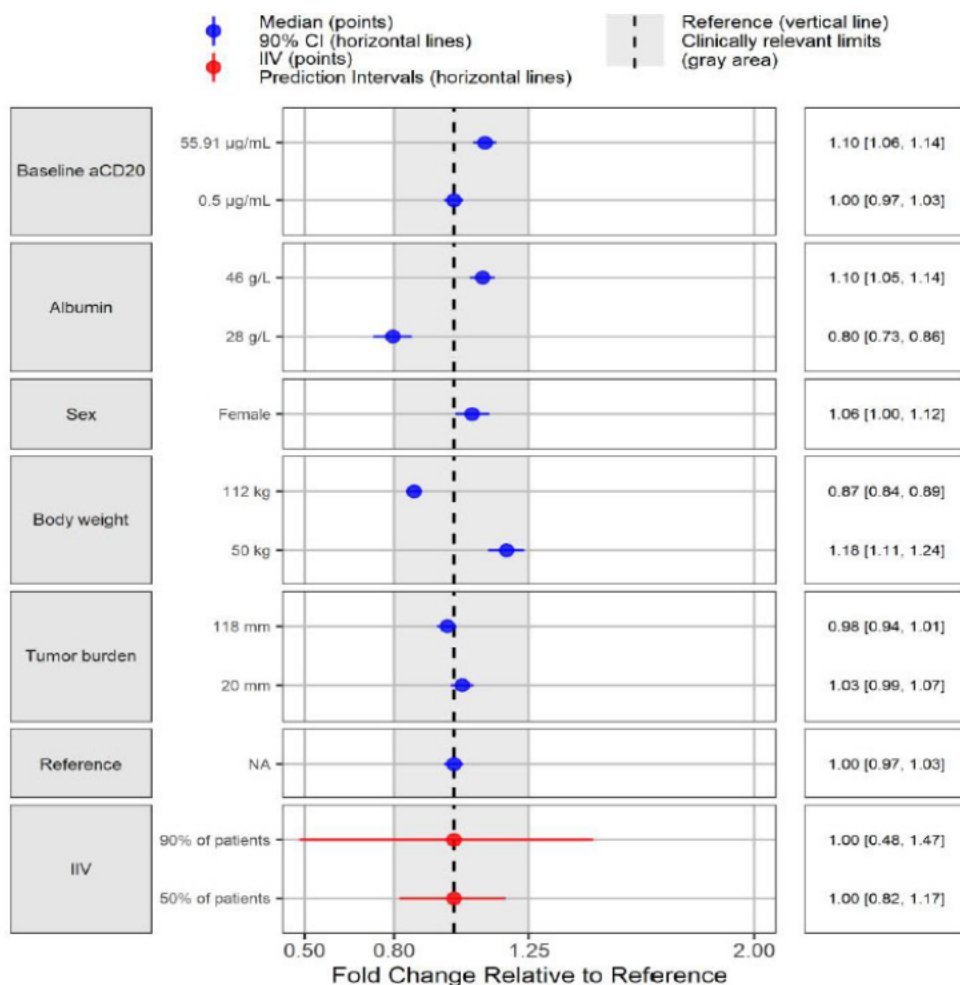
The Applicant's Position:

Given the totality of the data based on results from the mosunetuzumab PopPK analysis, together with subgroup analysis for the efficacy and safety, no clinically meaningful covariate was identified that warrants dose adjustment for mosunetuzumab.

The FDA's Assessment:

The FDA agrees with the Applicant's position. The Applicant's population PK analysis for mosunetuzumab is considered acceptable for the purpose of supporting analyses objectives. Body weight (37.1 to 163 kg), tumor burden (96.0 to 70900 mm²), albumin (19.0 to 480 g/L), baseline residual anti-CD20 drug concentrations, and sex (Female [n = 155, 35.3%] and Male [n = 284, 64.7%]) were found to be statistically significant covariates on mosunetuzumab pharmacokinetics with marginal impact on drug exposure that is not clinically meaningful (Figure 15).

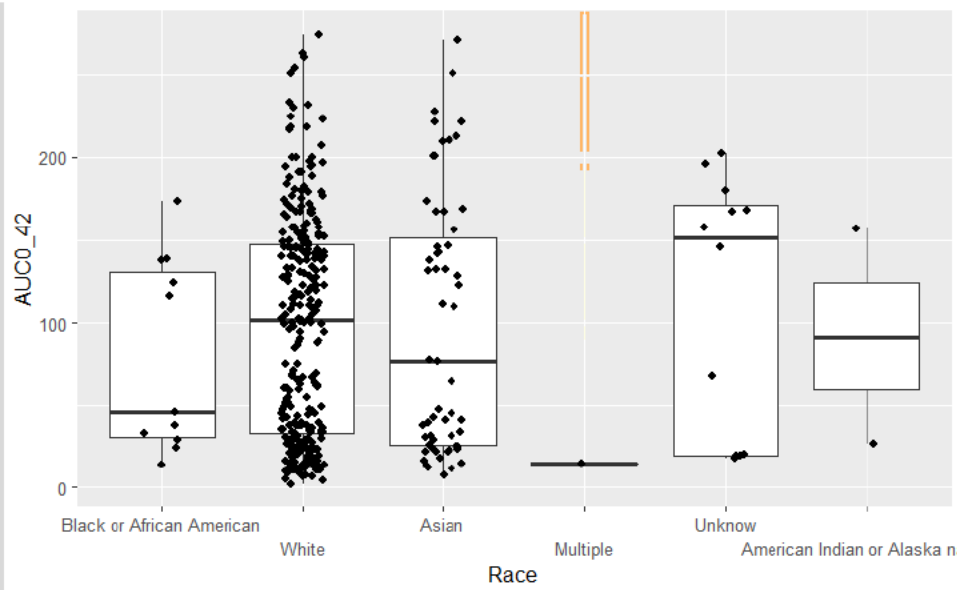
Figure 15: Forest Plots of Covariates Effects on AUC0-42



aCD20= prior anti-CD20 drug treatment concentrations, specifically Rituximab (R) and Obinutuzumab (G) in this popPK analysis; IIV= interindividual variability.

In addition, due to the limited sample size in races other than White and Asian, the Applicant only evaluated the PK difference in Asian vs. non-Asian. A further breakdown in races was shown in Figure 16. However, a comparison of the PK differences among race groups is limited by the sample size. The FDA will issue a PMR to conduct a randomized clinical trial in patients with relapsed or refractory follicular lymphoma to verify the clinical benefit of mosunetuzumab. The trial should include sufficient representation of racial and ethnic minorities to adequately reflect the U.S. patient population and allow for interpretation of the results in these patient populations. The PopPK analysis will be updated when more information becomes available to evaluate the PK differences among race groups.

Figure 16: Comparison of AUC0-42 by Race at 1/2/60/30 mg



Source: Reviewer's analysis.

Refer to Section 20.4.4 for details.

6.2.2.3. Dosage Recommendations for Restarting Therapy after Dose Delay

The FDA's Assessment:

The Applicant proposed the dosage recommendation as listed in Table 16 for restarting therapy after dose delay.

Table 16: Mosunetuzumab Treatment Resumption Guidelines for Dose Delay/Interruption

(b) (4)

The proposed dosage recommendations are based on the same instructions included in the GO29781 Study Protocol and the rationale to step-up dosing following the above-described dose delay scenarios is to mitigate the risk of CRS. While CRS associated with mosunetuzumab treatment occurs predominantly during the first cycle of treatment, the risk may re-emerge

when a patient is off treatment for a prolonged period of time. Therefore, to mitigate an increase of CRS risk in patients with dose delay, a repeat step-up dosing is recommended. In addition, in all scenarios outlined above, the recommendation ensures that the patient receives both 60 mg loading doses followed by the continued 30 mg Q3W doses in subsequent cycles to maintain cumulative on-study exposure similar to that achieved with the nominal proposed dosing regimen of 1/2/60/30 mg, given the established positive benefit-risk profile at this dosage and the positive E-R relationship for efficacy.

The above recommendations are supported by:

- Observed clinical data showing that among the 14 patients who met the above dose delay scenarios, 13 out of 14 followed the recommendations and did not experience CRS after treatment resumption. One patient experienced CRS after treatment resumption, however, this patient was enrolled before the proposed recommendations became effective following a protocol amendment and did not follow the above recommendations.
- Supportive population PK simulations showed that when the dose delay was longer, mosunetuzumab concentration would fall below the drug levels obtained with the step up doses (1 mg and 2 mg) on Cycle 1 Day 1 and Day 8, putting the patient at increased risk of CRS due to potential resensitization to mosunetuzumab treatment; repeat step-up doses as recommended above will maintain mosunetuzumab concentrations at or above concentration levels achieved with 2 mg prior to administration of the higher 60 mg loading dose and 30 mg base dose, consistent with the proposed dosing regimen (1/2/60/30 mg) and the associated CRS mitigation strategy. Population PK Model Simulations showing different dose delay scenarios are shown in Figure 17, Figure 18, Figure 19, Figure 20, Figure 21 and Figure 22 below.

Figure 17: Nominal Intended Registration Dose and Regimen

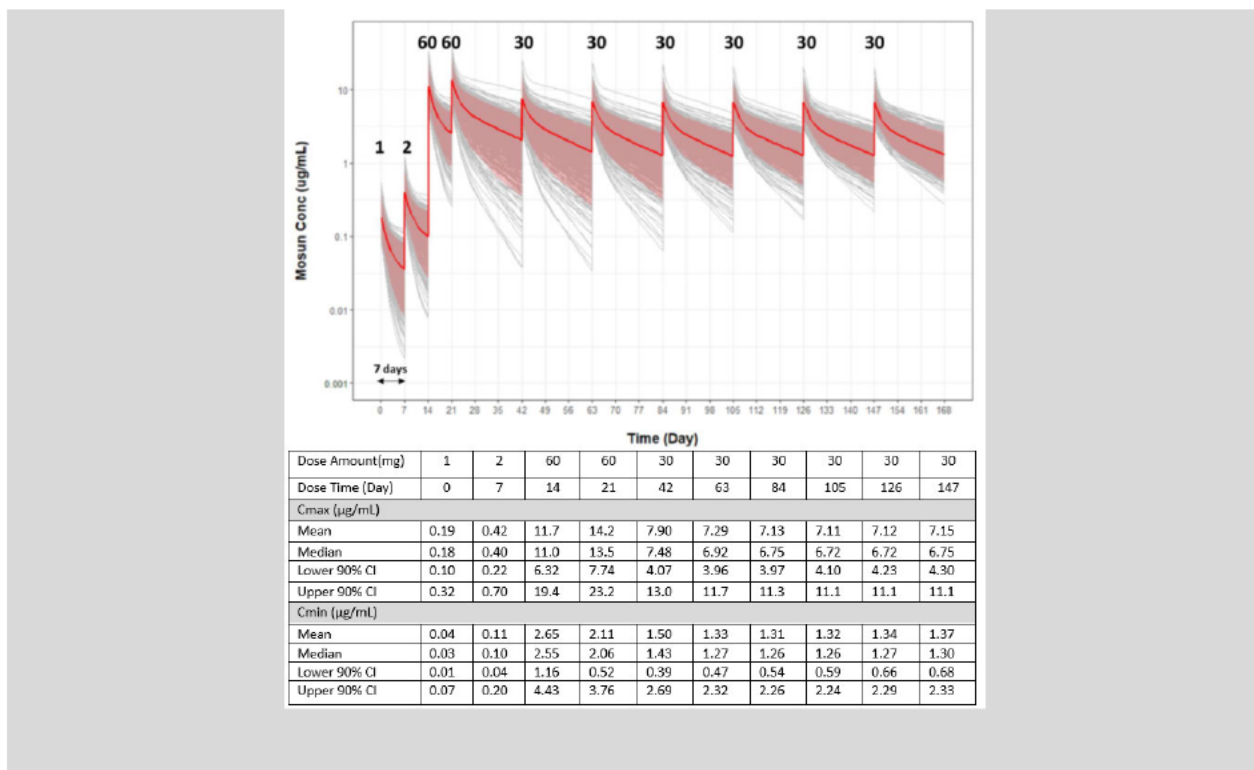


Figure 18: Dose Delay Scenario: Last Dose Administered Step-Up Dose 1, 1 mg; Dose Free Interval 15 Days

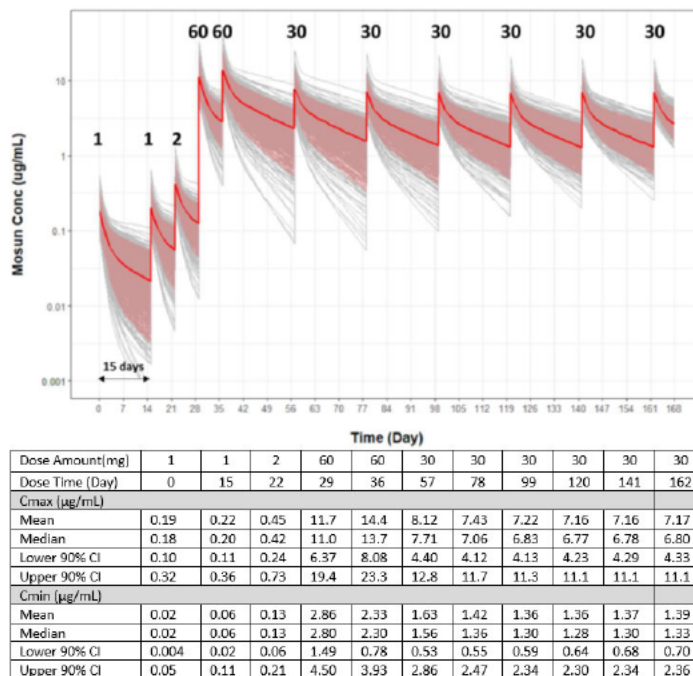


Figure 19: Dose Delay Scenario: Last Dose Administered Step-Up Dose 2, 2 mg; Dose Free Interval 42 Days

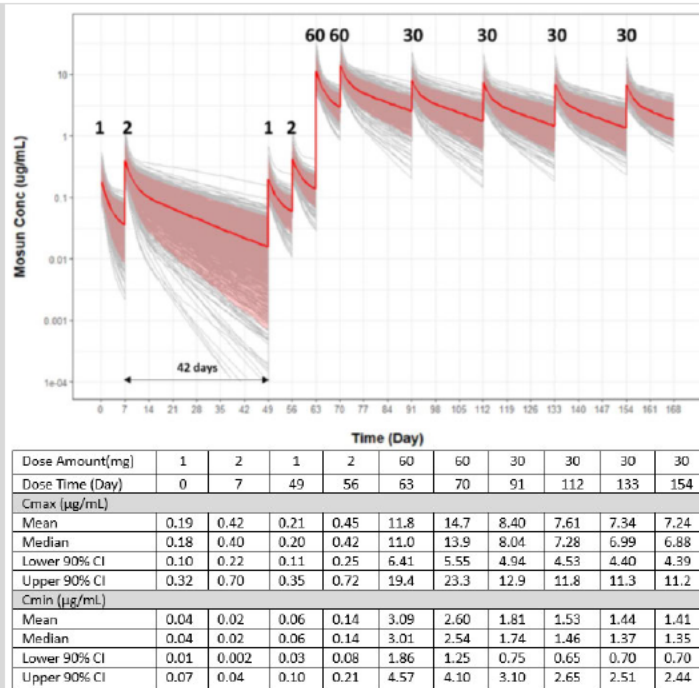


Figure 20: Dose Delay Scenario: Last Dose Administered Loading Dose 1, 60 mg; Dose Free Interval 42 Days

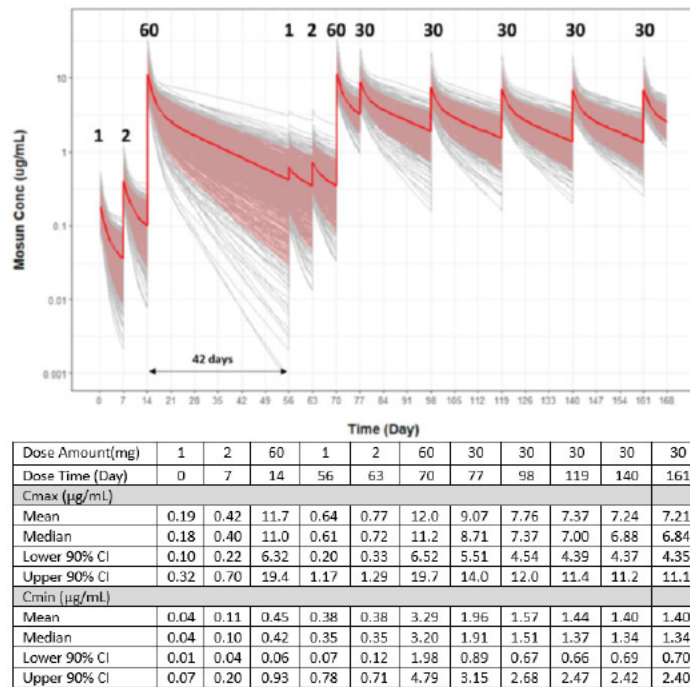


Figure 21: Dose Delay Scenario: Last Dose Administered Loading Dose 2, 60 mg; Dose Free Interval 42 days

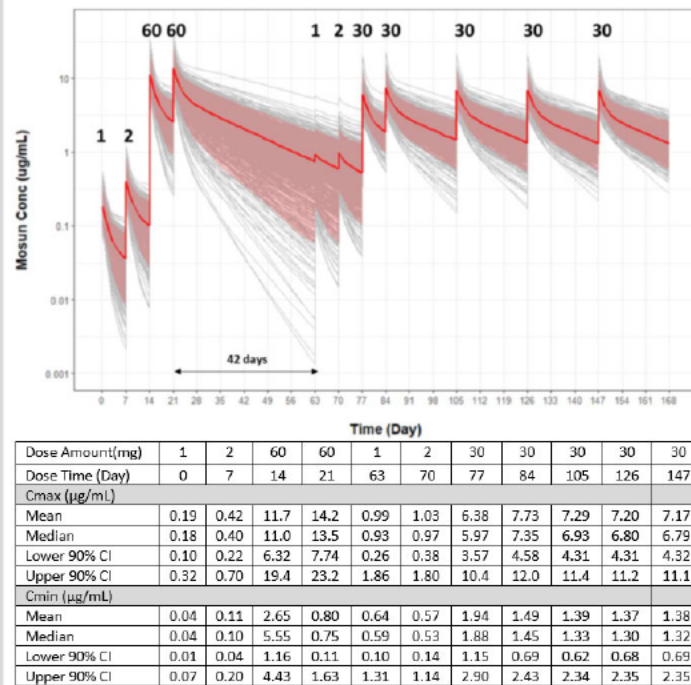
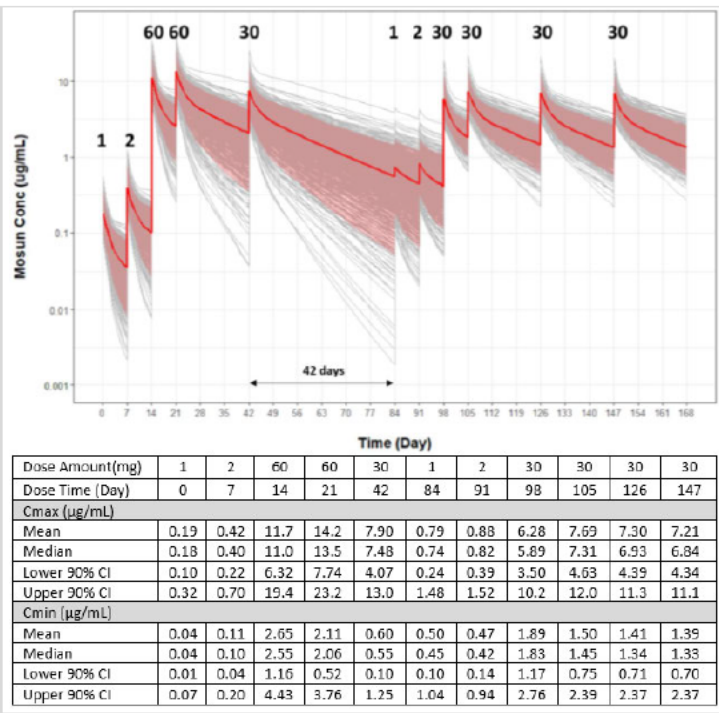


Figure 22: Dose Delay Scenario: Last Dose Administered Treatment Dose, 30 mg; Dose Free Interval 42 days



Source for Figures 17 – 22: Response to FDA information request received on 08/22/2022, 09/09/2022, 09/22/2022 and 10/04/2022.

6.2.2.4. Outstanding Issues

The Applicant’s Position:

Not applicable

The FDA’s Assessment:

No outstanding issues.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:

Summary of Pharmacokinetics

Characterization of clinical serum pharmacokinetics, including assessment of distribution and elimination characteristics, dose linearity characterization, source of pharmacokinetic (PK)

variability, and individual-level covariates for mosunetuzumab in patients with NHL are summarized below.

Key findings:

- Non-compartmental analyses (NCA) indicate that mosunetuzumab serum concentration reaches the maximal level (maximum drug concentration in serum [C_{max}]) at the end of infusion and declines in a bi-exponential fashion, with an apparent half-life ($t_{1/2}$) of approximately 3 to 10 days. The terminal half-life estimate was 16.1 days at steady state based on population pharmacokinetics (popPK) model simulations.
- The serum concentration-time data was well-described by a popPK model with two compartment and time-dependent clearance (CL), which was parameterized as an initial baseline clearance ($CL_{base} \sim 1.08$ L/day) which transitions over time to a steady state clearance ($CL_{ss} \sim 0.584$ L/day) with a transition half-life (HLtrans) of 16.3 days. The CL values are higher than the typical range of clearance of a typical IgG1 antibody, suggesting potential impact of target-mediated drug disposition (TMDD).
- The central volume of distribution (V1) was 5.49 L and peripheral volume of distribution (V2) was 6.17 L. The central volume of distribution of 5.49 L is larger than plasma volume, suggesting the potential impact of binding to immediately accessible targets following IV administration of mosunetuzumab.
- Mosunetuzumab exhibits linear and dose-proportional PK in the dose range studied (0.2 to 60 mg) and in the clinically active dose range (≥ 1.2 mg).
- No clinically meaningful baseline covariates were found for mosunetuzumab pharmacokinetics requiring dose adjustments.
  - Moderate to high inter-individual variability (IIV) was observed for mosunetuzumab key PK parameters (range from 18% to 86%).
  - Significant baseline covariate effects include body weight on CL_{ss} , V1 and V2, albumin on CL_{base} and V1, sex on CL_{ss} and V1, tumor burden on CL_{ss} , and baseline anti-CD20 (aCD20) drug concentrations on CL_{base} . However, none of these covariates resulted in more than 20% change in mosunetuzumab pharmacokinetics exposure (area under the concentration–time curve from time 0 to 42 days, AUC_{0-42}), when evaluated at extreme values compared to the typical patient.

Pharmacokinetics in Special Populations

See 6.2.2.2.

Material Comparability

PopPK modeling indicate similar pharmacokinetics between the v0.1 (used in dose escalation cohorts) and v0.2 materials (used in the dose escalation and expansion cohorts, including pivotal B11 FL RP2D cohort).

Exposure-Response Relationships

The exposure-response (ER) relationships for efficacy were characterized based on investigator (INV)-assessed clinical objective response data from 159 patients with R/R FL who had received more than two prior therapies and treated with IV administration of mosunetuzumab in Study GO29781. The ER relationships for safety were assessed based on 439 PK-evaluable patients with R/R NHL receiving IV administration of mosunetuzumab from Study GO29781. Key findings are summarized below.

ER analyses for biomarker:

- The ER analyses for pharmacodynamic biomarker support evidence of downstream pharmacologic activity and indicate on-study change in IFN- γ to be associated with increasing maximal receptor occupancy (RO_{max}) following Cycle 1 Day 1 dose (“1st Dose”). However, the ER relationships following the subsequent Cycle 1 mosunetuzumab doses remained relatively flat. The shift (i.e., reduction) in ER relationship is consistent with the mitigation of acute cytokine release from T cells upon repeat dosing of mosunetuzumab. The Cycle-1 step doses of 1 mg and 2 mg are pharmacodynamically active and CRS-mitigating. The ER and peripheral IFN- γ data support the use of Cycle 1 step-up dosing regimen to mitigate acute cytokine-driven toxicity of mosunetuzumab.

ER analyses for efficacy:

- The ER analyses indicate that clinical responses (complete response rate [CRR] and objective response rate [ORR]) increase with increasing mosunetuzumab exposure (AUC_{0-42}) and approach a plateau estimated by the model as the maximal clinical responses of 68.6 % and 81.4% for CRR and ORR, respectively.
- ER analysis showed a trend of longer median PFS with increased mosunetuzumab exposure (AUC_{0-42}).
- The duration of response (DOR) (for OR and CR) was similar at the 1/2/60/30 mg dose compared to the 1/2/13.5 mg dose. ER analysis showed a trend of longer DOR (for OR and CR) with increasing exposure (AUC_{0-42}).

ER analyses for safety:

- CRS following step-up dosing of mosunetuzumab is primarily low grade and the occurrence is mostly confined to Cycle 1. CRS events are less frequent at Cycle 2 and onwards.
- ER analyses indicate a positive E-R relationship where the occurrence of Grade ≥ 2 CRS increases modestly with higher maximal receptor occupancy (RO_{max}) values. ER analyses by dosing groups (Group A – fixed dosing regimen; Group B: Cycle-1 step-up dosing regimen) indicate that the exposure-dependent increase in Grade ≥ 2 CRS observed at the lower dose range (0.05 to 2.8 mg) tested in Group A using the fixed dosing regimen was mitigated in Group B by Cycle 1 step-up regimen.
- CRS ER analyses (stratified by mosunetuzumab Cycle 1 Day 1 dose, Day 8 dose, and Day 15 dose) indicated higher RO_{max} values to be associated with modest increasing rates of

Grade ≥ 2 CRS upon the initial doses in Cycle 1. However, E-R trends upon weekly repeat dosing in Cycle 1 suggest a pattern of similar/ decreased CRS risk at comparatively higher exposures in subsequent doses, thus supporting the step-up regimen approach as an effective CRS mitigation strategy.

- The Cycle 1 step-up dosing schedule mitigated the acute CRS risks and resulted in a favorable safety profile with predicted low frequency of Grade ≥ 2 CRS (less than 12%) at the RP2D/intended registration dose and schedule of 1/2/60/30 mg.
- Dosing of mosunetuzumab following the step-up dosing regimen does not lead to exposure-dependent increases for Grade ≥ 3 neutropenia, Grade ≥ 3 infections or infestations, any Grade ≥ 3 adverse events (AEs), or any Grade ≥ 1 AEs. Higher mosunetuzumab exposure does not lead to an earlier onset of AEs.

Immunogenicity

The potential of mosunetuzumab to induce an immune response is being assessed in the ongoing clinical Study GO29781. All patients in the study are being monitored as required at regular intervals for the development of anti-mosunetuzumab antibodies.

As of the ADA data cutoff date of 4 December 2020, there was no ADA detected in 418 ADA evaluable patients who received mosunetuzumab single agent IV treatments in Study GO29781. The observation of no ADA based on the available data is consistent with the expected mechanism of action of B cell killing.

The Applicant's Position:

Collectively, the PK and E-R analyses support intended registration dose and schedule of 1/2/60/30 mg in patients with R/R FL and support a positive benefit-risk profile.

The FDA's Assessment:

The FDA agrees with the Applicant's position. Mosunetuzumab PK properties, E-R relationships and immunogenicity assessment have been well characterized and support the proposed dose and schedule of 1/2/60/30 mg in patients with R/R FL.

- PK: see Section 6.2.1 and 6.2.2.2.
- E-R for Efficacy:
  - The E-R efficacy analyses indicated that clinical responses (CR ,ORR) increased with increasing mosunetuzumab exposure (AUC_{0-42}) and approached a plateau at the proposed dosage of 1/2/60/30 mg. The covariate analysis indicated that patients with larger tumors or with high predose anti-CD20 antibody concentrations are predicted to have a lower probability to attain CR, though still expected to be higher than 50% for CR.
  - The E-R efficacy analyses indicated a longer median PFS with increased mosunetuzumab exposure (AUC_{0-42}), and a longer median PFS at the 1/2/60/30 mg dose (B11 cohort, RP2D) compared to the 1/2/13.5 mg dose (B7 cohort).

- E-R for Safety:
  - No positive E-R relationships were observed for any AEs, any grade ≥ 3 AEs, any serious AE, Grade >3 neutropenia, Grade ≥ 3 infections or infestations, neurological AE (NAE) or DI-CCNAE (driving-impacting cognition or consciousness neurologic adverse event).
  - E-R for safety analysis support the proposed step-up dosing regimen of 1/2/60/30 mg to mitigate the risk of Grade ≥ 2 CRS.
- ER for Pharmacodynamic Biomarker:
  - E-R analyses for pharmacodynamic biomarker (IFN- γ) is acceptable and supportive. In addition, in response to FDA information request, E-R analyses for IL-6 was also provided. The E-R relationship for IL-6 follows a similar trend to IFN- γ . See details in Section 20.4.5.
- Immunogenicity:
  - No ADAs were detected in 418 ADA evaluable patients who received mosunetuzumab single agent IV administration in Study GO29781.

See Section 20.4.2 for additional PK parameters for each dose cohort studied in group A and B in study GO29781. See Section 20.4.4 and Section 20.4.5 for details regarding the Population PK and E-R analysis.

6.3.2. Clinical Pharmacology Questions

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

Data:

Exposure-response for clinical CRR and ORR were characterized in 159 patients with R/R FL across a 300-fold dose range (i.e., 0.2 to 60 mg) and across 600-fold of AUC_{0-42} values (0.400-251 day $\cdot\mu\text{g}/\text{mL}$), to properly inform the characterization of the ER relationships. Clinical response increases in an exposure-dependent manner and plateaus at the AUC_{0-42} values of approximately 92.7 and 38.4 day $\cdot\mu\text{g}/\text{mL}$ corresponding to the estimated E_{90} for CRR and ORR, respectively. The intended registration dose and schedule of 1/2/60/30 mg is predicted to achieve PK exposures at the plateau of the E-R curves for CRR and ORR and thus maximizes the therapeutic potential in the patient population. The proposed 1/2/60/30 mg leads to higher predicted CRR and ORR compared to the lower dose of 1/2/13.5 mg, which is consistent with the clinical observations (INV-assessed: CRR/ORR = 60%/77.8% and 47.8%/63.0% for B11 and B7 cohorts, respectively; IRF-assessed: CRR/ORR=60%/80% and 45.7%/67.4% for B11 and B7 cohorts, respectively).

The Applicant's Position:

Based on totality of data, the Applicant believes the mosunetuzumab clinical pharmacology program together with the efficacy results from Study GO29781 provides sufficient evidence of

effectiveness at the intended registration dose and schedule of 1/2/60/30 mg.

The FDA's Assessment:

The FDA agrees with the Applicant's position. Refer to Section 20.4.5 for details regarding the E-R analysis for efficacy.

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

Data:

See Section 6.2.2.2

The Applicant's Position:

The intended registration dose and schedule of 1/2/60/30 mg for mosunetuzumab is appropriate based on effectiveness (see Section 6.3.2.1), Cycle 1 step-up dosing mitigation of CRS, exposure-response for safety, and no dose adjustment for mosunetuzumab needed for the general patient population for which the indication is being sought i.e., R/R FL ≥ 2 Prior Therapies.

The FDA's Assessment:

The FDA agrees with the Applicant's position that the proposed dose and schedule of 1/2/60/30 mg for mosunetuzumab is appropriate for the general population for which the indication is being sought. See detailed discussion in Section 6.2.2.1.

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

Data:

See Section 6.2.2.2.

The Applicant's Position:

There is no alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors.

The FDA's Assessment:

The FDA agrees with the Applicant's position that no dose adjustment is needed in subpopulations based on intrinsic patient factors.

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

Data:

Mosunetuzumab is administered intravenously (bioavailability=1.0) and no food effect would be expected with parenteral administration.

Physiologically-based pharmacokinetics (PBPK) modeling and simulations based on IL-6 and CYP3A4 interaction indicated a low risk of cytokine-mediated drug-drug interaction (DDI) potential of mosunetuzumab on cytochrome P450 (CYP) enzyme expression or activity. The predicted area under the concentration-time curve (AUC) and maximum concentration (C_{max}) ratios (with mosunetuzumab co-administration/without mosunetuzumab co-administration) for midazolam, a sensitive CYP3A substrate was 1.37 and 1.17, respectively. No dose adjustment is recommended for mosunetuzumab when co-dosing mosunetuzumab with small molecule drugs which are CYP3A substrates.

The potential impact of baseline obinutuzumab (G) or rituximab (R) concentration on the PK and clinical response of mosunetuzumab was evaluated in the population PK and exposure-response (E-R) models based on study GO29781 including patients with R/R FL ≥ 2 prior therapies. Baseline G or R concentration was determined not to be a clinically meaningful covariate on PK and response. The lack of clinically meaningful changes in the clinical response of mosunetuzumab in the presence of residual R or G is consistent with expectations, given the indolent nature of the disease which allows for a broader time window for response. No dose adjustment is recommended for mosunetuzumab based on prior anti-CD20 therapies.

The Applicant's Position:

There was no evidence for clinically relevant food-drug or drug-drug interactions for mosunetuzumab.

The FDA's Assessment:

Mosunetuzumab can cause transient release of cytokines that may potentially suppress CYP450 enzymes. Based on evaluation of the totality of data, FDA considers the risk of drug interactions to be low. FDA's conclusion is based on the following considerations:

- The elevations of cytokines observed after mosunetuzumab doses are transient in nature and attenuate with repeat dosing.
- The highest drug-drug interaction risk is expected to occur from initiation of mosunetuzumab step-up dosing schedule up to 14 days after the second loading dose (60 mg) on Cycle 2 Day 1, and during and after CRS.
- Label recommends monitoring for toxicity or concentrations of drugs that are CYP450 substrates where minimal concentration changes may lead to serious adverse reactions.

See Section 20.4.7 for detailed assessment of the PBPK modeling and simulations to support the above conclusions.

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Miao Zhao, PhD

Xiling Jiang, PhD

Primary Clinical Pharmacology, Reviewer

Clinical Pharmacology, Team Leader

7 Sources of Clinical Data

7.1. Table of Clinical Studies

All studies pertinent to the evaluation of efficacy and safety are summarized in Table 17.

The FDA's Assessment:

The FDA agrees with the Applicant's information in the table below.

The review of efficacy was primarily based on an analysis of Study GO29781, an open-label, multicenter, single-arm, multi-cohort study that included a cohort of 90 patients with relapsed or refractory follicular lymphoma.

The review of safety is primarily based on data from 218 patients with B-cell non-Hodgkin lymphoma from Study GO29781 who received the dose and schedule of mosunetuzumab (1/2/60/30 mg) intended for registration.

All major efficacy and safety analyses were reproduced or audited based on a data cutoff of August 27, 2021. Statistical analyses by the reviewers were performed using R version 4.1.2 (2021-11-01, The R Foundation for Statistical Computing Platform) and JMP 8.0 (SAS Institute, Inc., Cary, NC).

Table 17: Applicant – Listing of Clinical Trials Relevant to this BLA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Studies to Support Efficacy and Safety								
GO29781	NCT02500407	Phase I/II multicenter, open-label dose escalation and expansion	Group A: Dose Escalation: mosunetuzumab, IV 0.05-2.8 mg q3w Group B: Dose Escalation: mosunetuzumab, IV 0.4/1/2.8-1/2/60 mg ^a Dose Expansion: mosunetuzumab, IV 1/2/60/30 mg ^b (RP2D)	Safety: safety, tolerability, PK, MTD, DLTs, RP2D Efficacy: Primary: CR rate (IRF) Secondary: CR rate (INV) ORR, DOCR, DOR, PFS (all by (IRF and INV) and OS	8 or 17 ^c x 3-weekly cycles	447 ^d Group A: 33 Group B: 414 of which 218 treated at RP2D, including 90 R/R FL after ≥2 prior therapies	Adult patients with R/R B-cell NHL	40 sites 7 countries (Australia, Canada, Germany, Spain, UK, S. Korea, US)

DLTs, dose-limiting toxicities, DOR, duration of response; DOCR, duration of complete response, INV, investigator; IRF, independent review facility; MTD, maximum tolerated dose; OS, overall survival; PFS, progression-free survival; RP2D, recommended Phase II dose.

^a Dose in mgs administered on C1D1/C1D8/C1D15, C2D1 and subsequent q3w cycles.

^b RP2D administered as 1 mg on C1D1, 2 mg on C1D8, 60 mg on C1D15 and C2D1, and 30 mg for C3D1 and subsequent q3w cycles.

^c Patients who achieved a CR after 8 cycles received a maximum of 8 cycles, and patients who achieved a PR or maintained stable disease [SD] after 8 cycles could receive a maximum of 17 cycles.

^d No. of patients, and sites of enrolment are for Group A and B (mosunetuzumab IV monotherapy) only at the time of the CCOD.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. G029781

Trial Design

The Applicant's Description:

The clinical efficacy and safety results supporting this application are from a single ongoing multicenter, open-label, Phase I/II dose-escalation and dose-expansion study G029781 of mosunetuzumab administered as a single agent (and in combination with atezolizumab) in patients with R/R hematologic malignancies expected to express CD20, including B-cell NHL and CLL.

The initial patients enrolled were treated with escalating doses of single-agent mosunetuzumab administered IV on Day 1 of each 3-weekly (q3w) cycle (Group A fixed dosing schedule). Subsequent protocol amendments were implemented to expand the study to evaluate a different IV dosing schedule (Group B Cycle 1 step-up dosing), include a dose expansion phase to evaluate mosunetuzumab at a recommended expansion dose in specific B-cell NHL histologies, and introduce efficacy as a co-primary objective. Further dose escalation and expansion cohorts were also introduced to evaluate mosunetuzumab IV in combination with atezolizumab (Group E), and mosunetuzumab administered as a single agent by SC injection (Groups D and F). The study was re-classified from Phase I/Ib to Phase I/II to reflect the overall size of the study, and the study objective to investigate the safety, efficacy, and PK/PD of the recommended Phase II dose (RP2D) in expansion cohorts with defined NHL histologies (protocol v12, dated 23 February 2021).

The G029781 study enrolled adult patients with a history of a hematologic malignancy that is expected to express the CD20 antigen, including FL, MZL, DLBCL, PMBCL, transformed indolent NHL, MCL, Richter's transformation, and CLL/SLL. Confirmation of CD20 expression was not required during eligibility screening prior to enrollment and was evaluated retrospectively based on data from a central lab. Patients included in the pivotal R/R FL expansion cohort had to have histologically-documented Grade 1-3a FL, measurable disease, must have relapsed after or failed to respond to at least two prior lines of systemic therapy and must have received prior treatment of an anti-CD20 directed therapy and an alkylating agent.

Results to support this application are from Groups A and B only, which evaluated mosunetuzumab as a single agent administered by IV infusion.

After completion of the first eight dose escalation cohorts, further enrolment into Group A was stopped beyond 2.8 mg (the highest assessed dose in Group A) to prioritize assessment of other dosing schedules and routes of mosunetuzumab administration. The Group B Cycle 1 step-up dosing schedule evaluated single-agent mosunetuzumab administered IV as incremental doses on C1D1, C1D8, and C1D15 dose levels followed by q3w dosing on Day 1 of subsequent cycles. The dose escalation evaluated 11 dose levels (ranging from 0.4/1/2.8 mg to 1/2/60 mg [B1-B11]), according to a standard 3+3 design. The Group B dose-expansion stage was designed to obtain additional safety, tolerability, PK, and clinical efficacy data with single agent mosunetuzumab administered IV by Cycle 1 step-up dosing in one or more dose expansion cohorts at dose levels at or below the MTD (which was not reached). The selected RP2D, which is also the intended registration dose, and schedule was 1/2/60/30 mg (i.e., 1 mg on C1D1, 2 mg on C1D8, 60 mg on C1D15 and C2D1, and 30 mg for C3D1 and subsequent q3w cycles), and was chosen based on cumulative data and additional analyses on exposure-efficacy and exposure-safety relationships (see 6.2.2.1). The RP2D and schedule was evaluated in four indication-specific expansion cohorts; R/R FL, R/R DLBCL/trFL, R/R MCL, and R/R Richter's transformation.

Patients who achieved a CR after 8 cycles received a maximum of 8 cycles, and patients who achieved a PR or maintained stable disease after 8 cycles could receive a maximum of 17 cycles. Patients who achieved a CR with initial single agent mosunetuzumab treatment and subsequently relapsed (PD) could receive re-treatment with mosunetuzumab for at least 8 additional cycles. Patients were withdrawn from treatment due to disease progression or relapse, unacceptable toxicity, use of NALT, patient or investigator decision or pregnancy. Mosunetuzumab dose could be interrupted (delayed) for specific treatment emergent AEs (e.g. DLTs, Grade 3 or serious AE) for up to 2 weeks in order to recover from the toxicity. The mosunetuzumab dose could be continued with or without dose reduction. Patients who completed or discontinued initial study treatment without disease progression continued to be monitored, including regularly scheduled tumor assessments in post-initial treatment follow-up. Patients who discontinued treatment due to disease progression or experienced disease progression in post-initial treatment follow-up could be followed for survival and subsequent anti-cancer therapy.

The FDA's Assessment:

The FDA agrees with the Applicant's description of the study design. Study GO29781 is an open-label, multicenter, multi-cohort study that included a cohort of patients with relapsed or refractory follicular lymphoma who have received at least two prior therapies, including an anti-CD20 monoclonal antibody and an alkylating agent. Patients were treated with mosunetuzumab at the recommended dose and schedule (1/2/60/30 mg).

Study Endpoints

The Applicant's Description:

The primary efficacy endpoint of IRF-assessed CR rate according to standard NHL response criteria (Cheson et al. 2007) was introduced when efficacy became a co-primary objective of the study at the time the study expanded to become a Phase Ib design (Protocol v4, dated 14 June 2017). This amendment was prospectively planned and implemented before any patient had been enrolled into the Group B histology-specific expansion cohorts.

CR rate was chosen as the primary endpoint as it is clinically relevant, directly attributable to drug effect and not the natural history of the disease, is based on objective and quantitative assessments, and appropriate for a single arm study. Several lines of evidence indicate that CR rate is reasonably likely to predict clinical benefit in patients with FL to support accelerated approval. The quality (depth) of response is associated with better outcomes both in the first-line (Shi et al. 2017; Trotman et al. 2018) and R/R setting (Liu et al. 2020) and two meta-analyses of large databases of published trial data suggest that CR rate may be a potential surrogate for PFS in FL (Zhu et al. 2017; Mangal et al. 2018). Additionally, the NCI Lymphoma Clinical Trials Planning Meeting Follicular Subcommittee recommended in trials for patients with high-risk R/R FL, the primary endpoints be PET-negative CR at the end of therapy and/or continuous CR at 30 months (Maddocks et al. 2017) (see Section 1.7.3. of the Clinical Overview, Module 2.5 for details).

In order to minimize the potential for investigator bias and ensure objectivity in interpretation of results by the investigator in this open-label study, the primary endpoint was based on tumor assessments reviewed independently by an IRF.

As GO29781 is a single arm study, the primary endpoint of IRF-assessed CR rate achieved by patients in the pivotal B11 FL RP2D cohort was compared statistically (exact binomial test with two-sided alpha level of 5%) with an historical control CR rate assumed to be (b) (4) % for the R/R FL ≥ 2 prior therapies population based on the CR rate reported for copanlisib in the CHRONOS-1 study (Dreyling et al. 2017).

Secondary efficacy endpoints evaluated in Study GO29781 were CR rate by INV, ORR, DOCR, DOR, PFS (all by IRF and INV), OS and PRO measures. The analysis of these endpoints was prospectively planned in the Statistical Analysis Plan (SAP; see below).

This primary analysis of efficacy was conducted when both of the following were met:

- At least approximately 6 months after the last patient in (LPI) in the B11 FL RP2D and B11 DLBCL/trFL RP2D expansion cohorts, whichever was later.
- Efficacy evaluable population included approximately 80 patients in this cohort for each histology.

Hypothesis testing for the primary endpoint was conducted once only at the time of the primary analysis, based on a clinical cutoff date of 15 March 2021.

The FDA's Assessment:

The pre-specified primary efficacy endpoint was CR rate per independent review facility per the 2007 international working group criteria (Cheson 2007). However, the FDA uses overall response rate as an intermediate endpoint reasonable likely to predict clinical benefit, supported by durability. In addition, the FDA disagrees with the Applicant's statement that CR rate may be a potential surrogate for PFS in patients with follicular lymphoma. The use of CR rate in patients with relapsed or refractory follicular lymphoma is not an established surrogate endpoint and has not been used as an intermediate endpoint to support a regulatory determination in follicular lymphoma. Of note, complete response rate at 30 months is an established surrogate endpoint in patients with previously untreated follicular lymphoma.

The proposed historical control CR rate of $(b)_{(4)}\%$ was not agreed upon with FDA. Comparison of response rates from single-arm trials against a historical rate is challenging because the historical benchmark is difficult to verify. Due to differences in population, trial design and other possible unknown confounders, the historical estimation is likely subject to biases which cannot be resolved. Consequently, the proposal for a hypothesis test or comparison against $(b)_{(4)}\%$ is not adequate for inferential purposes but instead is considered as supportive only, and the corresponding p-value is nominal.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The analyses conducted were prospectively planned and described in the Statistical Analysis Plan (SAP, dated 18 December 2020) which was reviewed by the FDA (Type B Pre-BLA Content and Format meeting, 21 January 2021) prior to the CCOD for the primary analysis. The SAP was amended (v2, 21 May 2021) to revise censoring rules for time-to-event endpoints for events occurring after NALT (at the recommendation of the Agency). There were no changes made to the planned analyses of the primary and key secondary endpoints according to the SAP after the database snapshot for either the primary, or updated analyses.

The FDA's Assessment:

The primary analysis for efficacy was conducted on the B11 pivotal cohort, which includes 90 patients with relapsed or refractory FL treated at the proposed registrational dose (i.e., 1/2/60/30 mg) in Group B of Study GO29781.

Response rates (ORR and CR) are summarized with 95% Clopper-Pearson Confidence Interval (CI) in the B11 pivotal cohort. Patients with missing/no response assessments are counted as non-responders.

Duration of response and duration of CR are summarized with the Kaplan-Meier method in the B11 pivotal cohort patients who achieved ORR and CR .

Protocol Amendments

The Applicant's Description:

The initial GO29781 study protocol, dated 23 April 2015 was amended 11 times up to the version current at the time of the CCOD for the updated analysis supporting the application (v12, dated 11 March 2021). The key amendments relevant to the evaluation of efficacy and safety in cohorts of patient receiving mosunetuzumab IV monotherapy were as follows:

- Group B to evaluate Cycle 1 step-up doing to minimize potential toxicity with mosunetuzumab IV was introduced (v2, 13 August 2016)
- Further enrolment into the dose escalation of Group A (q3w fixed dosing) was stopped beyond 2.8 mg to prioritize assessment of other dosing schedules and routes of administration (v4, 14 June 2017)
- The efficacy of mosunetuzumab using the Group B dosing schedule in patients with R/R FL as measured by IRF-assessed CR rates was added as a co-primary objective of the study. In addition, secondary objectives were expanded to includes PRO-based assessment of HRQoL in the NHL expansion cohorts (v6, 27 November 2017)
- Several amendments to the protocol were made to incorporate additional risk monitoring and mitigation plans based on evolving clinical data including additional guidance provided for mitigation, management and reporting of CRS events, and neurologic events.

None of the modifications to the protocol were considered to have an impact on the integrity of the trial or the interpretation of the efficacy or safety data.

The FDA's Assessment:

The FDA agrees with the Applicant's summary of the key protocol amendments for Study GO29781.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant's Position:

Study GO29781 was conducted in accordance with the principles of GCP (ICH E6), the principles of the Declaration of Helsinki, and applicable local, state, and federal laws, as well as other applicable national legal requirements. The appropriate Ethics Committees and Institutional Review Boards reviewed and approved this study.

The FDA's Assessment:

The FDA agrees with the Applicant's summary of compliance with good clinical practices.

Financial Disclosure

The Applicant's Position:

Information on financial disclosures for Study GO29781 is provided in Module 1.3.4 of the BLA.

The FDA's Assessment:

The FDA agrees with the Applicant's summary of financial disclosures. See Section 20.2 for additional information.

Patient Disposition

The Applicant's Position:

Between 15 September 2015 (first-patient enrolled) and 27 August 2021 (the CCOD for the updated analysis), 447 patients were enrolled into Groups A (dose escalation; n=33) and B (dose escalation and expansion; n=414) to receive mosunetuzumab as a single agent by IV infusion. Patients were enrolled at 40 sites in 7 countries (Australia, Canada, Germany, S. Korea, Spain, United Kingdom, and US).

In Group B, 218 patients received the RP2D/intended registration dose and schedule (the primary safety population), including 90 patients with R/R FL ≥ 2 prior therapies (primary efficacy population).

As of the CCOD, none of the patients in the pivotal B11 FL RP2D cohort continued to receive initial treatment, 41 patients were in post-initial treatment follow-up (without disease progression), 35 patients were in survival follow-up (including one patient who received re-treatment), 2 patients were active on first re-treatment, and 12 patients had discontinued from the study.

The FDA's Assessment:

The FDA agrees with the Applicant's position. As shown in Table 18, no patients in the pivotal B11 FL RP2D cohort and two in the B11 RP2D cohort were still on active treatment by the data cutoff. The major reason for treatment discontinuation was progressive disease, which accounted for 28% and 50% of patients in the pivotal B11 FL RP2D cohort and B11 RP2D cohort, respectively.

Table 18: FDA Summary of Patient Disposition

	B11 FL Cohort N = 90 n (%)	B11 RP2D Cohort N = 218 n (%)
Active on initial treatment	0	2 (<1)
Completed initial treatment	54 (60)	79 (36)
Discontinued initial treatment	36 (40)	137 (63)
Progressive disease	25 (28)	109 (50)
Physician decision	4 (4)	11 (5)
Adverse event	4 (4)	7 (3)
Withdrawal by subject	1 (1)	5 (2)
Death	0	2 (<1)
Anti-cancer therapy	2 (2)	2 (<1)
Other	0	1 (<1)
Source: FDA analysis		

Protocol Violations/Deviations

The Applicant's Position:

A total of 150 major protocol deviations were reported in 111 of the 414 patients (26.8%) in Group B. By category, the most common (>5% patients) major protocol deviations were 'failure to report AEs, SAEs, AESIs, DLTs, and pregnancy to the IEC/sponsor/regulatory authorities' and 'incomplete/missing/out-of-window tumor-related assessments'.

One patient with a non-hematological malignancy of melanoma was enrolled in error into the B11 DLBCL/trFL RP2D cohort. The patient's exclusion from the efficacy-evaluable population did not affect the results of the primary analysis in R/R FL patients supporting this application. The patient was included in the safety evaluable population because she received one dose of mosunetuzumab.

In the pivotal B11 FL RP2D efficacy cohort, 32 of the 90 patients had major protocol deviations and all were included in the efficacy analyses. The major deviations relating to tumor assessments, eligibility criteria, or treatment compliance were as follows:

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

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- Eleven patients had major deviations categorized as incomplete/missing/out-of-window tumor-related assessments as a bone marrow biopsy was not performed at screening and/or within 42 days of the radiographic complete response to confirm a CR. In each case, the CR was downgraded to a PR at that tumor assessment visit, and the efficacy endpoints of CR rate and duration of CR reflect this conservative assessment.
- One patient in the B11 FL RP2D cohort with negative serologic test results for acute or chronic hepatitis B (HBV) infection at screening received their first dose of mosunetuzumab prior to a positive hepatitis B virus (HBV) PCR result on the same day. Per protocol, patients with known active infections were to be excluded from the study. HBV PCR negativity was achieved and maintained during mosunetuzumab treatment with concomitant antiviral treatment and the patient achieved PR as their best overall response.
- One patient received 10 cycles of mosunetuzumab treatment despite achieving a CR after 8 cycles.
- One patient had a delayed treatment cycle due to the COVID-19 pandemic after a CR was achieved. Another patient had an incomplete infusion due to the COVID-19 pandemic; the patient completed the rest of the treatment cycles and achieved a CR. Two other patients were administered mosunetuzumab at a faster infusion rate than recommended per protocol. Both patients achieved CR as their best overall response.

A total of 11 major protocol deviations due to the COVID-19 pandemic were reported in 10 patients in Group B overall. None of the 5 major protocol deviations due to COVID-19 in the pivotal B11 FL RP2D cohort were attributed to incomplete/missing/out-of-window tumor assessments and therefore, response rates and the TTE analyses are not expected to be impacted by the missing data due to the COVID-19 pandemic.

Overall, none of the major protocol deviations were considered to have impacted the monitoring of patient safety, the study outcome, or the interpretation of the study results.

The FDA’s Assessment:

The FDA agrees with the Applicant’s summary of protocol deviations.

Data:

Table 19: Applicant – Demographic Characteristics of the Primary Efficacy Analysis Population

Demographic Parameters	B11 RP2D FL expansion (N=90) n (%)
Sex	
Male	55 (61.1)
Female	35 (38.9)
Age	

Demographic Parameters	B11 RP2D FL expansion (N=90) n (%)
Mean years (SD)	60.0 (12.0)
Median (years)	60.0
Min, max (years)	(29–90)
Age Group	
<65 years	60 (66.7)
≥65 years	30 (33.3)
≥75 years	7 (7.8)
Race	
White	74 (82.2)
Black or African American	4 (4.4)
Asian	8 (8.9)
American Indian or Alaska Native	1 (1.1)
Unknown	3 (3.3)
Ethnicity	
Hispanic or Latino	7 (7.8)
Not Hispanic or Latino	77 (85.6)
Not stated	5 (5.6)
Unknown	1 (1.1)
Body mass index (kg/m²)	
Median (kg/m ²)	27.5
Min, max	(17–45)
ECOG performance status	
0	53 (58.9)
1	37 (41.1)
Region (sites)	
United States (10)	40 (44.4)
Rest of the World*	
Canada (3)	13 (14.4)
Europe (8)	16 (17.8)
Asia (2)	4 (4.4)
Australasia (7)	17 (18.9)

*Rest of World countries were Spain, Germany and United Kingdom (Europe), S. Korea (Asia), Australia (Australasia), and Canada.

Source: Table 3 of SCE (Module 2.7.3).

The Applicant's Position:

The majority of patients in the pivotal B11 FL RP2D cohort were White (82.2%) (although almost all race groups were represented) and male (61.1%). The median age was 60 years (range:

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29-90 years) and 33.3% were ≥ 65 years. Per protocol, all patients were ECOG performance status 0 (58.9%) or 1 (41.1%).

The FDA's Assessment:

The FDA agrees with the Applicant's summary of demographic characteristics in the FL cohort of 90 patients. As noted in the Applicant's position, the majority of patients were White (82%) with limited representation from other races and ethnicities. In particular, there was an underrepresentation of Black or African American patients and Hispanic or Latino patients, who comprised only 4% and 8% of the primary FL population, respectively. In Section 2.1, the Applicant stated that the incidence of FL in Black or African American patients was 4%. This incidence was based on 70,882 patients with follicular lymphoma. Of these patients with follicular lymphoma, an incidence of 10% in Hispanic or Latino patients was observed. The FL cohort from study GO29781 has a sample size of 90 patients, therefore the similar incidence of Black or African American and Hispanic or Latino patients is influenced by the small sample size of the FL cohort.

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

Data:

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Table 20: Applicant – Baseline Disease Characteristics and Prior Cancer Treatment of the Primary Efficacy Analysis

Baseline Disease Parameters	B11 FL RP2D (N=90)
Ann Arbor Stage	
I	5 (5.6)
II	16 (17.8)
III	25 (27.8)
IV	44 (48.9)
Bulky disease (>6 cm)	31 (34.4)
FLIPI risk group at study entry	
low (0,1)	26 (28.9)
intermediate (2)	24 (26.7)
high (3-5)	40 (44.4)
Prior cancer therapy	
anti-CD20	90 (100)
alkylator	90 (100)
auto-SCT	19 (21.1)
CAR-T	3 (3.3)
PI3K inhibitor	17 (18.9)
immunomodulatory imide drugs	13 (14.4)
No. of prior lines of anti-lymphoma therapies	
Median (range)	3.0 (2–10)
2	34 (37.8)
3	28 (31.1)
>3	28 (31.1)
Refractory to:	
last prior therapy	62 (68.9)
any prior anti-CD20	71 (78.9)
double refractory to prior anti-CD20 and alkylator	48 (53.3)
Progressive disease within 24 months from start of first systemic therapy	47 (52.2)

Source: Table 3 of SCE (Module 2.7.3).

The Applicant's Position:

Most patients in the pivotal B11 FL RP2D cohort had advanced (Ann Arbor Stage III/IV) disease at study entry (76.7%). FLIPI risk factors ≥ 3 (defining the FLIPI high risk group) were present in 44.4% of patients at study entry. The median number of prior lines of anti-lymphoma therapies received was 3 (range: 2-10). The majority of patients who entered the study had FL that was

refractory to their last prior cancer therapy (68.9%), had been refractory to at least one time to a prior anti-CD20 therapy (78.9%), and were double refractory to a prior anti-CD20 therapy and an alkylator agent (53.3%). Early disease progression within 24 months of the frontline systemic therapy occurred in 52.2% of patients.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

The Applicant's Position:

Accountability and study treatment compliance, as required per protocol, were assessed by review of the pharmacy drug dispensing records and administration logs.

The most frequent concomitant treatments ongoing at baseline were either standard premedications for lymphoma patients who receive anti-cancer treatment (the most common being allopurinol) or were permitted medications to treat previous and concurrent medical conditions. The most frequent medications started after baseline were protocol-recommended premedications that patients were to receive prior to treatment with mosunetuzumab IV monotherapy (e.g. corticosteroids, antipyretics, and/or antihistamines, and uric acid reducing agents), hydration/electrolytes, and permitted concomitant therapy to manage adverse events (immunostimulants, e.g. G-CSFs, anti-infective prophylaxis for viral, fungal, bacterial, or pneumocystis infections, RBC and platelet transfusions).

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

The Applicant's Position:

The primary efficacy endpoint of IRF-assessed CR rate in the pivotal B11 FL RP2D cohort was met at the time of the primary analysis based on a CCOD of 15 March 2021. The CR rate with mosunetuzumab IV monotherapy at the RP2D at that time (57.8% (95% CI: 46.9, 68.1) was statistically significantly greater than the historical control CR rate of $\frac{(b)}{(4)}$ % for patients with R/R FL who have received at least 2 prior therapies (exact binomial test, two-sided p value <0.0001).

In the updated analysis based on a CCOD of 27 August 2021, the CR rate as assessed by IRF in the B11 FL RP2D cohort was 60.0% (95% CI: 49.1, 70.2) (54/90 patients).

A summary of the efficacy results for the B11 FL RP2D expansion cohort at the time of the updated efficacy analysis is shown in the table below.

Table 21: Applicant – Summary of Efficacy (B11 FL RP2D Expansion Cohort, Study GO29781, CCOD: 27 August 2021)

Efficacy Parameter	B11 FL RP2D expansion (N=90)	
	INV-assessed	IRF-assessed
Complete response rate n (%) (95% CI)	54 (60.0%) (49.1, 70.2)	54 (60.0%) (49.1, 70.2)
Objective response rate (CR or PR) n (%) (95% CI)	70 (77.8%) (67.8, 85.9)	72 (80.0%) (70.3, 87.7)
Duration of complete response Patients with event, n (%) Median, months (95% CI) ^d K-M event-free proportion, % at: 12 months (95% CI) 18 months	12/54 (22.2%) NE (17.8, NE) 80.4% (68.8, 92.0) 66.6% (45.5, 87.8)	16/54 (29.6%) NE (14.6, NE) 71.4% (57.9, 84.9) 63.7% (48.0, 79.4)
Duration of response Patients with event, n (%) Median, months (95% CI) ^d K-M event-free proportion, % at: 12 months (95% CI) 18 months	27/70 (38.6%) 22.8 (18.7, NE) 64.8% (53.1, 76.5) 62.5% (50.4, 74.7)	29/72 (40.3%) 22.8 (9.7, NE) 61.8% (50.0, 73.7) 56.9% (44.1, 69.6)
Duration of response in patients who achieved CR Patients with event, n (%) Median, months (95% CI) ^d K-M event-free proportion, % at: 12 months (95% CI) 18 months	12/54 (22.2%) 22.8 (19.9, NE) 84.3% (74.3, 94.3) 81.3% (70.0, 92.5)	16/54 (29.6%) 22.8 (18.7, NE) 76.4% (64.6, 88.1) 70.2% (56.7, 83.8)
Progression-free survival Patients with event, n (%) Median, months (95% CI) K-M event-free proportion, % 12 months (95% CI)	41 (45.6%) 21.1 (11.8, NE) 57.6% (46.8, 68.4)	42 (46.7%) 17.9 (10.1, NE) 57.7% (46.9, 68.4)
Overall survival Patients with event, n (%) Median, months (95% CI) K-M event-free proportion, % at: 12 months (95% CI)	8 (8.9%) NE (NE, NE) 93.0% (87.6, 98.4)	

Response rates, DOR and PFS are based on tumor assessments with or without ¹⁸F-PET according to Cheson et al.

2007 criteria.

Source: Table 6 of SCE (Module 2.7.3).

The FDA's Assessment:

The comparison of response rates from a single-arm trial against a historical rate is challenging because such a historical benchmark is difficult to verify and needs to be carefully reviewed and agreed upon prior to conducting any hypothesis test. Therefore, the hypothesis test or comparison against the historical control CR rate of $\frac{(b)}{(4)}\%$ is considered as supportive only, and the corresponding p-value is nominal.

Although CR rate was prespecified as the primary endpoint in the protocol and statistical analysis plan, FDA considers the intermediate endpoint of ORR and duration of response as assessed by an independent review facility according to standard criteria for NHL (Cheson 2007) to support substantial evidence of efficacy. In addition, the Applicant did not submit data (trial-level or patients-level) to support the use of CR rate as an intermediate endpoint to establish efficacy.

As noted above, the Applicant based the efficacy hypothesis testing on a historical CR rate. In single-arm trials, the FDA generally uses these historically based calculations for sample size determination and does not use the demonstration of statistical significance as the ultimate determination of effectiveness. In NHL, the observed ORR with a 95% CI and duration of response are used in the overall assessment of efficacy in the context of the observed safety findings to inform the benefit-risk of a given product.

For the B11 FL RP2D expansion cohort, the ORR rate is 80% (95% CI: 70.3%, 87.7%) and the estimated median DOR is 22.8 months (95% CI: 9.7, not estimable). The primary efficacy results were able to be reproduced by the statistical reviewer.

Among 72 patients who achieved CR or PR, median time to response was 1.4 months (range: 1.1, 8.9); the majority of these responders (94%) achieved their response by 4 months since the start of treatment and only 6% responded after 4 months. Among 54 patients who achieved CR, median time to response was 3 months (range: 1.2, 18.9).

For subgroup analysis accompanying the primary analysis in Table 21, see Section "Additional Analyses Conducted on the Individual Trial" below.

Data Quality and Integrity

The Applicant's Position:

No meaningful concerns are anticipated in the quality and integrity of the submitted datasets; these were sufficiently complete to allow for a thorough review of efficacy. Furthermore, no meaningful data integrity concerns were reported following completion of site inspections by

the Applicant. The Applicant submitted a Quality Briefing Document with Rolling Part 2 of the BLA, which provides a summary of quality evidence generated to support the Quality Strategy developed for the mosunetuzumab program.

The FDA's Assessment:

The FDA agrees with the Applicant's position. In general, the data quality of the study appeared acceptable with no errors identified for the major study endpoints.

Efficacy Results – Secondary and other relevant endpoints

The Applicant's Position:

Investigator-assessed CR rate

Investigator-assessed CR rate in the B11 FL RP2D cohort was 60.0% (95% CI: 49.1, 70.2) the same as the IRF-assessed CR rate. Concordance between IRF and Investigator on whether a patient achieved a CR was 93.3%.

Objective Response Rate

The objective response rate (ORR; PR or CR) by IRF assessment was 80.0% (95% CI: 73.0, 87.7) and consistent with the Investigator-assessed ORR rate of 77.8% (95% CI: 67.8, 85.9). Concordance between IRF and investigator on whether a patient achieved a CR or PR was 95.5%.

Duration of Complete Response

Of 54 patients in the pivotal B11 FL RP2D cohort who achieved a CR as assessed by the IRF, 16 patients (29.6%) subsequently had disease progression by the time of the CCOD. The median duration of complete response (DOCR) was not estimable. The K-M -estimated event-free rate among complete responders at 12 and 18 months after the first CR was 71.4% and 63.7%, respectively. Similar results were observed for DOCR by investigator assessment, with 80.4% and 66.6% of complete responders being event-free at 12 and 18 months, respectively, after the first CR (Table 21).

Duration of Response

The median duration of follow-up for DOR (by IRF) estimated using the reverse K-M method was 14.9 months (95% CI: 13.4, 16.6). At the CCOD, of the responders, 87.5% had either ongoing responses of at least 9 months or had progressed or died, 9.7% had DOR of <9 months but no longer had tumor assessments, and the remaining 2.8% had ongoing responses which continued to be assessed.

Of the 72 patients in the B11 FL RP2D cohort who achieved a response (CR or PR) as determined by the IRF, 29 patients (40.3%) had subsequently progressed or died. The K-M estimated median DOR was 22.8 months (95% CI: 9.7, NE), however this estimate was based on <10% of

responders remaining at risk and therefore may not be robust. Among responders, the event-free rates at 12 and 18 months after the first response were 61.8% and 56.9%, respectively. Similar results were observed for DOR by investigator assessment, with 64.8% and 62.5% of responders being event-free at 12 and 18 months, respectively, after the first response (Table 21). Concordance between the IRF and the investigator in DOR was 74.2%.

In the subgroup of responders in the B11 FL RP2D cohort who achieved a CR by IRF assessment (54 patients), an estimated 76.4% (95% CI: 64.6, 88.1) maintained their response at 12 months after the first response. For DOR in patients who achieved a CR by investigator assessment, 84.3% were event-free at 12 months.

Progression-free Survival

At the time of the CCOD, 46.7% of patients in the B11 FL RP2D cohort had an IRF-assessed PFS event. The K-M estimated median PFS was 17.9 months (95% CI: 10.1, NE). The 12-month PFS event-free rate was 57.7% (95% CI: 46.9, 68.4). Overall, consistent results were observed with INV-assessed PFS.

Overall Survival

Survival data was not mature at the CCOD, with 8 deaths reported (8.9%) in the B11 FL RP2D cohort. The K-M estimated 12- and 18-month survival rates were 93.0% (95% CI: 87.6, 98.4) and 89.6% (95% CI: 82.5, 96.6), respectively.

The FDA's Assessment:

In general, the FDA agrees with the Applicant's position. As noted in the Applicant's position, the median DOR for ORR was 22.8 months, however this estimate was based on <10% of responders remaining at risk. This is coupled with the median follow-up for DOR of 14.9 months. Therefore, to provide additional context for DOR, the landmark assessment of continued response at 12 months with 62% and at 18 months with 57% is supportive of durability. Additionally, FDA considers the time to event endpoints, including progression-free survival and overall survival, as not interpretable in single-arm trials. Therefore, the corresponding analysis of progression-free survival and overall survival results presented in Table 21 are considered exploratory analyses.

Dose/Dose Response

The Applicant's Position:

The Exposure-Response (E-R) relationships for efficacy were characterized based on INV-assessed clinical objective response data from 159 patients with R/R FL ≥ 2 prior therapies who were treated with single agent mosunetuzumab by IV administration in Study GO29781 (see Exposure-Response Report No. 1112149). These patients received mosunetuzumab doses

ranging from 0.2 to 1/2/60/30 mg (7 patients from Group A q3w fixed-dose escalation cohorts and 152 patients from Group B step-up dosing cohort), yielding a 600-fold range in mosunetuzumab exposures (AUC_{0-42}). The E-R analyses indicate that clinical responses (CR rate and ORR) increase with increasing mosunetuzumab exposure (AUC_{0-42}) and approach a plateau estimated by the model as the maximal clinical responses of 68.6% and 81.4% for CR rate and ORR, respectively. The model predictions for the proposed 1/2/60/30 mg regimen are at the plateau of the logistic regression E_{max} E-R curves, while lower doses had reduced CR rate and ORR predictions. The rationale for the intended registration dose and schedule of 1/2/60/30 mg based on integrated E-R analyses of efficacy and safety for Study GO29781 is summarized in Section 6.2.2.1.

The FDA's Assessment:

The FDA agrees with Applicant's position. Refer to Section 6.2, 6.3, and Section 20.4.5 for additional information.

Durability of Response

The Applicant's Position:

Objective responses occurring during mosunetuzumab IV monotherapy were durable, and extended beyond the fixed treatment duration of 8 or 17 q3w cycles (see Duration of Response, under Efficacy Results – Secondary and other relevant endpoints). With median follow-up for DOR of 14.9 months, the 18-month event-free rate was 56.9% (95% CI: 44.1, 69.6) for all responders, and 70.2% (95% CI: 56.7, 83.8) for patients who achieved a CR, indicating that patients who achieve a CR may have a higher probability of remission lasting at least 1.5 years.

The durability of response to mosunetuzumab IV monotherapy is further supported by the results from 46 patients with R/R FL ≥ 2 prior therapies treated at the B7 interim dose level (1.0/2.0/13.5 mg). The median follow-up for DOR in this lower dose cohort was 24.2 months [95% CI: 21.4, 28.3]), and the 18-month DOR rate (54.0% [95% CI: 35.5, 72.4]) was similar to the B11 FL RP2D cohort.

The FDA's Assessment:

The FDA agrees with the Applicant's position and the results of duration of response and duration of CR presented above. The median follow-up time for DOR was 14.9 months (95% CI: 13.4, 16.8) among 72 responders who achieved CR or PR. The median follow-up time for duration of CR was 13.6 months (95% CI: 10.8, 16.3) among 54 responders who achieved CR.

Persistence of Effect

The Applicant's Position:

Response to mosunetuzumab IV monotherapy occurs early in the majority of responders (median time to response is 1.4 months for all responses and 3.0 months for CRs). The durability of responses beyond the fixed treatment period of 8 cycles (5.5 months) for patients with CR and 17 cycles (11.8 months) for patients with PR or SD provides evidence for the persistence of mosunetuzumab efficacy over time.

The long-term persistency of the treatment effect of mosunetuzumab is not established, however the time-to-event endpoint K-M estimates at the primary efficacy analysis can be appreciated in the context of the disease setting and patient population under study. Although direct comparison of longer term benefit of mosunetuzumab IV treatment with an appropriate control is not possible in the confines of a single arm study and the lack of a comparator that would be considered the standard of care, the estimated 61.8% of patients who continued to benefit from remission after 12 months compares favorably with most approved therapies for patients with R/R FL who have received with ≥ 2 prior therapies treated for whom median DOR is approximately a year or less (see Table 22). Furthermore, the 12-month PFS event-free rate of 57.7% (95% CI: 46.9, 68.4) compares favorably with published real-world estimates of median PFS ranging from 1-1.1 year for third-line patients (represented at 37.8% in the B11 FL RP2D cohort) decreasing to 0.5 years for sixth-line patients (Alperovich et al. 2016; Batlevi et al. 2020).

A lack of tolerance effects is indicated by patients who received retreatment with mosunetuzumab. Of the 11 patients with R/R FL who received mosunetuzumab IV monotherapy retreatment for relapsed disease after an initial response of CR, 7 patients had an objective response to retreatment (5 CRs and 2 PRs) with duration of response to retreatment ranging from 5.3-20.7 months (ongoing at CCOD).

As no ADAs were detected in any patient (see Section 8.2.9) there is no evidence to support the potential impact of neutralizing antibodies as a theoretical mode of tolerance or resistance to therapy.

The FDA's Assessment:

In general, the FDA agrees with the Applicant's position. However, the comparison of time to events endpoints (e.g., the percentages of patients who continued to be in remission at 12 months, and PFS at 12 months) between this single-arm trial and select published literature and the conclusion that such a comparison is in favor of mosunetuzumab is not well established. Generally, FDA does not consider any inferential procedures to evaluate time to event endpoints in single-arm trials and considers these results to be descriptive and hypothesis generating only.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The Applicant's Position:

PRO-based assessments of HRQoL in patients in the NHL expansion cohorts were introduced as a secondary endpoint in protocol v6, prior to the first patient being enrolled in the expansion cohorts.

At baseline, patients in the R/R FL ≥ 2 prior therapies expansion cohorts reported normal physical functioning and slightly elevated baseline fatigue symptom scores of the EORTC QLQ-C30 questionnaire, minimal to some burden of lymphoma-specific symptoms and concerns as measured by the FACT-Lym subscale, and a low level of health status impairment at baseline as measured by the EQ-5D-5L index utility scores and VAS. Changes from baseline scores at PRO assessment visits during the first 8 cycles of initial treatment were highly variable between patients, however mean changes from baseline by visit were not clinically meaningful indicating that baseline HRQoL and health status across the cohort populations as a whole was maintained during treatment with single-agent mosunetuzumab.

In the B11 FL RP2D cohort, clinically meaningful improvements compared to baseline (≥ 10 -point for EORT QLQ-C30 and ≥ 3 -point for FACT-Lym) were observed for physical functioning score in up to 15.8% of patients, fatigue score in up to 37.9% of patients, and for lymphoma symptoms in up to 44.0% of patients at specific PRO assessment visits during the 8 cycles of initial treatment with mosunetuzumab IV monotherapy.

The FDA's Assessment:

For B11 FL RP2D cohort, the compliance rates were $>85\%$ until Cycle 8 Day 1 for all three questionnaires and remained $\geq 75\%$ afterwards. The FDA acknowledges the descriptive improvements for physical function, fatigue, and lymphoma symptoms. However, the FDA disagrees with the statement that the changes were clinically meaningful. For patient-reported disease improvement, a comparator arm along with a prespecified PRO endpoint and analysis plan are necessary for adequate interpretation. Additionally, the single-arm, open-label trial design limits the PRO data interpretation since a patients' knowledge of the treatment regimen may lead to systematic overestimation or underestimation of the treatment effect.

Additional Analyses Conducted on the Individual Trial

Data:

CR rate and ORR by Subgroup

Subgroup analyses of the CR rate and ORR by IRF assessment demonstrated the consistency of the treatment effect across relevant subpopulations defined by demographic (gender, age range categories, race/ethnicity, ECOG PS), baseline disease (bulky disease), prior treatment (number of prior systemic therapies, and refractory status to those prior treatments), and prognostic factors (FLIPI risk factor). CR rate and ORR for all subgroups were consistent with the response rates of the overall cohort. No major differences were observed among the

subgroups. Specifically, consistent CR rates were observed in high-risk patient populations, including those with double refractory disease (50%), those who progressed within 24 months of initial treatment (57%), and those with disease refractory to PI3K inhibitors (50%).

Time to Response

Among the 72 patients who achieved an objective response (CR or PR) by IRF in the B11 FL RP2D cohort, the median time to first response was 1.4 months (range: 1.1–8.9 months), while median time to first CR in the 54 patients who achieved a CR (by IRF) was 3.0 months (range: 1.1–18.9 months).

Response Beyond 8 Cycles of Mosunetuzumab IV Monotherapy

A late initial response or deepening of a response was observed in some patients who had SD or PR per Investigator assessment at the end of Cycle 8 and who received further mosunetuzumab treatment beyond 8 cycles. Of the 16 patients who received >8 cycles of mosunetuzumab IV monotherapy in the B11 FL RP2D cohort, 14 patients had tumor assessments beyond Cycle 8. Of these 14 patients, 6 patients who had a best response of SD or PR by the end of Cycle 8 had a late initial response or deepening of response (1 SD→PR, 5 PR→CR), 6 patients maintained SD (3) or their PR (3), and 1 patient progressed (SD→PD)(One other patient received mosunetuzumab doses beyond Cycle 8 despite having a CR at the end of Cycle 8 [captured as a major protocol deviation]). These data indicate the benefit of continuing mosunetuzumab IV monotherapy treatment beyond 8 cycles for patients who demonstrate disease control but have not yet achieved a complete response at Cycle 8.

Time to Next Treatment

Time to next treatment (TTNT) was defined as the time from the end of study treatment to the start of new anti-lymphoma treatment (NALT) or death. Thirty patients in the B11 FL RP2D cohort started NALT and 3 additional patients had died prior to starting NALT (33 events, 36.7%). The K-M–estimated median TTNT in the B11 FL RP2D cohort was not estimable. The 12–month event-free rate was 68.1% (95% CI: 58.3, 77.9).

The FDA’s Assessment:

In general, the FDA agrees with the Applicant’s position and the above results of subgroup analyses, time to response, response beyond 8 cycles of treatment, and time to next treatment. There were a limited number of patients (N = 16) that achieved a PR or SD with the initial 8 cycles of mosunetuzumab and received additional treatment (up to 17 cycles). As noted in the Applicant’s position, of 14 patients with response assessments beyond Cycle 8, 6 patients had a deepening of response and 6 patients maintained their initial responses. In the context of limited patient numbers, this data provides some preliminary supportive evidence for continuation of treatment with mosunetuzumab beyond 8 cycles for patients that achieve a PR or SD with initial therapy.

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:

Not applicable. See Sections below.

8.1.4. Assessment of Efficacy Across Trials

Not applicable as efficacy to support the application is based on the single pivotal study GO29781.

The FDA's Assessment:

The FDA agrees with the Applicant's position. The efficacy analysis is solely based on Study GO29781 and an integrated summary of efficacy was not included in the application. FDA notes that Study GO29781 was adequate to support the efficacy of the mosunetuzumab IV monotherapy in the indicated population.

8.1.5. Integrated Assessment of Effectiveness

The Applicant's Position:

Treatment with mosunetuzumab IV monotherapy induced durable complete remission in the majority of patients with R/R FL who had received at least two prior anti-lymphoma therapies, including patients who were refractory to multiple classes of prior treatment and with poor prognostic factors.

In the primary efficacy analysis based on a CCOD of 15 March 2021, the IRF-assessed CR rate of 57.8% (95% CI: 46.9, 68.1) with mosunetuzumab IV monotherapy at the intended registration dose at that time was statistically significantly greater than a historical control CR rate of (b) (4)% for patients with R/R FL ≥ 2 prior therapies (exact binomial test, two-sided p value < 0.0001) based on CR rates reported for copanlisib in the CHRONOS-1 study (Dreyling et al. 2017), and compares favorably with other approved therapies (Table 22).

Compared with therapies specifically approved to treat patients with R/R FL after 2 or 3 prior systemic therapies, the updated IRF-assessed CR rate based on a CCOD of 27 August 2021 (60.0% [95% CI: 49.1, 70.2]) and ORR 80.0% (95% CI: 70.3, 87.7) achieved by mosunetuzumab is greater than the respective response rates for the PI3K inhibitors idelalisib, copanlisib, duvelisib, and umbralisib, and the EZH2 inhibitor tazemetostat (CR range: 1–14%; ORR range: 34–69%; Table 22). The difference in response rate with mosunetuzumab appeared clinically meaningful as the lower bound 95% CI for the IRF-assessed CR rate (49.1%) and ORR (70.3%) exclude the reported point estimates for the respective response rates for the PI3K inhibitors. In addition, the K-M estimated median DOR in the pivotal B11 FL RP2D cohort of GO29781 was

22.8 months (95% CI: 9.7, NE), however this estimate was based on <10% of responders remaining at risk and therefore may not be robust. Among responders, an estimated 56.9% remained in remission at 18 months after the first response, which compares favorably with median DORs ranging from 10 to 13 months for these approved therapies (Table 22). The proportion of patients who achieved CR and the durability of responses for patients with R/R FL ≥ 2 prior therapies treated with mosunetuzumab approach the results of axicabtagene ciloleucel, a CAR-T therapy (60% CR, 91% ORR; Table 22). While CAR-T therapies have shown efficacy, their use may be limited by treatment delay associated with the ex-vivo T-cell manipulation (median time from leukapheresis to product infusion 27 days [range 19 to 250 days]) and complex CAR-T manufacturing, which may be prohibitive in patients with rapidly progressing disease, as well as the high incidence of CRS and neurological adverse events (see Section 8.2.11). Of available therapies approved for first- and/or second-line FL which can be used as third-line and subsequent therapy, the CR rates for the combinations of rituximab plus lenalidomide (R-Len) and obinutuzumab plus bendamustine (G-B) in the third-line R/R FL setting (13-34% and 20%, respectively) are lower than for mosunetuzumab, while objective responses (57%-81% and 75%, respectively) are similar (Table 22; FDA Multidisciplinary Review and Evaluation of UKONIQ® and TAZVERIK®). However, the studies which supported the regular approval of R-Len (MAGNIFY and AUGMENT) and G-B (GADOLIN) enrolled earlier-line, less refractory, and less heavily pretreated patients with R/R FL than the GO29781 study. The highest response rates with R-Len were observed in AUGMENT, which enrolled patients without rituximab-refractory disease, compared to MAGNIFY (47% rituximab-refractory for patients with FL ≥ 2 prior therapies) whereas 79% of patients in GO29781 were refractory to a prior anti-CD20 therapy. Compared to R-Len in patients with R/R FL ≥ 2 prior therapies in MAGNIFY, the DOR for mosunetuzumab appears longer. The response rates for G-B in GADOLIN in the third-line setting were based on patients with rituximab-refractory FL who had received a median of 2 (range 2-10) prior therapies whereas in GO29781, patients had received a median of 3 (2-10) prior therapies.

The deep and durable responses to single agent mosunetuzumab are clinically meaningful and may demonstrate advantages over approved therapies for the treatment of patients with R/R FL ≥ 2 prior therapies, a patient population with a high unmet medical need, who have rapidly progressing disease and need urgent disease control. To confirm the clinical benefit, the Applicant is conducting a randomized Phase III Study GO42909 to evaluate mosunetuzumab in combination with lenalidomide vs. rituximab in combination with lenalidomide in patients with FL after at least one line of systemic therapy with the primary efficacy endpoint of PFS. Study GO42909 is ongoing and enrolled the first patient on 27 October 2021.

Table 22: Applicant – Key Efficacy for Approved Therapies for R/R FL in ≥2 Prior Therapies Setting

Therapy (efficacy-evaluable patients)	Treatments specifically approved for R/R FL ≥2 prior therapies (accelerated approval)							Treatments approved for R/R FL (regular approval)			
	Idelalisib (N=72)	Copanlisib (N=104)	Duvelisib (N=83)	Umbralisib (N=117)	Tazemetostat		Axicabtagene ciloleucel (N=81)	Mosunetuzumab (n=90)	R-Len (N=115)	R-Len (N=67)	G-Benda (N=79)
					EZH2 WT (N=53)	EZH2 Mt (N=42)					
Study	101-09 DELTA	CHRONOS-1	DYNAMO	UTX-TGR-205	E7438-G000-101		ZUMA-5	GO29781	MAGNIFY	AUGMENT	GADOLIN
Prior therapies	≥2 ^a	≥2	≥1 ^b	≥2 ^c	≥2		≥2	≥2	≥2 ^d	≥2 ^d	≥2 ^d
Ann Arbor Stage III or IV	83% ^e	–	–	73%	–	–	–	77%	–	–	–
FLIPI high risk (3-5)	54% ^f	–	65%	–	–	–	–	44%	–	–	–
Median Prior Treatments (range)	4 (2–12)	3 (2–8)	3 (1–10)	3 (1–10)	3 (1–8)	2 (1–11)	3 (2–9)	3 (2-10)	3 (2-10)	3 (2-12)	2 (2-10)
Rituximab refractory	100%	57%	100%	32%	59%	49%	–	79% (prior anti-CD20)	47%	0	100%
Refractory to last prior therapy	86%	–	94%	36%	41%	49%	72%	69%	–	–	–
Tumor imaging ^f Response Criteria	CT/MRI IHP 2007	CT/MRI IHP 2007	CT/MRI, PET IHP 2007	CT/MRI, PET Lugano 2014	CT/MRI, PET IHP 2007		CT/MRI, PET Lugano 2014	CT/MRI, PET IHP 2007	CT/MRI IWG 1999	CT/MRI IHP 2007	CT/MRI IHP 2007
ORR (95% CI)	54% (42, 66)	59% (49, 68)	42% (31, 54)	43% (34, 52)	34% (23, 49)	69% (53, 82)	91% (83, 96)	80% (70, 88)	57% (48, 66)	81% (69, 89)	75% (63, 84)
CR	8%	14%	1%	3%	4%	12%	60%	60% (49, 70)	13%	34%	20%
Median DOR, mo	NE	12.2	10.0 ^g	11.1	13.0	10.9	NE (76% at 12 mo)	22.8 (62% at 12 mo)	5.1 (2.3, 8.5)	NR (19.6, –)	NR (19.5, –)
Median duration of follow-up, mo	8.1	5.7 (DOR fu)	10.2	20.1	35.9	22.0	14.5 (DOR fu)	14.9 (DOR fu)	–	–	–

CR, complete response; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EZH2, enhancer zeste homolog 2; FLIPI, Follicular Lymphoma International Prognostic Index; G-Benda, obinutuzumab plus bendamustine, IHP, International Harmonization Project; NE, not evaluable; ORR, objective response rate; R-Len, rituximab plus lenalidomide, WT, wild-type.

^a refractory to rituximab and alkylator.

^b refractory to rituximab and to either chemotherapy or radioimmunotherapy.

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.

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^c Approved indication in the US restricted to patients with R/R FL who have received 3 prior systemic therapies.

^d MAGNIFY, AUGMENT and GADOLIN studies enrolled patients with ≥ 1 prior therapy but data shown is subanalysis of patients with ≥ 2 Prior Therapies.

^e Salles et al. 2017.

^f Response rates and DOR shown are based on assessments by an independent review committee.

^g Due to early censoring, the estimated DOR may not be reliable.

Sources: Zydelig USPI; Copiktra USPI; Aliqopa USPI; Ukoniq USPI; Tazverik USPI; Yescarta USPI; FDA Multidisciplinary Review and Evaluation of UKONIQ® and TAZVERIK®.

The FDA's Assessment:

The efficacy of mosunetuzumab IV was based on GO29781, an open-label, multi-cohort, single-arm trial that included a cohort of 90 adult patients with relapsed or refractory follicular lymphoma who had received at least two prior therapies, including an anti-CD20 monoclonal antibody and an alkylating agent. The study excluded patients with active infections, history of autoimmune disease, prior allogeneic transplant, or any history of CNS lymphoma or CNS disorders.

Patients received mosunetuzumab at step-up doses of 1 mg on Cycle 1 Day 1 and 2 mg on Cycle 1 Day 8, followed by 60 mg on Cycle 1 Day 15, and 60 mg on Cycle 2 Day 1, then 30 mg every 3 weeks in subsequent cycles. A treatment cycle was 21 days. Mosunetuzumab was administered for 8 cycles unless patients experienced progressive disease or unacceptable toxicity. After 8 cycles, patients with a complete response discontinued therapy; patients with a partial response or stable disease continued treatment up to 17 cycles, unless patients experienced progressive disease or unacceptable toxicity.

The prespecified primary endpoint was complete response rate per independent review facility per the 2007 international working group criteria (Cheson 2007).

Among the 90 patients with relapsed or refractory FL, the median age was 60 years (range: 29 to 90 years), 33% were 65 years of age or older, 61% were male, 82% were White, 9% were Asian, 4% were Black or African American, and 8% were Hispanic or Latino. A total of 77% of patients had Stage III-IV disease, 34% had bulky disease, and all patients had an ECOG performance status of 0 or 1. The median number of prior therapies was 3 (range: 2 to 10), with 38% receiving 2 prior therapies, 31% receiving 3 prior therapies, and 31% receiving more than 3 prior therapies.

Seventy-nine percent of patients were refractory to prior anti-CD20 monoclonal antibody therapy, 53% were refractory to both anti-CD20 monoclonal antibody and alkylator therapy, 9% received prior rituximab plus lenalidomide therapy, 21% received prior autologous stem cell transplant, and 3% received prior CAR T therapy. Fifty-two percent of patients had progression of disease within 24 months of first systemic therapy.

Although CR rate is pre-specified as the primary endpoint in the protocol and statistical analysis plan, FDA considers the intermediate endpoint of ORR and duration of response (DOR) as assessed by an independent review facility according to standard criteria for NHL (Cheson 2007) as the basis for efficacy. For the B11 FL RP2D expansion cohort of 90 patients with FL, the ORR rate was 80% (95% CI: 70.3%, 87.7%), with 60% achieving a complete response. The median DOR per Kaplan-Meier method was 22.8 months (95% CI: 9.7, not estimable) with a median DOR follow-up of 14.9 months. Given the median DOR follow-up and that the KM estimate was based on <10% of responders remaining at risk, further support for DOR was assessed using the

landmark assessments of continued response at 12 months with 62% and at 18 months with 57%.

Based on the characteristics of the FL patient population enrolled in the expansion cohort of GO29781, the data support the determination that mosunetuzumab has clinically meaningful activity in patients with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy. Some limitations of the efficacy data include the limited racial and ethnic representation with 82% White, 9% Asian 4% Black or African American, and 8% Hispanic or Latino. Further characterization of mosunetuzumab in a broader ethnic and racial population is warranted and informed a postmarketing requirement. In addition, the proposed treatment regimen is to continue treatment in patients that achieve a PR or SD within the initial 8 cycles of therapy. The data for treatment beyond 8 cycles is limited with only 16 patients. Although, 6 patients had a deepening of response and 6 patients had a maintenance of response with continued treatment. The proposed treatment regimen is further supported by the data with duration of response. Nevertheless, continued evaluation of the long-term efficacy outcomes remains warranted.

For information on the efficacy data in the context of available therapy for patients with relapsed or refractory follicular lymphoma after at least 2 prior therapies, see Section 8.4.

8.2. Review of Safety

Data:

The safety database included 447 patients in the safety-evaluable population of Study GO29781 defined as all patients in Group A and Group B who received at least one dose of mosunetuzumab (as a single agent by IV administration). The primary safety analysis set comprised of 218 patients in the Group B expansion cohorts treated at the RP2D/intended registration dose and schedule of 1/2/60/30 mg (referred to as B11 RP2D), and includes 90 patients with R/R FL ≥ 2 prior therapies (referred to as B11 FL RP2D) and other histology-specific cohorts (88 DLBCL/trFL, 25 MCL, and 14 Richter's transformation; one patient with melanoma who was enrolled in error in the R/R DLBCL/trFL RP2D expansion cohort and included in safety analyses because they received one dose of mosunetuzumab treatment). In addition to the 218 patients treated with the registration dosing regimen, an additional 196 patients treated at other doses in Group B (Cycle 1 step-up) dose escalation and interim expansion cohorts (414 patients in total of mixed NHL histologies; referred as Group B) were included in the safety database to provide a comprehensive overview of the safety profile of single agent mosunetuzumab IV using the Cycle 1 step-up dosing schedule. Safety data from 33 patients with R/R NHL initially treated with escalating doses of mosunetuzumab IV monotherapy administered on a q3w fixed dosing schedule (referred as Group A) were also analyzed to complete the safety evaluation of mosunetuzumab IV monotherapy and to support exposure-response (E-R) modeling analyses and justification of RP2D determination. As the

dosing schedule was different, and patients in Group A received doses of mosunetuzumab per cycle of ≤ 2.8 mg, the starting dose in the Group B dose-escalation (C1D15 dose in the B1 cohort), Group A was analyzed separately from Group B (see Table 23).

The safety review is of data from Study GO29781 collected up to a clinical cutoff of 27 August 2021, and is an update to the primary analysis based on an earlier CCOD of 15 March 2021.

The FDA's Assessment:

The FDA's safety review was primarily focused on the 218 patients treated at the RP2D (1/2/60/30 mg) in Study GO29781, which includes the primary follicular lymphoma population of 90 patients, with a data cutoff of August 27, 2021. The safety data from the additional 196 patients with NHL (Group B) treated at different doses or schedules from the RP2D were considered supportive.

8.2.1. Safety Review Approach

The Applicant's Position:

The focus of the safety review in Study GO29781 was to establish the safety profile of mosunetuzumab in R/R NHL patients, including R/R FL patients who received ≥ 2 prior therapies.

The safety profile of single agent mosunetuzumab was assessed by analyzing the incidence and severity of all treatment-emergent AEs, serious AEs (including Grade 5 AEs), adverse events of special interest (AESIs), AEs leading to discontinuation, AEs leading to dose modification (dose reduction or interruption), clinical laboratory test abnormalities (hematology and chemistry), electrocardiograms (ECGs), vital signs, and anti-drug antibodies (ADAs).

Treatment-emergent AEs were defined as AEs with onset on the day of or after first administration of study treatment. After the initiation of the study drug, all AEs with an onset date between the first dose of study drug and 90 days after the last administration of study drug or initiation of another anti-cancer treatment, whichever occurred first, were reported. After this AE reporting period, only SAEs assessed to be related to prior study treatment were reported. Per protocol, all deaths attributed to progression of disease were to be reported as an AE (preferred term malignant neoplasm progression) if the event occurred during the protocol-specified reporting period.

Information on categorization of AEs is provided in Section 8.2.3.

The FDA's Assessment:

Safety analyses were conducted on the complete datasets provided by the Applicant with an August 27, 2021 data cutoff. The primary safety population was comprised of the 218 patients

with NHL in the group B dose expansion cohort of study GO29781 who received step-up dosing during cycle 1 of mosunetuzumab monotherapy at the RP2D of 1/2/60/30 mg. This data pool provided an adequate number of patients for a review of safety.

Ninety patients with follicular lymphoma in the B11 expansion cohort were analyzed separately to inform safety in the proposed indication in patients with relapsed or refractory follicular lymphoma.

The clinical review of safety for this BLA is based on the following:

- Clinical study report for study GO29781
- Protocol and statistical analysis plan for study GO29781
- Case report forms and safety narratives
- Summary of clinical safety
- Proposed labeling for mosunetuzumab

The Applicant reported adverse events using single MedDRA preferred terms (PTs). For increased sensitivity, FDA used a combination of grouped PTs, as defined in Appendix 19.5. Adverse events that involve more than one body system were consolidated and reported under the most commonly involved or most appropriate body system. Unless noted, all presented analyses use the FDA grouped PTs.

The Applicant reported treatment emergent deaths due to progressive disease as an adverse event per protocol. For FDA analyses, treatment emergent deaths due to progressive disease are categorized as death due to progressive disease and are not considered an adverse event.

Review of the Safety Database

Overall Exposure

Data:

Information on the safety database and analysis subsets relevant to the evaluation of the safety of single agent mosunetuzumab IV is summarized in the table below.

Table 23: Applicant – Safety Population, Size, and Denominators

	Safety Database for the Study Drug Individuals exposed to single agent mosunetuzumab IV to support the indication under review N=447	
Clinical Trial	GO29781	
Groups	Group A	Group B

	(mosunetuzumab IV by q3w fixed dosing) (n=33)	(mosunetuzumab IV by Cycle 1 step-up dosing) (n=414)
Controlled trials conducted for this indication	0	0
All other than controlled trials conducted for this indication	33 (R/R NHL)	414 (R/R NHL ^a) including 218 treated at intended registration dose and schedule (B11 RP2D) of which 90 were patients with R/R FL ≥2 prior therapies
Controlled trials conducted for other indications	0	0

^a All were patients with R/R NHL except for one patient with melanoma who was enrolled in error in the R/R DLBCL/trFL RP2D expansion cohort and included in the safety analyses because they received one dose of mosunetuzumab treatment.

The Applicant’s Position:

Single agent mosunetuzumab administered IV by Cycle 1 step-up dosing was evaluated in 196 patients with R/R NHL the Group B dose escalation at doses ranging from 0.4/1/2.8 mg to 1/2/60 mg (dose administered on C1D1/C1D8/C1D15, C2D1 and subsequent q3w cycles) and 218 patients at the proposed registration dose identified as the RP2D and schedule (1 mg on C1D1, 2 mg on C1D8, 60 mg on C1D15 and C2D1, and 30 mg for C3D1 and subsequent q3w cycles; see Section 6.2.2.1). Mosunetuzumab treatment was administered for a fixed duration, up to a maximum of 8 cycles for patients who achieved a CR after 8 cycles (approximately 5.5 months), or extended to 17 cycles for patients who achieved a PR or maintained stable disease after 8 cycles (approximately one year).

Patients in the B11 RP2D cohort received a median of 8 cycles (range: 1–17) of mosunetuzumab IV monotherapy treatment. Most patients received their planned doses of mosunetuzumab; the median dose intensity was 99.4% and 81.7% of patients achieved a dose intensity of >90%. The median duration of treatment of mosunetuzumab was 4.9 months (range 0.03–13.8), which corresponds approximately to the median of 8 x q3w cycles received. At the time of the CCOD, the median observation time in the B11 RP2D cohort was 14.3 months (range: 0.1–27.9 months).

Cumulative exposure to mosunetuzumab in Group B was less than in the B11 R2PD cohort, due to fewer median number of cycles received and the lower doses used in the dose escalation portion of the study to establish the RP2D. Generally, the extent of exposure to mosunetuzumab in the B11 FL RP2D cohort was similar to the B11 RP2D cohort, with the exception of a higher proportion of patients in the B11 FL RP2D cohort that received the full

8 cycles (58.9%) of treatment compared to the B11 RP2D cohort (36.7%), due to lower rates of early disease progression in the patients with R/R FL.

Overall, the extent of exposure to mosunetuzumab in Study GO29781 is consistent with the expected exposure and treatment duration for the indicated patient population.

The FDA's Assessment:

The FDA's safety review was focused on the 218 patients treated at the RP2D in Study G029781 (referred to as the primary safety population). The proposed dosing regimen was mosunetuzumab administered at 1.0 mg on Cycle 1 Day 1 (C1D1), 2.0 mg on C1D8, 60 mg on C1D15 and C2D1, and 30 mg for subsequent doses of a 21-day cycle. The median exposure duration for patients in the B11 RP2D cohort and FL cohort was similar, 4.9 months each. Eighty-one to eighty-two percent of patients achieved a relative dose intensity of >90% in the FL cohort and the B11 RP2D cohort. A larger percentage of patients received 8 cycles of therapy in the B11 FL cohort as compared to the B11 RP2D cohort which likely reflects the heterogeneity of the histologies included in the RP2D cohort, including aggressive NHL histologies. The safety data provided for patients treated beyond cycles 8 is limited for both cohorts.

Table 24: FDA Summary of Exposure

		B11 FL N = 90	B11 RP2D N = 218
Exposure duration, months	Median	4.9	4.9
	Range	(0.03-13.4)	(0.03-13.8)
	Q1, Q3	4.9, 5.9	1.4, 5.2
Relative dose intensity	Median	98.7	99.4
	≥90%	81.1	81.7
Number of treatment cycles	Median	8	8
	Min	1	1
	Max	17	17
Number of Cycles, n (%)	< 8	21 (23)	105 (48)
	8	53 (59)	80 (37)
	9-16	5 (6)	16 (7)
	17	11 (12)	17 (8)
Abbreviations: FL, follicular lymphoma; RP2D, recommended phase 2 dose (1/2/60/30 mg) Source: FDA analysis			

Relevant characteristics of the safety population:**Data:**

The demographics of the primary safety population (B11 RP2D cohort, n=218) was similar to the primary efficacy population (B11 FL RP2D, n=90; see Table 19) with respect to gender (66.5% male) and race (82.1% White) while the median age (64.0 years) and proportion of patients >65 years (43.1%) was slightly higher.

Patients with R/R NHL of the following histologies were represented in the B11 RP2D cohort: FL: 41.3%; DLBCL/trFL: 40.4%; MCL: 11.5%; Richter's transformation: 6.4%; and other histologies: 0.5%. A higher proportion of patients in the B11 RP2D cohort compared to the B11 FL RP2D cohort had ECOG PS 1 (54.1% vs. 41.1%), Stage IV disease at study entry (60.8% vs. 48.9%), and had received prior CAR-T therapy (13.8% vs. 3.3%), which may reflect the approval status of this therapeutic option at the time.

The Applicant's Position:

Overall, patients with R/R NHL in the primary safety population had similar demographic and baseline characteristics as patients with R/R FL in the primary efficacy population (and expected target population). The noted differences may be attributed to the more aggressive nature of DLBCL/trFL, which was represented in 40.4% of patients in the B11 RP2D cohort.

The FDA's Assessment:

The patient characteristics for patients in the B11 FL cohort and the B11 RP2D cohort are shown in the table below. In the 218 patients in the B11 RP2D cohort, the median age was 64, 67% were male, the majority of patients were White at 82%, and all patients had an ECOG status of 0-1. In the 90 patients in the B11 FL cohort, the median age was younger at age 60, 61% were male, 82% were White, and all patients had an ECOG status of 0-1. The median number of prior therapies was 3 in both cohorts. Of note, 38% of patients in the FL cohort had received 2 prior therapies. Fifty-two percent of patients in the FL cohort had progression of disease within 24 months (POD 24) disease.

Of note, there was limited representation regarding race and ethnicity with 3% to 4% Black or African American and 5% to 8% Hispanic or Latino. In addition, the median age in the FL cohort was 60. Despite this cohort consisting of patients with relapsed or refractory disease, the population was younger than the median age of initial diagnosis in the U.S. at age 63 years (SEER Cancer Statistics 2020).

Table 25: FDA Summary of Patient Demographics

Characteristic	B11 FL N = 90	B11 RP2D N = 218
Age		
Median	60	64
Range	(29, 90)	(24, 96)
≥65, n (%)	30 (33)	102 (47)
≥75, n (%)	7 (8)	39 (18)
Sex, n (%)		
Male	55 (61)	145 (67)
Female	35 (39)	73(33)
Race, n (%)		
White	74 (82)	179 (82)
Black	4 (4)	6 (3)
Asian	8 (9)	23 (11)
American Indian	1 (1)	1 (8)
Unknown	3 (3)	9 (4)
Ethnicity, n (%)		
Hispanic	7 (8)	10 (5)
Non-Hispanic	77 (86)	198 (91)
Not reported	5 (6)	6 (3)
Unknown	1 (1)	4 (2)
Country, n (%)		
US	40 (44)	95 (44)

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Non-US	50 (56)	123 (56)
Australia	17 (19)	56 (26)
Canada	13 (14)	26 (12)
Germany	6 (7)	7 (3)
Spain	8 (9)	16 (7)
Great Britain	2 (2)	4 (2)
Korea	4 (4)	14 (6)
ECOG PS, n (%)		
0	53 (59)	100 (46)
1	37 (41)	118 (54)
2	0	0
Diagnosis, n (%)		
FL	90 (100)	90 (41)
DLBCL/trFL	0	88 (40)
MCL	0	25 (11)
Richter's	0	14 (6)
Other	0	1 (<1)
Prior Therapies, n (%)		
Median (range)	3 (2-10)	3 (1-13)
1	0	5 (2)
2	34 (38)	74 (34)
3	28 (31)	65 (30)
≥3	28 (31)	74 (34)
Prior Therapy, n (%)		
Anti-CD20	90 (100)	218 (100)
Alkylator	90 (100)	214 (98)
ASCT	19 (21)	41 (19)
CD19	2 (2)	28 (13)
CAR-T	3 (3)	30 (14)
IMiD	13 (14)	23 (11)
PI3K	17 (19)	22 (10)
BTKi	6 (7)	46 (21)
Stage, n (%)		
1	5 (6)	9 (4)
2	16 (18)	26 (12)
3	25 (28)	50 (23)
4	44 (49)	132 (61)
Not reported	1 (1)	1 (<1)
FLIPI, n (%)		
0-1	26 (29)	-
2	24 (27)	-

3-5	40 (44)	-
Unknown	0	-
POD24, n (%)	47 (52)	144 (66)
Refractory, n (%)		
Last therapy	62 (69)	165 (76)
Anti-CD20	71 (79)	175 (80)
Anti-CD20 and Alkylator	48 (53)	138 (63)
Abbreviations: FL, follicular lymphoma; RP2D, recommended phase 2 dose (1/2/60/30 mg); US, United States; ECOG PS Eastern Cooperative Oncology Group Performance Status; DLBCL/trFL, diffuse large B cell lymphoma/transformed follicular lymphoma; MCL, mantle cell lymphoma; ASCT, autologous stem cell transplant; CAR-T, chimeric antigen T cell therapy; IMiD, immunomodulatory drug; PI3Ki, phosphoinositide 3-kinase inhibitor; BTKi, Bruton tyrosine kinase inhibitor; FLIPI, Follicular Lymphoma International Prognostic Index; POD24, Progression of disease within 2 years Source: FDA Analysis		

Adequacy of the safety database:

The Applicant’s Position:

The Applicant believes that the safety analysis set of 414 patients with R/R NHL including 218 patients treated with the registration dosing regimen (of which 90 patients with R/R FL $\geq$ 2 Prior Therapies represented the patient population for the proposed indication) is sufficient to adequately evaluate the incidence of toxicities and to support registration of mosunetuzumab for the proposed indication.

The adequacy of the total patient exposure of mosunetuzumab to support registration in the target population was discussed at a Type B End-of-Phase I meeting (17 March 2020. Ref ID: 4577186). The FDA considered the planned safety database at that time to be reasonable.

The FDA’s Assessment:

The size of the extended safety database of 414 patients with NHL who received mosunetuzumab monotherapy, the size of the primary safety database of 218 patients with NHL who received mosunetuzumab at the RP2D, and the size of the primary efficacy population of 90 patients with FL are considered adequate for review.

8.2.2. Adequacy of Applicant’s Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

No issues relating to safety data integrity or quality were identified for Study GO29781.

There were no reported major COVID-19-related protocol deviations with a potential impact on AE reporting.

The FDA's Assessment:

The FDA agrees with the Applicant's position. The quality of the safety data submitted was adequate for substantive review. The Applicant provided full datasets for patients enrolled in GO29781.

Categorization of Adverse Event

The Applicant's Position:

Verbatim descriptions for AEs entered by the investigators were assigned to preferred terms (PTs) by using MedDRA Version 24.0. AE severity (with the exception of CRS events) and routine laboratory parameters were graded using the NCI CTCAE v4.0. AEs were then presented by PT and system organ class (SOC).

Dedicated analyses were conducted for adverse events of special interest (AESI) specific for mosunetuzumab based on evolving clinical experience in clinical studies. The AESI categories were cytokine release syndrome (CRS), neurologic AEs and a subset of driving-impacting cognition or consciousness neurologic adverse event (DI-CCNAEs), hematologic AEs, hemophagocytic lymphohistiocytosis (HLH), tumor lysis syndrome, tumor flare, hepatic AEs, infections, and pneumonitis or interstitial lung disease (as requested by the FDA at the Type B Pre-BLA meeting held on 21 January 2021, to discuss content and format. Ref ID: 4749002). Search definitions used were based on either singular MedDRA Preferred Term [PT] or multiple PTs under defined SMQs, SOCs or specific adverse grouped terms as detailed in Table 3 of the GO29781 CSRs.

Per protocol, investigators graded CRS events according to the Lee 2014 grading criteria (Lee et al. 2014). CRS events based on the ASTCT 2019 grading criteria were derived programmatically from the reported data, based on the presence of fever and the presence and management of hypotension or hypoxia as reported in the CRS signs/symptoms eCRF (Lee et al. 2019). CRS events by both Lee 2014 and ASTCT 2019 grading are reported in the clinical study reports for the GO29781 study supporting this application. The summary of safety results presented in Section 8.2.4 below describe CRS events according to ASTCT 2019 grading criteria.

The FDA's Assessment:

The FDA agrees with the Applicant's position. All adverse events and serious adverse events were captured during the trial and for up to 90 days after the last dose of study treatment or until the initiation of another systemic anti-cancer therapy, whichever occurred first. The FDA's

review of safety is focused on treatment emergent adverse events (TEAE) that occurred within 30 days of the last dose of study treatment. Given the single-arm trial design and the absence of a comparator arm, FDA considers all TEAEs regardless of investigator attribution.

Routine Clinical Tests

The Applicant's Position:

Routine clinical tests included physical examinations, laboratory tests, ECGs and vital signs.

A complete physical exam was scheduled at screening with targeted symptom-directed physical exams schedule at subsequent visits. As part of the clinical examination, patients were routinely assessed for any signs or symptoms of neurologic toxicity.

Laboratory tests for hematology, serum chemistry and creatinine, coagulation parameters, LDH, C-reactive protein and serum ferritin were conducted at local laboratories at the study site. Viral serology and detection was conducted at screening.

Triplicate 12-lead electrocardiogram (ECG) recordings were scheduled at screening (baseline), before and at the end of infusion on Days 1 and 15 of Cycle 1 and before the infusion on Cycle 4. ECGs were also performed when clinically indicated.

Vital signs (systolic, and diastolic BP, respiratory rate, pulse oximetry, pulse rate and body temperature) were assessed before, during, at the end, and after infusions. In the event of a suspected anaphylactic reaction during mosunetuzumab administration patients were monitored with continuous electrocardiogram and pulse oximetry.

Specific tests for PK, ADAs, serum cytokines and other biomarkers in blood samples or other biological samples were conducted at a central lab/specialty bioanalytics lab.

The FDA's Assessment:

The FDA agrees with the Applicant's position. The frequency of safety monitoring was considered adequate in the context of the study.

8.2.3. Safety Results

Deaths

Data:

Table 26: Applicant – Summary of Deaths

	Treatment Group

	Group A N=33 n (%)	Group B N=414 n (%)	B11 RP2D N=218 n (%)	B11 FL RP2D N=90 n (%)
Total Deaths^a	17 (51.5)	174 (42.0)	82 (37.6)	8 (8.9)
Due to progressive disease ^b	15 (45.5)	148 (35.7)	68 (31.2)	6 (6.7)
Due to adverse event (non-PD)	1 (3.0)	6 (1.4)	4 (1.8)	1 (1.1)
Due to other reasons ^c	1 (3.0) ^d	20 (4.8) ^e	10 (4.6) ^f	1 (1.1)
Within 30 days after last dose	1 (3.0)	32 (7.7)	15 (6.9)	1 (1.1)
Due to progressive disease	0	29 (7.0)	14 (6.4)	1 (1.1)
Due to adverse event (non-PD)	1 (3.0)	3 (0.7)	1 (0.5)	0
Due to other reasons ^c	0	0	0	0
Beyond 30 days after last dose	16 (48.5)	142 (34.3)	67 (30.7)	7 (5.6)
Due to progressive disease ^b	15 (45.5)	119 (27.8)	54 (24.8)	5 (4.4)
Due to adverse event (non-PD)	0	3 (0.7)	3 (1.4)	1 (1.1)
Due to other reasons ^c	1 (3.0) ^d	20 (4.8) ^e	10 (4.6) ^f	1 (1.1)

^a All patient deaths are included, including those which occurred in the Initial or Re-treatment phases.

^b Includes death attributed to progression of disease occurring during adverse event reporting period which, per protocol, were reported as fatal adverse events of malignant neoplasm progression, see Table 11.

^c Patients who had discontinued mosunetuzumab study treatment and died outside of the AE reporting period. Primary cause of death given as "Other" on the Study Completion/Early Discontinuation eCRF page. Specific details provided by the investigator are in footnotes d, e, and f.

^d Death due to unknown cause (single patient in Group A).

^e Death due to unknown cause (3 patients), pulmonary hemorrhage, acute renal failure, graft-versus-host disease, bowel perforation (bacteremia), acute myeloid leukemia, sepsis, and cardiopulmonary respiratory failure (10 patients in Group B dose escalation) in addition to footnote f.

^f Death due to unknown cause (5), pneumonia, cardiac arrest, decline in health related to lung cancer, stroke and sepsis (unknown origin)(1 each) (10 patients in B11 RP2D).

Source: Tables 37 and 38 and of Update GO29781 CSR Report No.1111637; output

I_dd_INIT_GRPAB_SE_15MAR2021_29781.

Table 27: Applicant – Grade 5 Adverse Events

Adverse Event	Treatment Group			
	Group A N=33 n (%)	Group B N=414 n (%)	B11 RP2D N=218 n (%)	B11 FL RP2D N=90 n (%)
Deaths due to Adverse Event	5 (15.2%)	59 (14.3)	32 (14.7)	2 (2.2)
Initial Treatment Period				
Malignant neoplasm progression ^a	4 (12.1%)	53 (12.8)	28 (12.8)	1 (1.1)
Pneumonia	0	2 (0.5)	1 (0.5)	0
Sepsis	0	2 (0.5)	1 (0.5)	0
Cholangitis	0	1 (0.2)	1 (0.5)	0
Death ^b	0	1 (0.2)	1 (0.5)	1 (1.1)
Hemophagocytic lymphohistiocytosis	1 (3.0%)	0	0	0
Retreatment Period				
Malignant neoplasm progression ^a	0	2 (0.5)	0	0

^a Death attributed to progression of disease was a reportable AE per study protocol if the event occurred in the AE reporting period (within 90 days of the last dose of study drug, or before the initiation of another anti-cancer treatment).

^b Cause of death was unknown. A narrative for this patient and all other non-PD fatal AEs is provided.

Source: Table 7 of SCS (Module 2.7.4).

Table 28: Applicant – Grade 5 Adverse Events (non-PD) within 30 days of Last Dose of Study Drug^a

Study Cohort	Subject ID	Age/ Gender	Study Day of Death	Cause of Death	Related to Study Drug (Y/N)
A8 (2.8 mg)	(b) (6)	71/F	60	Hemophagocytic lymphohistiocytosis	Y
B7 (1/2/13.5 mg)		65/M	81	Pneumonia	Y ^b
B10 (1/2/40.5 mg)		69/M	106	Sepsis	N ^c
B11 RP2D (1/2/60/30 mg)		79/M	20	Sepsis	Y
		74/M	428	Cholangitis	N
		66/M	60	Death ^d	N

^a Includes all patients with onset of fatal AE or date of death within 30 days of last dose of study drug.

^b Immunosuppressed status of the patient was considered a contributing factor to the death.

^c Considered by investigator to be related to concurrent illness.

^d Patient was found unresponsive. Cause of death unknown.

Source: Table 8 of SCS (Module 2.7.4); output I_dd_INIT_GRPAB_SE_15MAR2021_29781.

The Applicant's Position:

A total of 82 of 218 patients (37.6%) in the B11 RP2D cohort had died. Table 26 summarizes deaths by cause. Progressive disease accounted for the majority of deaths (68/218 patients [31.2%]). A higher proportion of PD-related deaths occurred in patients with DLBCL, MCL, and Richter's transformation than in patients with FL. For this reason, the lowest proportion of deaths occurred in the B11 FL RP2D cohort (8/90 patients [8.9%]), than in the B11 RP2D cohort (82/218 [37.6%] or Group B overall (174/414 [42.0%]).

Of the remaining 14 deaths in the B11 RP2D cohort, 10 deaths were in patients who had discontinued mosunetuzumab treatment and occurred outside of protocol-specified AE reporting period with the primary cause of death as "Other" entered on the Study Completion/Early Discontinuation eCRF page. Specific details provided by the investigator are described in the footnote (f) to Table 26. The other 4 deaths in the B11 RP2D cohort were due to non-PD fatal AEs (i.e., other than malignant neoplasm progression, see below).

Grade 5 AEs were reported during the initial treatment with mosunetuzumab in 32/218 (14.7%) patients in the B11 RP2D cohort. The majority (28/32) of Grade 5 AEs were disease progression (PT of malignant neoplasm progression) occurring during the protocol-specified AE reporting

period. The 4 non-PD Grade 5 AEs were pneumonia, cholangitis, death 'not otherwise specified' (reported as PT of death; patient in B11 FL RP2D cohort), and sepsis (see Table 27).

Two additional non-PD Grade 5 AE of pneumonia and sepsis occurred in Group B at lower mosunetuzumab doses. One other patient (in the Group A fixed-dose cohort) died due to a fatal event of hemophagocytic lymphohistiocytosis (see Table 27).

The FDA's Assessment:

Treatment emergent deaths were assessed up to 90 days post treatment discontinuation. For safety, the FDA considers all-cause treatment emergent adverse events in the evaluation versus those indicated as treatment-related by the Applicant. The FDA concurs that as of the August 27, 2021 data cutoff, a total of 82 deaths occurred within the B11 RP2D safety population, with 4 deaths occurring with mosunetuzumab due to an adverse event. The 4 deaths included events of pneumonia, sepsis, cholangitis, and death unknown.

- For the event of death unknown, this represents a 66 year old African American male with follicular lymphoma who experienced ASTCT grade 3 CRS, confusional state (ICANS), and grade 4 acute kidney injury requiring continuous renal replacement therapy by Day 27. The CRS, acute kidney injury, and confusional state all resolved by Day 29. The patient was discharged from the hospital on Day 48, with a follow-up visit on Day 56 demonstrating a normal exam and labs. On Day 60, the patient was reported to have died due to unknown causes.

As noted in the Applicant's position, 28 patients in the B11 RP2D cohort were reported to have died due to malignant progression of disease while on treatment or within 90 days of last dose (Table 27 above). However, one patient, a 74 year old White male with DLBCL developed Grade 1 confusional state on Day 7 and Grade 4 hemophagocytic lymphohistiocytosis (HLH) on Day 8. Day 10 soluble IL2 receptor serum level was 20,000 pg/mL. By Day 13, the patient was reported to show "clinical disease progression, worsening of encephalopathy, and multiorgan dysfunction," which appeared consistent with a clinical presentation of HLH. Mosunetuzumab treatment was discontinued on Day 17 due to disease progression; however, the relative contribution of mosunetuzumab to the development of HLH versus the contribution of progressive disease to the development of HLH remains unclear. For additional information on the evaluation of HLH with mosunetuzumab, see Section 8.2.4 below.

The 90 Day Safety Update provided safety data collected through January 3, 2022. No new fatal AEs were reported in the B11 RP2D cohort in the safety update.

Serious Adverse Events

Data:

Table 29: Applicant – Most Frequent Serious Adverse Events (≥1%) by SOC and Preferred Term

Serious Adverse Events (SAE)	Treatment Group		
	Group B N=414 n (%)	B11 RP2D N=218 n (%)	B11 FL RP2D N=90 n (%)
Immune system disorders			
Cytokine release syndrome (by ASTCT)	59 (14.3)	45 (20.6)	21 (23.3)
Infections and infestations			
Pneumonia	11 (2.7)	7 (3.2)	2 (2.2)
Sepsis	6 (1.4)	4 (1.8)	1 (1.1)
Urinary tract infection	6 (1.4)	4 (1.8)	3 (3.3)
Pneumocystis jirovecii pneumonia	5 (1.2)	3 (1.4)	0
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)			
Malignant neoplasm progression	53 (12.8)	28 (12.8)	1 (1.1)
General disorders and administration site conditions			
Pyrexia	13 (3.1)	10 (4.6)	2 (2.2)
Blood and lymphatic system disorders			
Febrile neutropenia	8 (1.9)	3 (1.4)	0
Neutropenia/neutrophil count decreased	6 (1.4)	2 (0.9)	1 (1.1)
Respiratory, thoracic and mediastinal disorders			
Pleural effusion	4 (1.0)	4 (1.8)	1 (1.1)
Renal and urinary disorders			
Acute kidney injury	7 (1.7)	4 (1.8)	3 (3.3)
Psychiatric disorders			
Confusional state	4 (1.0)	3 (1.4)	1 (1.1)
Investigations			
Alanine aminotransferase increased	3 (0.7)	3 (1.4)	1 (1.1)
Aspartate aminotransferase increased	3 (0.7)	3 (1.4)	1 (1.1)

All serious AEs with incidence of ≥1% in Group B (N=414) or the B11 RP2D cohort (N=218) are shown.

Source: Table 9 of SCS (Module 2.7.4), output t_ae_ctc_SER_INIT_GRPBH_SE_15MAR2021_29781.

The Applicant's Position:

Serious adverse events (SAE) including the Grade 5 AEs, were reported in 114/218 (52.3%) of patients in the B11 RP2D cohort (Table 29). The most frequent SAEs (≥2% of patients) were CRS (20.6% by ASTCT 2019 grade), malignant neoplasm progression (12.8% [all reported as Grade 5 AEs]), pyrexia (4.6%), and pneumonia (3.2%). SAEs in the SOC of Infections and Infestations were reported in 17.0% of patients.

The majority of patients with serious CRS events experienced Grade 1–2 events at the highest grade. Serious pyrexia events were also predominantly Grade 1–2 and did not occur

concurrently with CRS.

Overall, 42/90 patients (46.7%) in the B11 FL RP2D cohort experienced SAEs. Compared to the B11 RP2D cohort there was a similar proportion of patients with serious CRS events (21 patients [23.3%] by ASTCT 2019) and a smaller proportion of patients with malignant neoplasm progression (1 patient [1.1%]). The frequency and nature of most commonly reported SAEs in the B11 RP2D cohort were similar to overall Group B.

The FDA's Assessment:

In general, the FDA agrees with the Applicant's summary of all-cause serious treatment emergent adverse events. The table below provides a summary of the FDA analysis of SAEs with an incidence of 2% or greater using grouped preferred terms in the B11 RP2D NHL and B11 FL pools. In the B11 RP2D cohort, 52% (114/218) experienced an SAE, most often due to CRS (21%), pneumonia (5%), pyrexia (5%), sepsis (3%), and a 2% incidence each of tumor flare, urinary tract infection, pleural effusion, and renal insufficiency.

Table 30: FDA Summary of Serious Adverse Events in ≥2% of Patients

	B11 FL N = 90 n (%)	B11 RP2D NHL N = 218 n (%)
Any SAE	42 (47)	114 (52)
Immune system disorders		
CRS (by ASTCT)	22 (24)	46 (21)
Tumor flare	2 (2)	4 (2)
Infections and infestations		
Pneumonia	2 (2)	10 (5)
Sepsis	3 (3)	7 (3)
UTI	4 (4)	5 (2)
COVID-19	2 (2)	2 (<1)
EBV	2 (2)	2 (<1)
General disorders		
Pyrexia	2 (2)	10 (5)
Respiratory, thoracic and mediastinal disorders		
Pleural effusion	1 (1)	4 (2)
Renal and urinary disorders		
Renal insufficiency	3 (3)	4 (2)
Abbreviations: FL, follicular lymphoma; RP2D, recommended phase 2 dose; NHL, non-Hodgkin lymphoma; CRS, cytokine release syndrome; ASTCT, American Society for Transplantation and Cellular Therapy; UTI, urinary tract infection; EBV, Epstein-Barr-Virus Source: FDA Analysis		

Dropouts and/or Discontinuations Due to Adverse Effects**Data:****Table 31: Applicant – Summary of Treatment Discontinuation**

	Treatment Group		
	Group B N=414 n (%)	B11 RP2D N=218 n (%)	B11 FL RP2D N=90 n (%)
Treatment Discontinuation due to Adverse Event	15 (3.6)	7 (3.2)	4 (4.4)
Treatment Discontinuation due to "Other"	258 (62.3)	130 (59.6)	32 (35.6)
Reasons for "Other"			
Progressive disease	224 (54.1)	109 (50.0)	25 (27.8)

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Physician decision	15 (3.6)	11 (5.0)	4 (4.4)
Withdrawal by subject	8 (1.9)	5 (2.3)	1 (1.1)
Use of another anti-cancer therapy	5 (1.2)	2 (0.9)	2 (2.2)
Death	4 (1.0)	2 (0.9)	0
Other	1 (0.2) ^a	1 (0.5) ^a	0

Table shows reasons for discontinuation from initial mosunetuzumab IV monotherapy treatment (i.e., not re-treatment).

^a Patient with melanoma who was enrolled in error into the B11 R/R DLBCL/trFL cohort and received one dose of initial treatment discontinued treatment on Day 3 due to disease diagnosis not meeting the eligibility criteria.

Source: Table 5 of Update GO29781 CSR Report No.1111637.

Table 32: Applicant – Adverse Events Leading to Treatment Discontinuation

Adverse Events	Treatment Group		
	Group B N=414 n (%)	B11 RP2D N=218 n (%)	B11 FL RP2D N=90 n (%)
Patients with Adverse Event^a	19 (4.6)	9 (4.1)	4 (4.4)
Cytokine release syndrome (ASTCT)	2 (0.5)	2 (0.9)	2 (2.2)
Sepsis ^b	3 (0.7)	1 (0.5)	0
Epstein-Barr viremia	1 (0.2)	1 (0.5)	1 (1.1)
Hodgkin's disease	1 (0.2)	1 (0.5)	1 (1.1)
Cholangitis ^b	1 (0.2)	1 (0.5)	0
Lung neoplasm malignant	1 (0.2)	1 (0.5)	0
Myocardial infarction	1 (0.2)	1 (0.5)	0
Subdural hematoma	1 (0.2)	1 (0.5)	0
Alanine aminotransferase increased	1 (0.2)	0	0
Arthritis	1 (0.2)	0	0
Atrial flutter	1 (0.2)	0	0
Candida sepsis	1 (0.2)	0	0
Clostridium difficile infection	1 (0.2)	0	0
Liver function test increased	1 (0.2)	0	0
Neutropenia/neutrophil count decreased	1 (0.2)	0	0
Pneumonia ^b	1 (0.2)	0	0

^aTotal number of patients with AEs leading to discontinuation includes patients with treatment discontinuation due to adverse event and treatment discontinuation due to death from Table 14 due to data being reported in different pages of the eCRF.

^bFatal AEs that led to study treatment discontinuation include 2 sepsis, cholangitis and pneumonia (see Table 11).
Source: t_ae_DSC_INIT_GRPBH_SE_15MAR2021_29781; t_aesi_bysmq_INIT_GRPBH_SE_15MAR2021_29781.

The Applicant's Position:

Adverse events led to the discontinuation of mosunetuzumab treatment in 9/218 patients (4.1%) in the B11 RP2D cohort (Table 32). In 7 patients (3.2%) the AEs were serious and were fatal events of sepsis and cholangitis (see Table 27), Grade 4 Epstein-Barr viremia, Grade 3 CRS (ASTCT; Grade 4 by Lee 2014), subdural hematoma and myocardial infarction, and Grade 2 CRS. At the RP2D, the two serious CRS events, were the only AEs that led to mosunetuzumab discontinuation in more than one patient (both in the B11 FL RP2D cohort) and both events resolved. The CRS, sepsis, and myocardial infarction events which led to treatment discontinuation were considered to be related to mosunetuzumab by the investigator.

A similar proportion of patients in the B11 FL RP2D cohort (4.4%) and Group B (4.6%) discontinued mosunetuzumab due to AEs compared to the B11 RP2D cohort.

The FDA's Assessment:

In general, the FDA agrees with the Applicant's summary of all-cause adverse events leading to treatment discontinuation. For safety, the FDA considers all-cause treatment emergent adverse events in the evaluation versus those indicated as treatment-related by the Applicant. The FDA analysis of TEAEs in the B11 RP2D leading to treatment discontinuation is consistent with the data presented in Table 32 above. Overall, treatment discontinuation due to a TEAE occurred in 4% (9/218). The most common adverse event leading to discontinuation was CRS.

Dose Interruption/Reduction Due to Adverse Effects

The Applicant's Position:

Adverse events led to the mosunetuzumab dose being interrupted (delayed) or modified (reduced) in 73/218 of patients (33.5%) in the B11 RP2D cohort. The most frequently reported events ($\geq 2\%$ of patients) were neutropenia/neutrophil count decreased (25 patients [11.5%]; predominantly Grade 3 or 4), and CRS (17 patients [7.8%] by ASTCT 2019 grade; predominantly Grade 1 or 2). Dose interruptions due to AEs were the most frequent action taken with mosunetuzumab and in most cases the event resolved and patients were able to continue mosunetuzumab treatment.

Per protocol, dose reductions in mosunetuzumab were permitted if it was determined by the investigator that the clinical benefit may be maintained. A reduced dose was to be considered for the next dose when resuming dosing following the occurrence and resolution of Grade 3 CRS, other study-treatment-related Grade 3 toxicity, serious adverse event, or a DLT. Reductions in mosunetuzumab dose were infrequent, occurring in 7 patients (3.2%) in the B11 RP2D cohort and most frequently resulted from AEs with onset in Cycle 1. The AEs that led to dose reductions in more than one patient were erythematous rash/rash and Grade ≥ 3 CRS.

The overall frequency and the most commonly reported AEs leading to dose interruption or modification of mosunetuzumab were similar in the B11 RP2D cohort, B11 FL RP2D cohort, and overall Group B.

The FDA's Assessment:

In general, the FDA agrees with the Applicant's position. The table below provides a summary of the FDA analysis of adverse events leading to a dose interruption. In the B11 RP2D cohort of 218 patients, 33% experienced adverse events leading to dose interruption, most often due to neutropenia, infection, and CRS.

For dose reductions, as noted by the Applicant, 3% (7/218) of patients in the B11 RP2D cohort experienced an adverse event leading to dose reduction, most often due to CRS and rash.

Table 33: FDA Summary of Adverse Events Leading to Dose Interruption

Adverse Event	B11 FL N = 90 n (%)	B11 RP2D N = 218 n (%)
AE leading to dose interruption	33 (37)	72 (33)
Neutropenia	15 (17)	25 (12)
Infection	11 (12)	25 (11)
Upper respiratory tract infection	4 (4)	7 (3)
Pneumonia	2 (2)	7 (3)
CRS (ASTCT)	7 (8)	17 (8)
Grade 1	3 (3)	7 (3)
Grade 2	4 (4)	10 (5)
Transaminase elevation	2 (2)	5 (2)
Pyrexia	2 (2)	5 (2)
Thrombocytopenia	2 (2)	4 (2)
Abbreviations: FL, follicular lymphoma; RP2D, recommended phase 2 dose (1/2/30/60 mg); CRS, cytokine release syndrome; ASTCT, American Society for Transplantation and Cellular Therapy Source: FDA analysis		

Significant Adverse Events

The Applicant's Position:

Marked hematological and other laboratory abnormalities and events that led to withdrawal, dose interruption or reduction of mosunetuzumab treatment, or significant additional concomitant therapy are described in other sections of this document.

The FDA's Assessment:

Refer to FDA assessments in the relevant sections.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Table 34 summarizes the incidence of treatment-emergent AEs by category in patients in Group B and subpopulations of study GO29781.

Table 34: Applicant – Summary of Treatment-Emergent Adverse Events (Mosunetuzumab IV Monotherapy Administered by Cycle 1 Step-up Dosing)

	Treatment Group		
	Group B N=414 n (%)	B11 RP2D N=218 n (%)	B11 FL RP2D N=90 n (%)
All-grade AEs	408 (98.6)	214 (98.2)	90 (100.0)
Grade 3-5 AEs	296 (71.5)	157 (72.0)	63 (70.0)
Grade 3-4 AEs	273 (65.9)	145 (66.5)	63 (70.0)
Grade 5 (Deaths due to AEs)	59 (14.3)	32 (14.7)	2 (2.2)
Grade 5 (Deaths due to AEs) excluding PD SAEs	6 (1.4)	4 (1.8)	1 (1.1)
Treatment Discontinuation due to AEs	19 (4.6)	9 (4.1)	4 (4.4)
Dose Interruption or Modification due to AEs	139 (33.6)	73 (33.5)	34 (37.8)
Dose Interruption due to AEs	135 (32.6)	72 (33.0)	33 (36.7)
Dose Modification due to AEs	11 (2.7)	7 (3.2)	5 (5.6)

Source: Adapted from Table 4 of SCS (Module 2.7.4); output t_ae_DSM_INIT_SCS_SE_15MAR2021_29781.

Treatment-emergent adverse events reported in $\geq 10\%$ of patients in either Group B (N=414) or the B11 RP2D cohort (N=218) are summarized in Table 35.

Table 35: Applicant – Summary of Common (≥10%) Treatment-Emergent Adverse Events

System Organ Class (SOC)/PTs	Treatment Group					
	Group B N=414 n (%)		B11 RP2D N=218 n (%)		B11 FL RP2D N=90 n (%)	
	All grade	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3
General disorders and administration site conditions						
Fatigue	113 (27.3)	4 (1.0)	70 (32.1)	2 (0.9)	33 (36.7)	0
Pyrexia	83 (20.0)	5 (1.2)	53 (24.3)	4 (1.8)	26 (28.9)	1 (1.1)
Edema peripheral	52 (12.6)	1 (0.2)	30 (13.8)	0	10 (11.1)	0
Chills	41 (9.9)	2 (0.5)	23 (10.6)	1 (0.5)	12 (13.3)	1 (1.1)
Skin and subcutaneous tissue disorders						
Rash	64 (15.5)	2 (0.5)	42 (19.3)	2 (0.9)	14 (15.6)	1 (1.1)
Pruritus	46 (11.1)	0	31 (14.2)	0	19 (21.1)	0
Dry skin	32 (7.7)	0	27 (12.4)	0	14 (15.6)	0
Gastrointestinal disorders						
Diarrhea	78 (18.8)	2 (0.5)	38 (17.4)	0	15 (16.7)	0
Constipation	69 (16.7)	2 (0.5)	36 (16.5)	0	16 (17.8)	0
Nausea	69 (16.7)	1 (0.2)	38 (17.4)	1 (0.5)	15 (16.7)	0
Abdominal pain	42 (10.1)	3 (0.7)	25 (11.5)	2 (0.9)	9 (10.0)	1 (1.1)
Metabolism and nutrition disorders						
Hypophosphatemia	92 (22.2)	60 (14.5)	49 (22.5)	32 (14.7)	24 (26.7)	15 (16.7)
Hypokalemia	62 (15.0)	6 (1.4)	34 (15.6)	4 (1.8)	17 (18.9)	2 (2.2)
Hypomagnesemia	51 (12.3)	1 (0.2)	29 (13.3)	0	11 (12.2)	0
Infections and infestations						
Upper respiratory tract infection	49 (11.8)	5 (1.2)	21 (9.6)	3 (1.4)	8 (8.9)	2 (2.2)
Immune system disorders						
Cytokine release syndrome (by ASTCT)	133 (32.1)	7 (1.7)	86 (39.4)	6 (2.8)	40 (44.4)	2 (2.2)
Nervous system disorders						
Headache	78 (18.8)	1 (0.2)	44 (20.2)	1 (0.5)	28 (31.1)	1 (1.1)
Respiratory, thoracic and mediastinal disorders						
Cough	61 (14.7)	0	33 (15.1)	0	16 (17.8)	0
Investigations						
Alanine aminotransferase increased	36 (8.7)	13 (3.1)	23 (10.6)	10 (4.6)	11 (12.2)	5 (5.6)
Blood and lymphatic system disorders						
Neutropenia/neutrophil count decreased	114 (27.5)	102 (24.6)	60 (27.5)	53 (24.3)	26 (28.9)	24 (26.7)
Anemia/hemoglobin decreased	68 (16.4)	35 (8.5)	33 (15.1)	18 (8.3)	12 (13.3)	7 (7.8)
Thrombocytopenia/platelet count decreased	34 (8.2)	20 (4.8)	25 (11.5)	15 (6.9)	9 (10.0)	4 (4.4)
Musculoskeletal and connective tissue disorders						
Back pain	49 (11.8)	4 (1.0)	17 (7.8)	1 (0.5)	9 (10.0)	1 (1.1)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)						
Malignant neoplasm progression	53 (12.8)	53 (12.8)	28 (12.8)	28 (12.8)	1 (1.1)	1 (1.1)

System Organ Class (SOC)/PTs	Treatment Group					
	Group B N=414 n (%)		B11 RP2D N=218 n (%)		B11 FL RP2D N=90 n (%)	
	All grade	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3
Psychiatric disorders						
Insomnia	44 (10.1)	0	25 (11.5)	0	9 (10.0)	0

Table includes treatment-emergent AE with incidence rate of ≥10% in Group B (N=414) or the B11 RP2D cohort (N=218).

Source: adapted from output t_ae_ctc_INIT_GRPBH_SE_15MAR2021_29781.

The Applicant's Position:

The majority of patients treated with mosunetuzumab IV monotherapy by Cycle 1 step-up dosing at the intended registration dose and schedule experienced at least one AE of any grade (see Table 34). Most AEs were Grade 1–2 in severity. The most common AE reported was CRS (39.4% by ASTCT 2019 grade), which were predominantly Grade 1–2, limited primarily to Cycle 1, and were manageable and reversible (all CRS events resolved). Other common AEs (≥ 20% incidence) in the B11 RP2D cohort were fatigue, neutropenia/neutrophil count decreased, pyrexia, hypophosphatemia, and headache.

By SOC, AEs were most frequently reported (≥50% patients) under General Disorders and Administration Site Conditions (61.5%) driven mainly by fatigue and pyrexia, Skin and Subcutaneous Tissue Disorders (56.4%) driven mainly by rash and pruritus, Gastrointestinal Disorders (55.0%) driven mainly by diarrhea, constipation, and nausea, and Metabolism and Nutrition Disorders (52.3%) driven mainly by hypophosphatemia, hypokalemia and hypomagnesemia.

Overall, the nature, severity, and frequency of the most common AEs in the B11 RP2D cohort were similar to those in B11 FL RP2D cohort, and overall Group B.

Grade 3-4 AEs were reported in 66.5% of patients in the Group B11 RP2D cohort (Table 34). The most frequently reported Grade 3–4 AEs (≥5% in the B11 RP2D cohort) were neutropenia/neutrophil count decreased (24.3%), hypophosphatemia (14.7%), anemia/hemoglobin decreased (8.3%), thrombocytopenia/platelet count decreased (6.9%), and hyperglycemia (5.5%). The majority of Grade 3-4 AEs were manageable with dose modification or interruption of mosunetuzumab.

Based on the single-arm design of the GO29781 study, for the proposed label, ADRs from mosunetuzumab IV monotherapy treatment were identified based on review of AEs (PTs or grouped PTs) with incidence ≥10% (all grades) or ≥5% for Grade 3-4 based on the B11 RP2D population (N=218). Events with an incidence of <10% (all grades) or <5% (Grade 3-4) could be included if there was a medical rationale supporting the assessment (such as a known class effect/known effect from mechanism of action), and at least one of the observed reports was

assessed by the Applicant as related to mosunetuzumab. Medical judgment would be further applied to adjudicate potential ADRs, taking into consideration the extent to which the AE was consistent with the pharmacology of the drug, apparent dose response trend, re-challenge response, temporality and the consistency of the pattern of symptoms across studies/indications, confounders and quality of information. AEs that met these criteria are the basis for the adverse reactions summarized in Table 36.

Table 36: Applicant – Adverse Reactions



(b) (4)

Source: Table 5 of draft Prescribing Information.

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

- Blood and lymphatic system disorders: Febrile neutropenia (2%)
- Infections and infestations: Urinary tract infection (7%), pneumonia (6%)
- Investigations: Aspartate aminotransferase increased (7%)
- Metabolism and nutrition disorders: Tumor lysis syndrome (1%)
- Neoplasms benign, malignant, and unspecified (including cysts and polyps): Tumor flare (2%)

The FDA’s Assessment:

Treatment emergent adverse events were assessed from the start of study drug until 30 days after the last study drug administration. In the B11 RP2D cohort, any grade TEAEs were reported in 98% and Grade 3 or 4 adverse events occurred in 66%. The FDA analysis of TEAEs (>5%) using FDA grouped preferred terms (Section 20.5) is displayed in the table below in decreasing order of incidence by system organ class and preferred term. The most common TEAEs (excluding laboratory abnormalities) in the B11 RP2D cohort (≥20%) were cytokine release syndrome, fatigue, rash, pyrexia, headache, cough and edema. The most common Grade 3 or 4 adverse events (≥3%) were pneumonia, cytokine release syndrome, sepsis, and renal insufficiency. For laboratory abnormalities, see the Laboratory Findings section below.

For adverse reactions, the FDA disagrees with the Applicant’s definition as stated above. Given the single-arm trial design of GO29781, FDA considers all TEAEs as an adverse drug reaction unless unequivocally due to the underlying disease or an extraneous cause. For the mosunetuzumab prescribing information (USPI), the adverse reactions included are based on the FDA definition.

Table 37: FDA Summary of Treatment Emergent Adverse Events Occurring in >5% of Patients

System Organ Class and Preferred Term	B11 FL N = 90 n (%)		B11 RP2D N = 218 n (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Immune system disorders CRS (ASTCT)	40 (44)	2 (2)	86 (39)	6 (3)
General disorders and administration site conditions				
Fatigue	39 (43)	0	80 (37)	2 (<1)
Pyrexia	26 (29)	1 (1)	53 (24)	4 (2)
Edema	15 (17)	1 (1)	43 (20)	1 (<1)
Chills	12 (13)	1 (1)	23 (11)	1 (<1)
Flushing	7 (8)	0	11 (5)	0
Hyperhidrosis	6 (7)	0	8 (4)	0

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System Organ Class and Preferred Term	B11 FL N = 90 n (%)		B11 RP2D N = 218 n (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Skin and subcutaneous tissue disorders				
Rash	35 (39)	4 (4)	78 (36)	5 (2)
Pruritis	19 (21)	0	31 (14)	0
Xerosis	15 (17)	0	30 (14)	0
Skin exfoliation	9 (10)	0	13 (6)	0
Urticaria	5 (6)	0	7 (3)	0
Nervous system disorders				
Headache	29 (32)	1 (1)	45 (21)	1 (<1)
Peripheral neuropathy	18 (20)	0	28 (13)	0
Dizziness	11 (12)	0	23 (11)	0
Insomnia	11 (12)	0	23 (11)	0
Pain	5 (6)	0	10 (5)	0
Respiratory, thoracic, and mediastinal disorders				
Cough	20 (22)	0	43 (20)	0
Dyspnea	10 (11)	1 (1)	21 (10)	2 (<1)
Nasal congestion	7 (8)	0	12 (6)	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain	25 (28)	1 (1)	39 (18)	2 (<1)
Arthralgia	10 (11)	0	15 (7)	0
Bone pain	6 (7)	0	8 (4)	0
Gastrointestinal disorders				
Diarrhea	15 (17)	0	38 (17)	0
Nausea	15 (17)	0	38 (17)	1 (<1)
Constipation	16 (18)	0	36 (17)	0
Abdominal pain	11 (12)	1 (1)	28 (13)	2 (<1)
Vomiting	8 (9)	0	15 (7)	2 (<1)
Oropharyngeal pain	6 (7)	0	10 (5)	0
Dyspepsia	6 (7)	0	9 (4)	0
GERD	5 (6)	0	8 (4)	0
Infections and Infestations				
URI	13 (14)	2 (2)	37 (17)	4 (2)
Pneumonia	7 (8)	3 (3)	17 (8)	7 (3)
UTI	9 (10)	1 (1)	16 (7)	3 (1)
LRI	4 (4)	0	10 (5)	2 (<1)
Renal and Urinary disorders				
Renal insufficiency	12 (13)	5 (6)	22 (10)	6 (3)
Metabolism and nutrition disorders				
Decreased appetite	6 (7)	0	16 (7)	1 (<1)
Vascular disorders				
Hypotension	5 (6)	0	11 (5)	1 (<1)

System Organ Class and Preferred Term	B11 FL N = 90 n (%)		B11 RP2D N = 218 n (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Cardiovascular disorder Chest pain	5 (6)	0	7 (3)	0

Abbreviations: FL, follicular lymphoma; RP2D, recommended phase 2 dose (1/2/30/60 mg); GERD, gastroesophageal reflux disease; CRS, cytokine release syndrome; ASTCT, American Society for Transplantation and Cellular Therapy; URI, upper respiratory infection; UTI, urinary tract infection; LRI, lower respiratory tract infection
Source: FDA analysis

Laboratory Findings

Data:

The most frequent treatment-emergent laboratory parameter abnormalities (reported in $\geq 10\%$ of patients in the B11 RP2D cohort) are shown in Table 38.

Table 38: Applicant – Most Frequent^a Treatment-Emergent Laboratory Abnormalities

Laboratory abnormalities	B11 RP2D N=218 n (%)			
	Sample size ^b	All Grades	Grade $\geq 3^c$	Grade 4
Hematology				
↓Lymphocytes	202	192 (95.0)	186 (92.1)	144 (71.3)
↓Hemoglobin	217	152 (70.0)	41 (18.9)	0
↓Leukocytes	217	133 (61.3)	47 (21.7)	9 (4.1)
↓Neutrophils	175	101 (57.7)	66 (37.7)	34 (19.4)
↓Platelets	217	97 (44.7)	26 (12.0)	11 (5.1)
↑Lymphocytes	202	27 (13.4)	3 (1.5)	0
Chemistry				
↑Creatinine	217	192 (88.5)	7 (3.2)	2 (0.9)
↓Phosphate	217	163 (75.1)	88 (40.6)	3 (1.4)
↓Albumin	216	134 (62.0)	9 (4.2)	0
↓Calcium	217	120 (55.3)	9 (4.1)	2 (0.9)
↑SGOT/AST	217	98 (45.2)	9 (4.1)	3 (1.4)
↓Sodium	217	92 (42.4)	13 (6.0)	0
↑Glucose	213	86 (40.4)	86 (40.4)	3 (1.4)
↓Magnesium	217	86 (39.6)	0	0
↑GGT	214	81 (37.9)	16 (7.5)	1 (0.5)

Laboratory abnormalities	B11 RP2D N=218 n (%)			
	Sample size ^b	All Grades	Grade $\geq 3^c$	Grade 4
↑SGPT/ALT	217	79 (36.4)	12 (5.5)	1 (0.5)
↓Potassium	217	71 (32.7)	10 (4.6)	1 (0.5)
↑Alkaline phosphatase	217	53 (24.4)	3 (1.4)	0
↑Urate	214	47 (22.0)	47 (22.0)	19 (8.9)
↑Bilirubin	217	41 (18.9)	10 (4.6)	0
↑Potassium	217	33 (16.1)	6 (2.8)	1 (0.5)
↑Calcium	217	25 (11.5)	8 (3.7)	4 (1.8)
↑Magnesium	217	23 (10.6)	8 (3.7)	1 (0.5)

^a Table only shows any worsening grade laboratory shifts from baseline measured in $\geq 10\%$ of patients.

^b Number of patients with a baseline and at least one post-baseline assessment for lab parameter.

^c Includes shifts from NCI CTCAE Grade < 3 to Grade ≥ 3 , and shifts from Grade 3 to Grade 4.

Source: Table 71 and 74 of Update GO29781 CSR.

The Applicant's Position:

Among the patients in the B11 RP2D cohort, the most frequent treatment-emergent Grade ≥ 3 worsening laboratory parameter shifts ($\geq 10\%$ of patients) were decreases in lymphocytes (the pharmacodynamic action of mosunetuzumab to deplete B-cells), neutrophils, leukocytes, hemoglobin, and platelets for hematology laboratory parameters, and decreases in phosphate, increases in glucose and urate for chemistry laboratory parameters. These laboratory abnormalities are consistent with neutropenia/neutrophil count decreased, anemia, thrombocytopenia/platelet count decreased, hypophosphatemia, and hyperglycemia being the most frequently reported Grade 3-4 AEs in the B11 RP2D cohort (see Section 6.14.1.2.2 and 6.14.2.2.2 of CSR).

One patient in B11 RP2D, and 10 patients in Group B overall, were identified as potential Hy's law cases due to laboratory results of $> 3 \times \text{ULN}$ for AST or ALT and/or $> 2 \times \text{ULN}$ for total bilirubin. These liver enzyme abnormalities occurred in patients who later experienced disease progression or occurred concurrently with CRS or as symptoms of CRS (see Section 6.14.2.2.1 of CSR).

The FDA's Assessment:

The FDA agrees with the Applicant's position and the summary of laboratory-shift results for the B11 RP2D cohort. Cytopenias were common during treatment with mosunetuzumab. The evaluation of laboratory data indicates that the frequency of all grade cytopenias and Grade 3-4 cytopenias were higher than those reported as a TEAEs. Based on the laboratory data in the B11 RP2D cohort, Grade 3-4 neutropenia, anemia, and thrombocytopenia occurred in 38%, 19%, and 12% of patients, respectively. Additionally, Grade 4 neutropenia occurred in 19% and Grade 4 thrombocytopenia occurred in 5% of patients. Based on the incidence and severity of cytopenias, FDA has included a Warning and Precaution for cytopenias in the USPI. The table below provides the rates of treatment emergent laboratory abnormalities in the B11 FL cohort per laboratory shift evaluation.

Table 39: FDA Summary of Treatment Emergent Hematology and Chemistry Laboratory Abnormalities in the B11 FL Cohort

Laboratory abnormalities	All Grades N = 90 n (%)	Grade 3-4 N = 90 n (%)
Hematology		
Decreased Lymphocytes	83 (100)	81 (98)
Decreased Hemoglobin	61 (68)	11 (12)
Decreased Leukocytes	54 (60)	12 (13)
Decreased Neutrophils	42 (58)	29 (40)
Decreased Platelets	41 (46)	9 (10)
Increased Lymphocytes	9 (11)	2 (2)
Chemistry		
Increased Creatinine	79 (88)	4 (4)
Decreased Phosphate	70 (78)	41 (46)
Decreased Albumin	52 (58)	1 (1)
Decreased Calcium	52 (58)	2 (2)
Increased SGOT/AST	35 (39)	4 (4)
Decreased Sodium	30 (33)	2 (2)
Increased Glucose	38 (42)	38 (42)
Decreased Magnesium	31 (34)	0
Increased GGT	31 (34)	8 (9)
Increased SGPT/ALT	29 (32)	6 (7)
Decreased Potassium	30 (33)	5 (6)
Increased Alkaline phosphatase	23 (26)	0
Increased Urate	20 (22)	20 (22)
Increased Bilirubin	11 (12)	3 (3)
Increased Potassium	33 (16.1)	6 (2.8)
Increased Calcium	25 (11.5)	8 (3.7)
Increased Magnesium	23 (10.6)	8 (3.7)

Laboratory abnormalities	All Grades N = 90 n (%)	Grade 3-4 N = 90 n (%)
Source: FDA Analysis		

^aIncludes shifts from NCI CTCAE Grade <3 to Grade ≥3, and shifts from Grade 3 to Grade 4.

Vital Signs

Data:

No clinically relevant effects of mosunetuzumab on absolute or change from baseline values for diastolic or systolic blood pressure, heart rate, respiratory rate, temperature, weight, and oxygen saturation were observed across the safety population as a whole.

The changes in vital signs for individual patients in the B11 RP2D cohort, B11 FL RP2D cohort, and Group B were consistent with the reported AEs.

The FDA's Assessment:

The FDA agrees that the observed changes in vital signs that are clinically relevant are in the context of patients experiencing adverse events. The most relevant vital sign changes were in the setting of CRS following mosunetuzumab administration and included pyrexia, hypoxia, and hypotension. Of 86 patients in the B11 RP2D cohort that experienced CRS per ASTCT criteria, pyrexia, hypoxia, and hypotension occurred in 100%, 23%, and 36%, respectively.

Electrocardiograms (ECGs)

Data:

Across the safety population as a whole, there were no clinically relevant effects of mosunetuzumab on heart rate, PR duration, QRS duration, QT duration, QTcB, QTcF, and RR duration, as assessed by absolute or change from baseline values at scheduled ECG assessments during the study.

The majority of ECG abnormalities were considered to be not clinically significant by the investigator. Of 11 patients in Groups A and B who had clinically significant post-baseline ECG abnormalities, 4 patients had ECG abnormalities at baseline.

Adverse events in the SOC of Cardiac Disorders were reported in 10.3% of patients (Group A and B); most were Grade 1 or 2. Grade 3 events were reported in 4 patients, all in Group B (atrial flutter, atrioventricular block second degree, and myocardial infarction (all serious), and atrial fibrillation). In the 11 patients who had clinically significant post-baseline ECG abnormalities, cardiac-related AEs were reported in 5 patients, and all were Grade 1 or 2.

The Applicant's Position:

Based on the available data, there were no clinically relevant effects of mosunetuzumab on cardiac function and cardiac disorders are not considered a risk for mosunetuzumab.

The FDA's Assessment:

The FDA agrees with the Applicant's position and has provided additional information. Triplicate ECG recordings were required at baseline, pre and post infusion on C1D1 and C1D15 and preinfusion on C4D1. Based on FDA grouping of related preferred terms in the B11 RP2D cohort, ECG-related TEAEs in the SOC cardiac disorders included sinus tachycardia (4%), tachycardia (2%), atrial fibrillation (2%), arrhythmia (<1%), bradycardia (<1%), and sinus bradycardia (<1%). In the FL cohort, ECG-related TEAEs in the SOC cardiac disorders included sinus tachycardia (3%), tachycardia (2%), and bradycardia (1%).

QT Assessment

The Applicant's Position:

As a monoclonal antibody, mosunetuzumab is not expected to interact directly with the human ether-à-go-go-related gene (hERG) channel and the risk for QT prolongation following mosunetuzumab treatment is considered to be low. Clinical data indicate that mosunetuzumab does not have a clinically relevant effect on QTcF interval across a wide dose range (0.05 to 60 mg) (see Electrocardiograms (ECGs) above). No dedicated QT study was conducted. The QT assessment plan was discussed at the Type B Pre-BLA content and format meeting (21 January 2021. Ref ID: 4749002) where the Agency agreed with the Applicant's proposal to not conduct a dedicated QT study and that a separate QT evaluation report was not necessary.

The FDA's Assessment:

The FDA agrees with the Applicant's position. A dedicated QT assessment was not required and was not conducted as per ICH E14 Q&A (R3). However, 2 patients (<1%, Grade 1 and 2, one patient each) developed "electrocardiogram QT prolongation" in the B11 RP2D cohort, both less than 500 ms.

Immunogenicity

Data:

As of the CCOD used for the ADA analyses (4 December 2020), no anti-drug antibodies (ADAs) were detected in any patient at any assessment in the 418 ADA-evaluable patients who received mosunetuzumab IV monotherapy in Study GO29781.

The Applicant's Position:

Based on the available data, the impact of immunogenicity on safety is low.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

8.2.4. Analysis of Submission-Specific Safety Issues

8.2.4.1 CRS

Data:

In the B11 RP2D cohort, CRS events by ASTCT 2019 grade were reported in 39.4% of patients. The majority were Grade 1–2 severity (95.1% [117/123 CRS events]). Grade 3 CRS events were reported in 5 patients (2.3%) and Grade 4 CRS event was reported in a single patient (0.5%) diagnosed with FL in leukemic phase. Serious CRS events were reported in 20.6% patients in the B11 RP2D cohort (see Table 29); the majority were Grade 1–2 at maximum severity and considered serious predominantly due to the requirement for hospitalization or prolonged hospitalization.

CRS events occurred predominantly in Cycle 1 and were mainly associated with Day 1 and Day 15 dose administrations, with the highest frequency of CRS events driven by Grade 1 and 2 events following the C1D15 dose in B11 RP2D. The frequency of CRS events decreased in the subsequent treatment cycles. The 6 Grade 3-4 CRS events, all of which were serious, followed C1D15 and C2D1 infusions. The median duration of CRS events was 3 days (range: 1-29 days)

Most CRS events were managed with supportive care (i.e., symptomatic management of constitutional symptoms), with or without anti-IL-6/corticosteroid therapy. CRS events requiring dose interruption/modification were reported in 17 patients (7.8%) in the B11 RP2D cohort while CRS events that led to mosunetuzumab treatment discontinuation were reported in 2 patients (0.9%; see Table 32). All CRS events resolved.

The most common treatments administered for any grade CRS were fluids (for hypotension), steroids, tocilizumab, and low flow oxygen (for hypoxia). By ASTCT grade:

- Of 80 Grade 1 ASTCT CRS events reported in 61 patients in the B11 RP2D cohort, most events (66/80 [82.5%]) were not treated with tocilizumab, corticosteroids, fluids, vasopressors, or oxygen. Tocilizumab was administered for 7 Grade 1 CRS events (8.8%). Steroids were administered concurrently with 9 Grade 1 CRS events (11.3%), of which 2 of the events (2.5%) also included tocilizumab administration.
- Of 37 Grade 2 ASTCT CRS events reported in 33 patients in the B11 RP2D cohort, 25 events (67.6%) were treated with fluids, and 18 events (48.6%) were treated with low flow oxygen. Tocilizumab was administered for 10 Grade 2 CRS events (27.0%). Steroids were administered concurrently with 14 Grade 2 CRS events (37.8%), of which 4 of the events (10.8%) were treated with both steroids and tocilizumab.
- Of 5 Grade 3 ASTCT CRS events in 5 patients, 4 events were treated with a single vasopressor, and 2 events were treated with high-flow oxygen (the other 3 events were treated with low flow oxygen). Tocilizumab was administered for 4 of the 5 Grade 3 CRS events (80%), which included all 4 events treated with single vasopressor. Steroids were administered concurrently with 4 Grade 3 CRS events (80%), of which 3 of the events were treated with both steroids and tocilizumab.
- A single Grade 4 ASTCT CRS event required treatment with multiple vasopressors. The patient also received tocilizumab and concurrent steroids.

The overall frequency and severity of CRS events between the B11 RP2D cohort, B11 FL RP2D cohort, and overall Group B were generally similar. One difference noted was the frequency of CRS events following the C1D15 mosunetuzumab infusion, which was slightly higher in the B11 RP2D cohort (when the 60 mg dose was administered; 33.3% by ASTCT 2019 grade) compared to overall Group B (24.4% by ASTCT 2019 grade), driven mainly by a slightly higher incidence of serious CRS events of Grade ≥ 2 severity.

The Applicant's Position:

Consistent with the mechanism of action of mosunetuzumab, CRS is a serious safety concern that may result in life-threatening consequences if not managed appropriately. To mitigate the risk of CRS, comprehensive product labelling is proposed (see table of adverse reactions, Warnings and Precautions and Dosage and Administration sections of the prescribing information), as well as (b) (4) enhanced patient labeling in the form of a voluntary non-REMS program Medication Guide (as per 21 CFR 208) (b) (4). The primary aims of these materials are to educate

healthcare providers (HCPs) on early recognition and management of CRS, and patients on early recognition and presentation to healthcare facilities.

The FDA's Assessment:

CRS events were reported and graded according to the Lee 2014 grading criteria. CRS events were also summarized by the ASTCT 2019 grading criteria. The FDA's review is focused on CRS events per ASTCT criteria.

All patients received prophylaxis for CRS with corticosteroid premedication one hour prior to each mosunetuzumab dose during Cycle 1 and 2 (i.e., dexamethasone 20 mg intravenously or methylprednisolone 80 mg administered intravenously). Corticosteroid premedication became optional for Cycle 3 and beyond unless the patient experienced a CRS event. Oral acetaminophen or paracetamol and/or diphenhydramine were administered per institutional standard.

Hospitalization Requirements

Administration of mosunetuzumab occurred in a clinical setting with immediate access to intensive care, in addition to neurology and nephrology consultation services on Study GO29781. For the dose escalation portion of Study GO29781, patients received inpatient monitoring through 72 hours after any mosunetuzumab dose that exceeded a previously tested dose level. Following the dose escalation portion, hospitalization was no longer required unless clinically indicated at the study investigator's discretion and in consultation with the Medical Monitor. Patients were, however, observed for at least 90 minutes after completion of each infusion. Therefore, the data from the B11 RP2D cohort represent IV administration of mosunetuzumab in an outpatient healthcare setting with post-infusion monitoring and access to intensive care. Of note, per protocol version 12, for patients that experience Grade 1 or 2 CRS, hospitalization was to be considered for the next dose of mosunetuzumab. For patients that experienced Grade 3 CRS and were able to receive subsequent treatment, hospitalization was mandatory for the next dose.

CRS Incidence and Severity

In the B11 RP2D cohort per ASTCT criteria, 39% of patients (86/218) experienced a CRS event, with 21% (45/218) considered serious, primarily due to the need for hospitalization. Of the 86 patients, the most frequently reported CRS signs and symptoms included pyrexia (100%), chills (36%), hypotension (35%), tachycardia (24%), hypoxia (22%), and headache (16%). The majority of patients experienced Grade 1 or Grade 2 CRS at 28% (61/218) and 15% (33/218), respectively. Two percent of patients (5/218) experienced grade 3 CRS with only one patient (<1%) experiencing grade 4 CRS. Most patients (33%) experienced CRS after the Cycle 1, Day 15 dose. The median duration of CRS was 3 days (range: 1 to 29 days), with 75% of events lasting 5 days or less. Recurrent CRS occurred in 11% of patients.

The incidence of CRS by dose was Cycle 1 Day 1 at 15% (33/218), Cycle 1 Day 8 at 5% (10/207),

Cycle 1 Day 15 at 33% (67/201), Cycle 2 Day 1 at 4% (9/198), and Cycle 3 Day 1 at 1% (2/167). The Grade 3 CRS events occurred on Cycle 1 Day 15 and Cycle 2 Day 1. The one Grade 4 CRS event occurred on Cycle 1 Day 15. The time to onset was shortest with the first dose of mosunetuzumab and progressively increased with subsequent doses. The median time to onset on Cycle 1 Day 1 was 5 hours (range: 1 to 73 hours) and Cycle 1 Day 15 was 25 hours (range: 0.1 to 391 hours). See the table below for an overview of CRS in the FL cohort and the B11 RP2D cohort.

Neurologic adverse events occurring concurrently with CRS were observed in 16% (14/86) of patients in the B11 RP2D cohort. The most common neurologic manifestations included headache, confusional state, and anxiety. Additionally, increased liver function tests occurring concurrently with CRS was observed in 3% (3/86) of patients, primarily as AST/ALT increased.

The incidence of CRS per ASTCT in the B11 FL cohort was slightly higher (44%) than in the B11 RP2D cohort, with 23% of events being serious CRS events. The pattern of most frequently reported signs and symptoms of CRS was similar to the B11 RP2D cohort except for a higher incidence of headache (28%). A greater proportion of patients experienced CRS events with Cycle 1 Day 1 (23%, 21/90) than was observed in the B11 RP2D cohort at 15%. The frequency of CRS events with Cycle 1 Day 15 was similar in both cohorts (36% and 33%, respectively). Recurrent CRS occurred in 21% of patients (19/90) in the B11 FL cohort. Concurrent neurologic adverse events occurred in 10% of patients and concurrent increased liver function tests were observed in 2% in the B11 FL cohort.

Management of CRS

Per the protocol, management of CRS included interruption of mosunetuzumab (as applicable), supportive therapy, anti-IL-6 or corticosteroid therapy, and considerations for the next dose of mosunetuzumab. Tocilizumab and corticosteroids could be considered for prolonged Grade 1 CRS (>2 days) in patients with significant symptoms and/or comorbidities per investigator discretion. For patients with Grade 2 CRS, tocilizumab was to be considered followed by corticosteroids if refractory hypotension after 1-2 doses of tocilizumab. Administration of tocilizumab and corticosteroids were prespecified for Grade 3 and Grade 4 CRS.

The management of CRS in patients in the B11 FL cohort and B11 RP2D cohort was similar except for the use of tocilizumab without corticosteroids, which was used in 18% of patients with CRS in the B11 FL cohort and 24% of patients with CRS in the B11 RP2D cohort (Table 41 and Table 42). The use of corticosteroids with or without tocilizumab, IV fluids, pressors, oxygen, and intensive care were consistent across the populations. Since the use of tocilizumab and/or corticosteroids were not prespecified for Grade 1 or Grade 2 CRS, there was heterogeneity in the patient cases that received tocilizumab versus those who did not receive tocilizumab, precluding any meaningful interpretation of the data. Further, all cases of CRS resolved and the outcomes in patients treated with supportive therapy, corticosteroids, tocilizumab, or the combination of corticosteroids and tocilizumab were descriptively similar.

Therefore, the use of tocilizumab and corticosteroids for the management of mosunetuzumab-induced CRS, especially Grade 1 and 2 CRS, remains uncertain and further prospective evaluation is warranted .

Table 40: FDA Overview of CRS Events in B11 FL Cohort an B11 RP2D Cohort

	B11 FL N = 90 n (%)		B11 RP2D N = 218 n (%)	
Any Grade CRS event	40 (44)		86 (39)	
Grade 1	32 (36)		61 (28)	
Grade 2	16 (18)		33 (15)	
Grade 3	1 (1)		5 (2)	
Grade 4	1 (1)		1 (<1)	
Serious adverse event	21 (23)		45 (21)	
Hospitalization	21 (23)		44 (20)	
Life-threatening	1 (<1)		2 (<1)	
Event leading to dose interruption	7 (8)		17 (8)	
Event leading to dose withdrawal	2 (2)		2 (<1)	
	N = 40		N = 86	
CRS event resolved	40 (100)		86 (100)	
Concurrent neurologic event	9 (22)		14 (16)	
Headache	4 (10)		5 (6)	
Confusional state	1 (2)		3 (3)	
Anxiety	2 (5)		2 (2)	
Fear	1 (2)		1 (1)	
Insomnia	1 (2)		1 (1)	
Delirium	0		1 (1)	
Dizziness	0		1 (1)	
Concurrent liver enzyme elevation	2 (5)		3 (3)	
Any Grade CRS by Dose	N	n (%)	N	n (%)
Cycle 1 Day 1	90	21 (23)	218	33 (15)
Cycle 1 Day 8	89	5 (6)	207	10 (5)
Cycle 1 Day 15	88	32 (36)	201	67 (33)
Cycle 2 Day 1	87	9 (10)	198	9 (4)
Cycle 3 Day 1	83	2 (24)	167	2 (1)
Abbreviations: FL, follicular lymphoma; RP2D, recommended phase 2 dose (1/2/30/60 mg); CRS, cytokine release syndrome; C1D1, cycle 1, day 1)				
Source: FDA analysis				

Table 41: FDA Summary of Management of Any Grade CRS Events Among Patients with CRS in B11 FL and B11 RP2D

	B11 FL N = 90 n (%)	B11 RP2D N = 219 n (%)
Patients with CRS per ASTCT	40	86
Treatment		
Steroids	10 (25)	22 (26)
Tocilizumab	7 (17)	21 (24)
Steroids + Tocilizumab	4 (10)	9 (10)
Fluids	11 (27)	23 (27)
Single Pressor	1 (2)	4 (5)
Multiple Pressors	1 (2)	1 (1)
Oxygen low flow	8 (20)	18 (21)
Oxygen high flow	1 (2)	2 (2)
ICU	5 (12)	9 (10)
Abbreviations: FL, follicular lymphoma; RP2D, recommended phase 2 dose; CRS, cytokine release syndrome; ICU, intensive care unit Source: FDA Analysis		

Table 42: FDA Summary of Grade 1-4 CRS Events in B11 FL and B11 RP2D

Treatment	Grade 1		Grade 2		Grade 3		Grade 4	
	FL N = 90	RP2D N = 218	FL N = 90	RP2D N = 218	FL N = 90	RP2D N = 218	FL N = 90	RP2D N = 218
Patients With CRS	32	61	16	33	1	5	1	1
Steroids	5 (16)	9 (15)	5 (31)	11 (33)	1 (100)	4 (80)	1 (100)	1 (100)
Tocilizumab	3 (9)	7 (11)	3 (19)	10 (30)	1 (100)	4 (80)	1 (100)	1 (100)
Steroids + Tocilizumab	1 (3)	2 (3)	2 (12)	4 (12)	1 (100)	3 (60)	1 (100)	1 (100)
Fluids	0	0	11 (69)	23 (70)	0	0	0	0
Single Pressor	0	0	0	0	1 (100)	4 (80)	0	0
Multiple Pressors	0	0	0	0	0	0	1 (100)	1 (100)
Oxygen low flow	0	0	8 (50)	16 (48)	0	3 (60)	0	0
Oxygen high flow	0	0	0	0	1 (100)	2 (40)	0	0
ICU	0	0	3 (19)	4 (12)	1 (100)	4 (80)	1 (100)	1 (100)
Abbreviations: FL, follicular lymphoma; RP2D, recommended phase 2 dose (1/2/30/60 mg); CRS, cytokine release syndrome; ICU, intensive care unit Source: FDA analysis								

For additional analyses and information on CRS with mosunetuzumab, see Section 6.2.2.1.

Risk Mitigation

Based on the CRS profile with mosunetuzumab, a box warning for CRS is warranted along with a corresponding medication guide. This is based on the occurrence of serious and life-threatening cases of CRS observed and the need for providers to be accurately aware of the risk. Additionally, the USPI includes the statement that mosunetuzumab should only be administered by a qualified healthcare professional with appropriate medical support to manage severe reactions such as cytokine release syndrome. The management of CRS in relation to mosunetuzumab will be included in the USPI.

(b) (4)

8.2.4.2 Infections

Data:

Infection AEs (broadly defined under the SOC of Infections and Infestations) were reported in 46.8% patients in the B11 RP2D cohort. The majority of infections were Grade 1–2 severity. Grade ≥ 3 infections were reported in 15.1% of patients. The most frequently reported Grade 3 event (in $\geq 2\%$ of patients) was pneumonia (5 patients [2.3%]). Grade 4 events were sepsis (3 patients [1.4%]) and Epstein-Barr viremia and septic shock (1 patient [0.5%] each). Grade 5 infections of pneumonia and sepsis were reported in 1 patient (0.5%) each (see Table 27). Serious infections were reported in 37 patients (17.0%), with pneumonia (7 patients [3.2%]) being the most frequent.

The majority of serious infections did not appear to occur in the context of neutropenia. In the B11 RP2D cohort, four serious infections, enterocolitis bacterial (Grade 3), herpes zoster

(Grade 2), and two events of sepsis (Grade 5 and Grade 4) occurred concurrently with neutropenia/neutrophil count decreased events.

At the CCOD, 76 patients (34.9%) had all events resolved and the remaining 26 patients (11.9%) had at least one unresolved or ongoing event.

The frequencies of infection events and serious events were similar between the B11 RP2D and the B11 FL RP2D cohorts, and Group B overall.

The Applicant's Position:

Serious infections are anticipated with mosunetuzumab administration due to its mode of action resulting in B-cell depletion. Based on the increased risk of infections associated with mosunetuzumab, serious infections are included in the Warnings and Precautions section of the product labelling with guidance not to administer mosunetuzumab in the presence of active infections and to consider prophylactic antibacterial, antiviral and/or antifungal medications, as appropriate. Certain infections (e.g., upper respiratory tract infections, urinary tract infection, and pneumonia) are included as clinically important adverse reactions in the prescribing information.

FDA Assessment:

In general, the FDA agrees with the Applicant's position. The FDA agrees with the reported 47% incidence of infections in the B11 RP2D cohort (N = 218) of which 17% were serious infections, including pneumonia in 5% of patients, sepsis in 3%, and urinary tract infection and upper respiratory infection in 2% each. The 14% incidence of Grade 3 or 4 infections in the B11 RP2D cohort was similarly driven by pneumonia (3%), sepsis (3%), and upper respiratory infections (2%). Two patients in the B11 RP2D cohort died due to pneumonia and sepsis, respectively. The incidence of infections in the B11 FL cohort (N = 90) at 51% (46/90) was slightly higher than that observed in the B11 RP2D cohort. Twenty percent (18/90) of patients experienced a serious infection, including urinary tract infections in 4% of patients, sepsis in 3% of patients, and COVID-19, Epstein-Barr viremia, and pneumonia in 2% of patients each. The incidence of Grade 3 or 4 infections was 17% (15/90), most often due to pneumonia (3%), sepsis (3%), COVID-19 (2%), and upper respiratory infections (2%). There were no fatal infections observed in the FL cohort. Infections remained unresolved in 10% of patients (9/90) in the B11 FL cohort at the time of the data cutoff.

Based on the risk of serious, severe, and fatal infections associated with mosunetuzumab, the FDA agrees with inclusion of a Warning and Precaution for infections in the USPI.

8.2.4.3 Tumor Flare

Data:

155

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

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.

Tumor flare events were identified by PT of tumor flare, as suspected tumor flare events, or by AESI Grade ≥ 2 tumor flare/tumor inflammation specific for mosunetuzumab.

A total of 9/218 patients (4.1%) in the B11 RP2D cohort experienced events that met the definition of tumor flare events following initial treatment with mosunetuzumab.

The reported tumor flare events included tumor flare and pleural effusion (4 patients [1.8%] each), and tumor inflammation (1 patient [0.5%]). All reported events were of Grade 2 or Grade 3 maximum severity. Grade 3 events were tumor flare (3 patients [1.4%]) and pleural effusion (2 patients [0.9%]). Serious tumor flare events were reported in 4 patients (1.9%). The median time to onset of first tumor flare events was 13 days (range: 5–84 days), with median duration of 10 days (range: 1–77 days). At the CCOD, the majority of the events (8 of 9 events [88.9%]) had resolved.

Similar frequencies of tumor flare events and serious tumor flare events were noted between the B11 RP2D and the B11 FL RP2D cohorts and Group B overall. Further details for tumor flare events are provided in the SCS, Section 2.7.6.

The Applicant's Position:

Consistent with the mechanism of action, tumor flare is likely due to the rapid influx of T cells to tumor sites and can result in enlargement and mass effect compromising surrounding structures. Since there is the potential for clinically significant impact based on compromise of anatomical site of lesions secondary to mass effect, tumor flare is listed as a clinically important adverse reaction and included in the Warnings and Precautions section of the product labelling with monitoring and management advice to allow prescribers to plan and manage patients appropriately.

FDA Assessment:

The FDA agrees with the Applicant's position and the data presented above. The incidence of grade 2 and greater tumor flare in the B11 RP2D cohort and B11 FL cohort were 4% (9/218) and 3% (3/90), respectively. Only one tumor flare adverse event in the RP2D B11 cohort had not resolved by the clinical cutoff date.

The FDA agrees with the Applicant that the risk of tumor flare and the potential for airway compromise or organ impairment secondary to mass effect is clinically important. Because of the risk, the FDA agrees with inclusion of tumor flare as a Warning and Precaution for mosunetuzumab in the USPI.

8.2.4.4 Tumor Lysis Syndrome

Data:

156

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

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.

Two TLS events were reported in 2 patients in the B11 RP2D cohort. Both events (a Grade 4 event in a patient with R/R FL and a Grade 3 event in a patient with R/R MCL) were assessed as serious and were preceded by a CRS event on the prior study day. Both patients had received allopurinol prophylaxis. Both TLS events resolved, with no change in mosunetuzumab dose.

No additional TLS events were reported in other cohorts in Group B. Further details for TLS events are provided in Section 2.7.5 of the SCS.

The Applicant's Position:

TLS is an oncological emergency when it occurs, however it is well understood by HCPs in the hematology treatment landscape. (b) (4)

(b) (4)

FDA Assessment:

The FDA agrees with the data presented above. (b) (4)

(b) (4)

(b) (4) In addition, as noted by the Applicant, tumor lysis syndrome is well understood by healthcare providers in the treatment of patients with hematologic malignancies.

8.2.4.5 Hemophagocytic Lymphohistiocytosis

FDA Assessment:

Hemophagocytic lymphohistiocytosis was identified as an adverse event of special interest by the Applicant for mosunetuzumab and was specifically monitored and evaluated in Study GO29781. There were 4 identified cases of HLH in the overall safety population. One case (0.4%, 1/218) occurred in the B11 RP2D cohort and the 3 other cases occurred in patients receiving different doses or regimens of mosunetuzumab monotherapy. A brief summary of the cases is provided below.

1. B11 RP2D Cohort (1/2/60/30 mg): A 74 year old White male with diffuse large B-cell lymphoma who received the mosunetuzumab step up doses of 1 mg on Cycle 1 Day 1 and 2mg on Cycle 1 Day 8. The patients developed Grade 4 hemophagocytic lymphohistiocytosis (HLH) on Day 8. Day 10 soluble IL2 receptor serum level was 20,000 pg/mL. By Day 13, the patient was reported to show "clinical disease progression, worsening of encephalopathy, and multiorgan dysfunction," which appeared consistent with a clinical presentation of HLH. Mosunetuzumab treatment was discontinued due to disease progression; however, the relative contribution of mosunetuzumab to the development of HLH versus the contribution of progressive disease to the development

of HLH remains unclear. The patient died due to progressive disease along with ongoing HLH.

2. Dose Escalation Group A (2.8 mg every 3 weeks): A 74 year old Asian female with Richter's transformation received mosunetuzumab through Cycle 2 Day 1 (2 doses). The patient developed Grade 2 HLH on study Day 58 based on high ferritin and low fibrinogen along with a constellation of signs and symptoms that started on study Day 15. The patient developed septic shock, electrolyte imbalance, and seizure as part of HLH. With the evaluation for HLH, a prior marrow aspirate and lymph node biopsy showed concurrent EBV infection, which possibly contributed to the development of HLH. The patient ultimately died due to HLH on study Day 60.
3. Dose Escalation Group B (20 mg every 3 weeks, step-up doses): A 67 year old White male with Richter's transformation received mosunetuzumab for the complete treatment regimen of 17 cycles. Approximately 46 days following the last dose of mosunetuzumab, the patient developed CMV and EBV infections and a bone marrow biopsy was consistent with HLH, along with correlative laboratory findings such as high ferritin. The patient was treated with etoposide and dexamethasone for HLH. The patient's HLH was resolving with treatment, however, the patient died due to renal failure around 9 months following his last dose of mosunetuzumab.
4. Dose escalation Group B (6 mg every 3 weeks, step-up doses): A 72 year old White male with small lymphocytic lymphoma (SLL) received mosunetuzumab through Cycle 1 Day 15 (3 doses). The patient died due to progressive disease on study Day 26. Upon autopsy, the cause of death was multi-organ failure due to HLH and chronic active EBV infection with progressive SLL. The relationship with EBV infection and HLH in the setting of progressive disease remains unclear.

The cases of HLH raise concern regarding an association of HLH with mosunetuzumab, however the relationship remains unclear at this time. Further, the contribution of EBV viremia also remains unclear. However, based on the mechanism of action of mosunetuzumab, there is a potential risk for potentiation of infections such as EBV and CMV and the development of HLH. Continued prospective evaluation of HLH in ongoing trials evaluating mosunetuzumab is warranted to further characterize the risk of HLH with mosunetuzumab. Additionally, a PMR to evaluate safety with longer term use of mosunetuzumab will be issued and HLH will be included in the assessment.

8.2.4.6 Neurologic toxicity

FDA Assessment:

Neurologic toxicity was identified as an adverse event of special interest by the Applicant for mosunetuzumab and monitored and evaluated in Study GO29791. On Study GO29781, all patients were required to undergo a baseline complete neurologic exam prior to the first administration of mosunetuzumab. If new or worsening neurologic toxicity occurred, it was

recommended that the patient be referred to a neurologist and corticosteroids would potentially be considered for treatment. Imaging was performed as clinically indicated. Per the protocol, neurologic adverse events (NAE) were defined as adverse events that mapped to either the system organ class (SOC) Nervous System Disorders or Psychiatric disorders. Based on this, 56% of patients in the B11 RP2D (N = 218) cohort experienced at least one neurologic adverse event as compared to 69% of patients in the B11 FL cohort (N = 90) as shown in Table 43 below. The majority of NAEs were Grade 1 and 2 in both cohorts, with 5% of events being Grade 3 in the B11 RP2D cohort and 4% being Grade 3 in the B11 FL cohort. Serious NAEs were observed in 6% in the B11 RP2D cohort and 4% in the B11 FL cohort. Twenty-one percent of events in both cohorts were unresolved at the time of data cutoff (August 2021).

The Applicant also identified a subset of NAEs with preferred terms that could potentially impact cognition, consciousness, and the ability to drive, i.e., driving-impacting cognition or consciousness neurologic adverse event (DI-CCNAE), including but not limited to: amnesia, aphasia, confusional state, delirium, depressed level of consciousness, disturbance in attention, encephalopathy, hallucination, hepatic encephalopathy, insomnia, memory impairment, seizure, visual hallucination, and vertigo. Using this definition, 12% of patients in the B11 RP2D cohort and 10% of patients in the B11 FL cohort experienced DI-CCNAEs, respectively. The majority were Grade 1 or 2, with 3% being Grade 3 in the B11 RP2D cohort. The most common events in the B11 RP2D cohort were confusional state (4%), fatigue (2%), and neurotoxicity (1%).

In the evaluation of neurotoxicity, the FDA was able to confirm the results provided by the Applicant using the definition of adverse events that mapped to the Nervous System Disorder and Psychiatric SOCs and the definition of DI-CCNAE. To further evaluate neurologic toxicity, the FDA performed analyses using the definitions below, which includes the preferred terms observed in the respective safety populations for mosunetuzumab:

1. Central Neurologic Toxicity
  - a. Mental Status Change: amnesia, cognitive disorder, confusional state, delirium, depressed level of consciousness, disturbance in attention, memory impairment, somnolence, encephalopathy, hallucination
  - b. Aphasia, ataxia, balance disorder, dizziness, dyskinesia, gait disturbance, neurotoxicity, seizure, syncope, toxic neuropathy, tremor
2. Peripheral Neuropathy
  - a. Burning sensation, dysaesthesia, hyperaesthesia, hypoaesthesia, neuralgia, paraesthesia, peripheral neuropathy, peripheral motor neuropathy, peripheral sensory neuropathy

NAE due to Nervous System Disorders in the B11 RP2D Cohort

In the B11 RP2D cohort, neurologic adverse events under the nervous system disorders SOC occurred in 39% of patients, with 3% (7/218) having Grade 3 events. There were no Grade 4

neurologic events. Grade 1 neurologic TEAEs occurred in 35% of patients (77/218), Grade 2 in 7% (16/218), and Grade 3 in 3% (7/218). The most common manifestations of NAE due to nervous system disorders were headache (21%), peripheral neuropathy (13%), and dizziness (11%). The Grade 3 events included encephalopathy, cerebrovascular accident, headache, presyncope, syncope, and toxic neuropathy. Using the grouped terms for mental status change as defined above, 6% of patients experienced mental status change, which included confusional state (4%), and disturbance in attention, cognitive disorder, encephalopathy, somnolence, and delirium at <1% each. For central neurologic toxicity, excluding mental status change, tremor occurred in 2%, neurotoxicity in 1%, and ataxia, balance disorder, gait disturbance, syncope, and toxic neuropathy occurred in <1% each.

There were 2 patients that experienced an event of immune effector cell associated neurotoxicity (ICANS), which is described further below.

Serious neurologic TEAEs under the nervous system disorders SOC occurred in 3% (7/218) of patients. Dose interruption due to nervous system disorders occurred in 2% (5/218) of patients. In 10% of patients in the RP2D cohort (19/218), the nervous system disorder was unresolved at the data cutoff, mostly due to the 3% incidence of unresolved headache.

NAE due to Nervous System Disorders in the B11 FL Cohort

Using the nervous system disorder SOC, 54% of patients in the FL cohort experienced a NAE, with one patient each (1%) having a Grade 3 event due to headache and presyncope. Grade 1 neurologic TEAEs occurred in 52% (47/90) of patients, Grade 2 in 8% (7/90), and Grade 3 in 2% (2/90). The most common manifestations of nervous system disorder were similar to that seen in the B11 RP2D cohort and included headache (33%), peripheral neuropathy (20%), and dizziness (12%). Using the grouped terms for mental status change as defined above, 4% of patients experienced mental status change characterized by confusion in 3% and a 1% incidence each of disturbance in attention and cognitive disorder.

There were no serious neurologic TEAEs due to nervous system disorders in the B11 FL cohort. There were 2 dose interruptions (2%, 2/90). In 12% of patients (11/90), the nervous system disorder was unresolved at the time of data cutoff and could be largely attributed to the incidence of peripheral neuropathy in 7% (6/90) and headache in 6% (5/90) of patients.

NAE due to Psychiatric System Disorders in the B11 RP2D Cohort

Neurologic adverse events under the psychiatric system disorders SOC occurred in 19% of patients in the B11 RP2D cohort. Grade 1 events occurred in 12% of patients (27/218) and grade 2 events in 7% (7/218). The single Grade 3 event of confusional state under psychiatric system disorder SOC was included in the analysis of mental status change described above. The most common manifestations in the B11 RP2D cohort were insomnia (11%) and anxiety (3%).

Only 1 patient experienced a serious TEAE due to a psychiatric system disorder, which was due to fear. There were no dose interruptions due to a psychiatric system disorder. In 5% of patients (10/218), the psychiatric disorder was unresolved at the data cutoff, largely driven by the 4% of patients with unresolved insomnia.

NAE due to Psychiatric System Disorders in the B11 FL Cohort

In the B11 FL cohort, NAEs under the psychiatric system disorders SOC, 23% of patients in the FL cohort experienced a psychiatric system disorder. Grade 1 events occurred in 14% of patients (13/90) and Grade 2 events in 10% (9/90). The most common manifestations were insomnia (13%), anxiety (4%), and depression (3%).

There was 1 serious NAE due to a psychiatric system disorder in the B11 FL cohort due to fear. There were no dose interruptions. In 4% of patients (4/90), the psychiatric disorder was unresolved at the data cutoff, largely due to insomnia in 3% of patients.

ICANS

There were two patients in the B11 RP2D cohort who experienced ICANS, a Grade 1 event and a Grade 2 event. The Grade 1 event occurred in the setting of a Grade 2 CRS event and resolved within 3 days. There was no information provided by the Applicant on the manifestations of the ICANS event. The Grade 2 event occurred in the setting of Grade 4 CRS and the primary manifestation was a confusional state. The ICANS event, along with CRS, was treated with corticosteroids (and tocilizumab) and resolved within 2 days.

Driving Restrictions

Prior to protocol version 10 (September 26, 2019), patients treated with mosunetuzumab were advised to refrain from driving or operating dangerous machinery for the first 3 cycles of treatment. Following September 26, 2019, no baseline driving restriction was in place for patients with follicular lymphoma and an event-based restriction was in place. Essentially, any patient that developed CRS or any adverse reaction that impairs consciousness should refrain from driving or operating dangerous machinery. The table below summarizes the patients enrolled before and after September 26, 2019.

Enrolled	B11 FL N = 90	B11 RP2D N = 218
Before September 26, 2019	28 (31%)	102 (47%)
After September 26, 2019	62 (69%)	116 (53%)

With the initiation of the event-driven driving restrictions, no additional safety events occurred compared to the time in which the baseline driving restrictions were in place. Additionally, 53% to 69% of the patients were enrolled during the event-driven approach. Therefore, the driving restrictions to be included in the label will be consistent with the event-driven approach for patients that experience CRS or any adverse reactions that impairs consciousness.

Unresolved NAE in B11 RP2D

At the time of the safety data cutoff (August 2021), 45 patients (21%) had unresolved NAEs. Based on updated information provided from the Applicant using a data cutoff of July 8, 2022, 16 patients (7%) died with unresolved NAEs (12 due to progression of disease, 2 due to infectious adverse events, and 2 unknown), 4 patients (2%) withdrew from the study with unresolved NAEs, 17 patients (8%) still had unresolved NAEs, and 8 patients (4%) had resolving NAEs. The most common unresolved NAEs remained insomnia, peripheral neuropathy, and headache.

Conclusion:

Sixty-nine percent of patients in the B11 FL cohort and 56% of patients in the B11 RP2D cohort experienced at least one neurologic adverse event. The majority of the neurologic adverse events were grade 1 and grade 2. However, serious events occurred in 6% and Grade 3 severe events occurred in 5%. In addition, 21% of patients had unresolved NAEs at the data cutoff. The signs and symptoms of neurologic toxicity included headache, peripheral neuropathy, dizziness, and mental status change (including confusional state, disturbance in attention, cognitive disorder, delirium, encephalopathy, and somnolence). Two cases of ICANS were also observed. The most common psychiatric manifestation were insomnia and anxiety. Given the risk of neurologic toxicity, labeling should include neurologic toxicity as a Warning and Precaution, including driving restrictions, to ensure safe use of mosunetuzumab.

Table 43: FDA Overview of Neurologic Adverse Events and Psychiatric Disorders in B11 FL and B11 RP2D

	B11 FL N = 90 n (%)	B11 RP2D N = 218 n (%)
Total number of patients with at least one NAE	62 (69)	122 (56)
Grade 1	56 (62)	104 (48)
Grade 2	17 (19)	35 (16)
Grade 3	4 (4)	11 (5)
Grade 4	0	0
Serious adverse event	4 (4)	14 (6)
Event leading to dose interruption	5 (6)	10 (5)
Event leading to dose withdrawal	0	1 (0.5)
Events resolved	43 (48)	77 (35)
Event unresolved or ongoing	19 (21)	45 (21)
Total patients with treatment received for event	29 (32)	50 (23)
Time to onset of first event Median, days (range)	16 (1-518)	15 (1-518)
Duration of event Median, days (range)	4 (1-344)	5 (1-344)
Abbreviations: NAE, neurologic adverse event Source: FDA analysis		

Table 44: FDA Overview of DI-CCNAE in B11 FL and B11 RP2D

	B11 FL N = 90 n (%)	B11 RP2D N = 218 n (%)
Total number of patients with at least one event	9 (10)	26 (12)
Grade 1	7 (8)	16 (7)
Grade 2	1 (1)	5 (2)
Grade 3	1 (1)	6 (3)
Grade 4	0	0
Serious adverse event	2 (2)	10 (5)
Event leading to dose interruption	0	2 (<1)
Event leading to dose withdrawal	0	1 (<1)
Events resolved	9 (10)	20 (9)
Event unresolved or ongoing	0	6 (3)
Total patients with treatment received for event	1 (1)	6 (3)
Time to onset of first event		
Median, days (range)	21 (1-206)	19 (1-207)
Duration of event		
Median, days (range)	2 (1-22)	3 (1-259)
Abbreviations: DI-CCNAE, Driving Impacting Neurological Events; FL, follicular lymphoma; RP2D, recommended phase 2 dose (1/2/30/60 mg) Source: FDA analysis		

Table 45: FDA Summary of Neurologic Adverse Events Due to Nervous System Disorders in B11 RP2D

B11 RP2D N = 218	Any Grade		Grade 3	Unresolved at time of DCO
	n	%	n (%)	n (%)
Nervous System Disorder SOC	86	39%	7 (3)	19 (10)
Presentation by PT or grouped PT				
Headache	45	21%	1 (0.5)	7 (3)
Peripheral neuropathy	28	13%	0	9 (4.1)
Paresthesia	8	3.7%	0	2 (0.9)
Peripheral neuropathy	7	3.2%	0	2 (0.9)
Peripheral sensory neuropathy	7	3.2%	0	4 (1.8)
Burning sensation	2	0.9%	0	0
Neuralgia	2	0.9%	0	0
Peripheral motor neuropathy	1	0.5%	0	0
Dysaesthesia	1	0.5%	0	1 (0.5)
Hypoaesthesia	1	0.5%	0	0
Dizziness	21	10%	0	0
Tremor	5	2.3%	0	1 (0.5)
Mental status changes	13	6%	2 (0.9)	3 (1.4)
Confusional state	8	3.7%	1 (0.5)	2 (0.9)
Disturbance in attention	2	0.9%	0	0
Cognitive disorder	1	0.5%	0	0
Encephalopathy	1	0.5%	1 (0.5)	0
Somnolence	1	0.5%	0	1 (0.5)
Delirium	1	0.5%	0	0
Presyncope	4	1.8%	1 (0.5)	0
Muscular weakness	4	1.8%	1 (0.5)	1 (0.5)
Dysgeusia	3	1.4%	0	0
Neurotoxicity	3	1.4%	0	1 (0.5)
Loss of balance	2	1.0%	0	0
Ataxia	1	0.5%	0	0
Balance disorder	1	0.5%	0	0
ICANS	2	0.9%	0	0
Syncope	1	0.5%	1 (0.5)	0
Cerebrovascular accident	1	0.5%	1 (0.5)	1 (0.5)
Allodynia	1	0.5%	0	0
Head discomfort	1	0.5%	0	0
Restless legs	1	0.5%	0	0
Sciatica	1	0.5%	0	0
Taste disorder	1	0.5%	0	1 (0.5)
Abbreviations: SOC, system organ class; RP2D, recommended phase 2 dose (1/2/30/60 mg); DCO, data cutoff; PT, preferred term; ICANS, immune effector cell associated neurotoxicity Data cutoff: August 27, 2021 Source: FDA analysis				

Table 46: FDA Summary of Neurologic Adverse Events Due to Psychiatric Disorders in B11 RP2D

B11 RP2D N = 218	Any Grade		Grade 3	Unresolved at time of DCO
	n	%	n (%)	n (%)
Psychiatric Disorder SOC	42	19%	0	10 (5%)
Presentation by PT or grouped PT				
Insomnia	23	10.5%	0	8 (3.7%)
Anxiety	7	3.2%	0	1 (0.5%)
Depression	3	1.4%	0	1 (0.5%)
Delirium	1	0.5%	0	0
Fear	1	0.5%	0	0
Irritability	1	0.5%	0	0
Mixed anxiety and depression	1	0.5%	0	0
Altered mood	1	0.5%	0	0
Mood swings	1	0.5%	0	0
Restlessness	1	0.5%	0	0
Abbreviations: RP2D, recommended phase 2 dose (1/2/30/60 mg); DCO, data cut off; POT, preferred term Data cutoff: August 27, 2021 Source: FDA Analysis				

Table 47: FDA Summary of Neurologic Adverse Events Due to Nervous System Disorders in B11 FL

B11 FL N = 90	Any Grade		Grade 3	Unresolved at time of DCO
	n	%	n (%)	n (%)
Nervous System Disorder SOC	49	54%	2 (2)	11 (12)
Presentation by PT or grouped PT				
Headache	29	32%	1 (1)	5 (6)
Dizziness	11	12%	0	0
Peripheral neuropathy	18	20%	0	6 (7)
Paresthesia	5	6%	0	1 (1)
Peripheral neuropathy	5	6%	0	1 (1)
Peripheral sensory neuropathy	5	6%	0	3 (3)
Burning sensation	1	1.1%	0	0
Dysaesthesia	1	1.1%	0	1 (1)
Hypoaesthesia	1	1.1%	0	0
Neuralgia	1	1.1%	0	0
Dysgeusia	3	3.3%	0	0
Presyncope	3	3.3%	1 (1)	0
Allodynia	1	1.1%	0	0
Ataxia	1	1.1%	0	0
Mental status changes	4	4.4%	0	0
Confusional state	3	3.3%	0	0
Cognitive disorder	1	1.1%	0	0
Disturbance in attention	1	1.1%	0	0
Head discomfort	1	1.1%	0	0
Sciatica	1	1.1%	0	0
Taste disorder	1	1.1%	0	1 (1)
Tremor	1	1.1%	0	1 (1)
Abbreviations: FL, follicular lymphoma; SOC, system organ class; DCO, data cutoff; PT, preferred term Data cutoff: August 27, 2021 Source: FDA Analysis				

Table 48: FDA Summary of Psychiatric System Disorders in B11 FL

B11 FL N = 90	Any Grade		Grade 3	Unresolved at time of DCO
	n	%	n (%)	n (%)
Psychiatric disorders SOC	21	23%	0	4 (4)
Presentation by PT or grouped PT				
Insomnia	11	12%	0	3 (3)
Anxiety	4	4.4%	0	0
Depression	3	3.3%	0	1 (1)
Fear	1	1.1%	0	0
Mixed anxiety and depression	1	1.1%	0	0
Altered mood	1	1.1%	0	0
Restlessness	1	1.1%	0	0

Abbreviations: FL, follicular lymphoma; SOC, system organ class; DCO, data cutoff
 Data cutoff: August 27, 2021
 Source: FDA Analysis

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

The Applicant’s Position:

Patient-reported outcomes are discussed in Section 8.1.2.

The FDA’s Assessment:

See the FDA’s assessment in Section 8.1.2.

8.2.6. Safety Analyses by Demographic Subgroups

The Applicant’s Position:

Subgroup analyses of overall frequency of adverse events by category (i.e., all grade, Grade 3-4, fatal and serious AEs, and AEs leading to withdrawal, dose interruption or modification) were conducted for the intrinsic factors of age, gender and race in Group B of Study GO29781, to yield the largest subpopulations to allow a meaningful interpretation of the results.

The frequency of adverse events by category reported during initial treatment with mosunetuzumab IV monotherapy in Group B was generally similar between patients aged 18–65 years (N=246) and those aged >65 years (N=168), male (N=269) and female (N=145) patients. The safety analysis by race subgroup was conducted on White (N=320) and Asian (N=67) patients only, as the numbers of patients in other racial groups were too small to draw any meaningful conclusions. AEs for the majority of AE categories were reported in a higher proportion of patients in the White subgroup when compared to the Asian subgroup; however, the difference in the sample sizes of these subgroups could potentially be a reason for the observed imbalances. Of note, no Grade 5 PD was reported among these 67 Asian patients at the time of CCOD.

The FDA’s Assessment:

The FDA’s safety analysis based on age and sex is summarized in the tables below. Safety analysis based on race subgroups was not completed due to the small numbers of racial and ethnic minority patients enrolled in the safety population for whom conclusions about safety and effectiveness could not be drawn. The numbers of patients older than 75 years of age were also too small to conduct a meaningful analysis. The limited enrollment of older patients and racial and ethnic minorities is a significant limitation. To address this, a PMR will be issued to verify the clinical benefit of mosunetuzumab in a randomized trial in patients with relapsed or refractory follicular lymphoma and the trial should enroll sufficient numbers of racial and ethnic minority patients to reflect the racial and ethnic diversity of the U.S. patient population and allow for interpretation of the results in these patients.

Age Subgroup	Safety Population N = 218 n (%)
< 65 years	116 (53)
65 to < 75 years	63 (29)
≥75 years	39 (18)
Source: FDA analysis	

Table 49: FDA Summary of Adverse Events by Age

Adverse Event Category	Age <65 years N = 116 n (%)	Age 65 to <75 years N = 63 n (%)	Age ≥75 years N = 39 n (%)
All Grade TEAEs	114 (98)	62 (98)	38 (97)
Grade 3 or 4 TEAEs	78 (67)	43 (68)	24 (61)
Serious TEAEs	63 (54)	29 (46)	22 (56)
Fatal TEAEs	15 (13)	9 (14)	8 (20)
CRS per ASTCT (All Grades)	52 (46)	21 (33)	13 (33)
Nervous System TEAEs (All Grades)	62 (53)	34 (54)	22 (56)
Psychiatric System TEAEs (All Grades)	10 (9)	2 (3)	3 (8)
Infections	51 (44)	30 (48)	21 (54)
Abbreviations: TEAE, treatment emergent adverse event Source: FDA analysis			

Sex Subgroup	Safety Population N = 218 n (%)
Male	145 (66)
Female	73 (33)
Source: FDA analysis	

Table 50: FDA Summary of Adverse Events by Sex

Adverse Event Category	Male N = 145 n (%)	Female N = 73 n (%)
All Grade TEAEs	142 (98)	72 (99)
Grade 3 or 4 TEAEs	100 (69)	45 (62)
Serious TEAEs	82 (57)	32 (44)
Fatal TEAEs	24 (17)	8 (11)
CRS (All Grades)	60 (41)	26 (36)
Nervous System TEAEs (All Grades)	76 (52)	42 (57)
Psychiatric System TEAEs (All Grades)	8 (5)	7 (10)
Infections	71 (49)	31 (42)
Abbreviations: TEAE, treatment emergent adverse event Source: FDA analysis		

Race/Ethnicity	Safety Population N = 218 n (%)
White	179 (82)
Black or African American	6 (3)
Asian	23 (11)
American Indian	1 (<1)
Unknown	9 (4)
Hispanic or Latino	10 (5)
Source: FDA analysis	

8.2.7. Specific Safety Studies/Clinical Trials

The Applicant's Position:

No dedicated studies have been conducted to evaluate any specific safety concern.

The FDA's Assessment:

Not applicable.

8.2.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

In accordance with the International Council for Harmonisation (ICH) guidelines ICH S9 (2009), no carcinogenicity studies have been conducted because mosunetuzumab is intended to treat patients with advanced cancer.

The FDA's Assessment:

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

Human Reproduction and Pregnancy

The Applicant's Position:

No pregnancies were reported during the GO29781 study.

The FDA's Assessment:

The FDA agrees with the Applicant's position. FDA notes that the mosunetuzumab USPI will include a Warning and Precaution for embryo-fetal toxicity.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

Only adult patients were eligible for inclusion in Study GO29781 and all enrolled patients were ≥ 18 years.

The Agency agreed to an initial Pediatric Study Plan (iPSP-2) amendment for mosunetuzumab

(b) (4)

The Applicant has requested a deferral (under section 505B(a)(3)(A)(iii) of PREA)

(b) (4)

(b) (4)

The FDA's Assessment:

The FDA agrees with the Applicant's position. FDA notes that no studies were conducted in pediatric patients and the development of mosunetuzumab is focused on adult patients with B-cell non-Hodgkin lymphoma. For information on the requested deferral of pediatric investigations, see Section 10.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No information is currently available. There were no reported cases of overdose of mosunetuzumab in the GO29781 study.

The FDA's Assessment:

Not applicable

8.2.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

Not applicable.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

It is expected that safety issues can be adequately managed through labeling, additional risk minimization measures and routine postmarketing surveillance.

The FDA's Assessment:

The FDA agrees with the Applicant's position. In the postmarket setting, the Applicant will be required to complete an integrated safety analysis in patients with follicular lymphoma and other lymphoid malignancies to further characterize the incidence and severity of neurologic adverse reactions, hematologic adverse reactions, hemophagocytic lymphohistiocytosis, infections, and pneumonitis/interstitial lung disease, that may develop with longer term use of mosunetuzumab.

Integrated Assessment of Safety

The Applicant's Position:

The overall safety profile of mosunetuzumab at the RP2D/intended registration dose appears manageable with no unexpected safety signals, considering the advanced nature of the disease and the heavily pretreated patient population under study. The AE profile consisted of CRS (majority were Grade 1-2, limited to Cycle 1, manageable and all resolved); hematologic and associated laboratory abnormalities (limited clinical significance, manageable and reversible); and low rates of treatment discontinuation. The current pharmacovigilance plan and product label include guidance for patient management of CRS, serious infections, tumor flare, and TLS, and these measures are considered adequate to manage the risks. The tolerability of mosunetuzumab was evident by the low proportion of patients who discontinued mosunetuzumab due to AEs. Most AEs requiring intervention could be adequately managed and resolved following dose interruptions (withholding of dose), and/or supportive care. Dose interruptions generally did not prevent patients continuing to receive their planned mosunetuzumab dose for the majority of the duration of treatment.

The mosunetuzumab safety profile demonstrates advantages over other approved treatments for R/R FL ≥ 2 Prior Therapies. The treatment discontinuation rate due to AEs (4.1%) is lower compared to PI3K inhibitors (15-35%) or tazemetostat (8%) (see Table 4 of Clinical Overview, Module 2.5), indicating good tolerability. The CRS profile appears to be milder than CAR-T therapy. Compared to axicabtagene ciloleucel, CRS events reported for mosunetuzumab were less frequent and less severe with fewer Grade ≥ 3 CRS, and the absence of fatal CRS events. Mosunetuzumab also compares favorably with axicabtagene ciloleucel with respect to neurotoxicity profile with a lower incidence and severity of neurologic adverse events, including Grade ≥ 3 and serious events with no fatal neurologic adverse events. Mosunetuzumab also has other advantages over axicabtagene ciloleucel, being immediately available for patients,

avoiding the ex-vivo T-cell manipulation and the resulting delay in treatment that may be prohibitive in patients with rapidly progressing disease, and offers the option to be administered in an outpatient setting. Furthermore, mosunetuzumab avoids the requirement for lymphodepleting chemotherapy and associated toxicities prior to axicabtagene ciloleucel administration.

In conclusion, the Applicant considers the benefits of mosunetuzumab summarized in Section 8.1.5 outweigh the risks and that the overall benefit-risk assessment of mosunetuzumab for patients with R/R FL who received ≥ 2 prior therapies, based on the results from Study GO29781, to be positive. Mosunetuzumab IV monotherapy offers a new treatment option with a novel mechanism of action and demonstrates clinically meaningful advantages over approved therapies for the treatment of patients with R/R FL ≥ 2 prior therapies, a patient population with a high unmet medical need, who have rapidly progressing disease and need for urgent disease control.

The FDA's Assessment:

In general, the FDA agrees with the Applicant's position. The safety data support that mosunetuzumab demonstrated a tolerable safety profile in patients with relapsed or refractory B-cell NHL, including follicular lymphoma. However, based on the FDA's evaluation of the data, the identified risks of neurotoxicity, including ICANS, and cytopenias are warranted to include as Warnings and Precautions in labeling. Conversely, the FDA disagreed with (b) (4) (b) (4). Finally, given the median exposure of 8 cycles in the B11 RP2D cohort, there is limited safety data in patients that receive up to 17 cycles of mosunetuzumab treatment.

9 SUMMARY AND CONCLUSIONS

9.1. Statistical Issues

The FDA's Assessment:

Complete response rate is pre-specified as the primary endpoint in the protocol and SAP; however, FDA considers that the efficacy is established on the basis of ORR and duration of response as assessed by an independent review facility according to standard criteria for NHL (Cheson 2007). For the B11 FL RP2D expansion cohort, the ORR rate is 80% (95% CI: 70.3%, 87.7%) and median DOR is 22.8 months (95% CI: 9.7, not estimable) based on a CCOD of 15 March 2021.

Additionally, FDA does not agree that the comparison of the CR rate based on Study GO29781 against the proposed historical control rate of (b) (4)% is inferential. Comparison of response rates from single-arm trials against a historical rate is challenging and should only be considered

supportive.

9.2. Conclusions and Recommendations

The FDA's Assessment:

The benefit-risk assessment is favorable for mosunetuzumab, a bispecific CD20 directed CD3 T cell engager indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy.

Efficacy:

Efficacy of mosunetuzumab is based on the results from GO29781, an open-label, multicenter, multicohort study in 90 patients with relapsed or refractory follicular lymphoma who had received at least two prior therapies, including an anti-CD20 monoclonal antibody and an alkylating agent.

Patients received step-up doses of 1 mg on Cycle 1 Day 1 and 2 mg on Cycle 1 Day 8, followed by 60 mg on Cycle 1 Day 15, and 60 mg on Cycle 2 Day 1, then 30 mg every 3 weeks in subsequent cycles. A treatment cycle was 21 days. Mosunetuzumab was administered for 8 cycles unless patients experienced progressive disease or unacceptable toxicity. After 8 cycles, patients with a complete response discontinued therapy; patients with a partial response or stable disease continued treatment up to 17 cycles, unless patients experienced progressive disease or unacceptable toxicity.

Efficacy was established on the basis of objective response rate and duration of response as assessed by an independent review facility according to standard criteria for NHL (Cheson 2007). Among the 90 patients, the ORR per IRF was 80% (95% CI: 70, 88), with 60% achieving a complete response. With a median follow-up for DOR of 14.9 months, the estimated median DOR was 22.8 months (95% CI: 10, not reached). Of the 72 responders, 62% remained in response at 12 months and 57% at 18 months.

Safety:

The safety profile of mosunetuzumab was primarily supported by analysis of 218 patients with B-cell NHL that received the recommended dose and regimen (1/2/60/30). The median duration of treatment was 8 cycles (range 1 to 17), with 52% exposed for at least 8 cycles. The most common adverse events ($\geq 20\%$) were cytokine release syndrome (39%), fatigue (36%), rash (34%), pyrexia (24%), and headache (21%). The most common Grade 3 to 4 laboratory abnormalities ($\geq 10\%$) were decreased lymphocyte count (92%), decreased phosphate (41%), increased glucose (40%), decreased neutrophil count (38%), increased uric acid (15%), decreased white blood cell count (22%), decreased hemoglobin (19%), and decreased platelets (12%). Serious adverse events occurred in 52%, most often due to CRS (21%), pneumonia (5%), pyrexia (5%), sepsis (3%), and a 2% incidence each of tumor flare, urinary tract infection, pleural effusion, and renal insufficiency. Adverse events leading to treatment interruption occurred in

33%, most often due to neutropenia, infection, and CRS. Adverse events leading to treatment discontinuation occurred in 4%, most often due to CRS. Thus, the primary safety issues identified with mosunetuzumab include CRS, neurologic toxicity (including ICANS), infections, cytopenias, and tumor flare.

Benefit-Risk:

Mosunetuzumab has an overall favorable benefit-risk in patients with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy. In the 90 patients with relapsed or refractory FL enrolled in the GO29781 study, the median age was 60 years (range: 29 to 90 years), 33% were 65 years of age or older, 61% were male, 82% were White, 9% were Asian, 4% were Black or African American, and 8% were Hispanic or Latino. A total of 77% of patients had Stage III-IV disease, 34% had bulky disease, and all patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The median number of prior therapies was 3 (range: 2 to 10), with 38% receiving 2 prior therapies, 31% receiving 3 prior therapies, and 31% receiving more than 3 prior therapies.

In this population, the overall response rate of 80%, with 60% achieving complete response, with durability and a tolerable safety profile constitutes a meaningful clinical benefit and a favorable benefit-risk evaluation. To support accelerated approval, the efficacy data are considered in the context of available therapy for the patients with relapsed or refractory follicular lymphoma in the 3rd line setting and beyond. Available therapy includes anti-CD20 therapy (i.e., rituximab and obinutuzumab) as a single agent and in combination, bendamustine monotherapy and in combination, and immunotherapy combinations such as rituximab plus lenalidomide. In the 3rd line setting and beyond, the ORRs for these therapies, including single-agent and combinations, ranges from 57% to 80% with associated durability. In the 90 patients with FL treated with mosunetuzumab, all patients received prior anti-CD20 monoclonal antibody and an alkylating agent and the median number of prior therapies was 3. A total of 79% of patients were refractory to prior anti-CD20 monoclonal antibody therapy, 53% were refractory to both anti-CD20 monoclonal antibody and alkylator therapy, 9% received prior rituximab plus lenalidomide therapy, 21% received prior autologous stem cell transplant, and 3% received prior CAR T therapy. Therefore, the overall response of 80% with associated durability for mosunetuzumab provides data to support a clinically meaningful benefit in the context of available therapy for patients with relapsed or refractory follicular lymphoma in the 3rd line setting and beyond.

Thus, the benefit-risk of mosunetuzumab is deemed favorable to support accelerated approval for the following indication:

- Treatment of adult patients with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy

Confirmatory Trial

The Applicant has an ongoing randomized trial in patients with relapsed or refractory follicular lymphoma. Study GO42909 is an open-label, multicenter, randomized (1:1) trial evaluating mosunetuzumab in combination with lenalidomide compared to rituximab in combination with lenalidomide in approximately 400 patients with relapsed or refractory follicular lymphoma after at least 1 prior line of systemic therapy. The primary endpoint is progression-free survival per an independent review committee. The secondary endpoints include complete response rate, overall response rate, overall survival, patient-reported outcomes, and time to next treatment.

As of August 31, 2022, 184 patients have been enrolled out of the planned 400 patients. The FDA considers this ongoing trial to be supportive of accelerated approval for the indication described above. A PMR will be issued based on this trial to verify and describe the clinical benefit of mosunetuzumab in patients with relapsed or refractory follicular lymphoma (Section 14).

X

X

Xin Wang, MD
Primary Statistical Reviewer

Lisa Rodriguez, PhD
Statistical Team Leader

X

X

Pamela Seam, MD
Primary Clinical Reviewer

Nicholas Richardson, DO, MPH
Clinical Team Leader

10 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

This application was not presented to the Oncologic Drugs Advisory Committee or other external consultations because the application did not raise significant efficacy or safety issues for the recommended indication.

11 Pediatrics

The Applicant's Position:

see Section 8.2.9.

The FDA's Assessment:

Mosunetuzumab is a CD20-directed CD3 T-cell bi-specific antibody that causes the release of proinflammatory cytokines and induces lysis of B-cells. The molecular target of CD20 is relevant to pediatric patients with mature B-cell lymphoma. Therefore, per the Pediatric Research Equity Act (PREA) as amended by the FDA Reauthorization Act (FDARA), the agreed initial Pediatric Study Plan (iPSP) for mosunetuzumab included a plan, based on the molecular target of CD20, to request a partial waiver (b) (4) and a deferral (b) (4)

(b) (4) The mosunetuzumab BLA (b) (4) included a pediatric study plan with a request for a partial waiver (b) (4)

(b) (4)

Therefore, the Agency will grant a full waiver for pediatric assessment requirements under PREA, as amended by FDARA, for mosunetuzumab for all pediatric age groups based on the rarity of pediatric patients with relapsed or refractory mature B-cell NHL making pediatric studies impossible or highly impracticable.

12 Labeling Recommendations

The Applicant’s Position:

Data:

This is an original application. Please see annotated label in Module 1.14.1.2 for proposed labeling.

The FDA’s Assessment:

The table below provides a high-level summary of the changes made by the FDA to the US Prescribing Information (USPI) for LUNSUMIO (mosunetuzumab-axgb) BLA 761263; see the USPI and Medication Guide attached to the approval letter for final labeling.

Table 51: FDA Summary of Labeling

Section	FDA’s proposed Labeling
Highlights	A boxed warning summary for cytokine release syndrome added to Highlights. Indication statement corrected to include established pharmaceutical class; accelerated approval language added.
Boxed Warning	FDA added a boxed warning to address the risk of cytokine release syndrome.
Section 1 Indications and Usage	FDA generally agreed with the applicant’s proposal but modified the accelerated approval language to include only response rate.
Section 2 Dosage and Administration	FDA modified this section (b) (4); FDA added a table of dosage modifications and recommendations for the treatment of neurologic toxicity, including ICANS; FDA added a table of dosage modifications and recommendations for other adverse reactions.
Section 3 Dosage Forms and Strengths	FDA generally agreed with the applicant’s proposal with some minor edits.
Section 4 Contraindications	FDA agreed with the applicant’s proposal not to include contraindications.
Section 5 Warnings and Precautions (W&P)	FDA removed the applicant’s proposed W&P (b) (4) and added W&Ps for neurologic toxicity, cytopenias, and embryo-fetal toxicity. Other W&P included in the USPI are

Section	FDA's proposed Labeling
	for cytokine release syndrome, infections, and tumor flare.
Section 6 Adverse Reactions	FDA modified this section to align with current labeling practice for inclusion of adverse reactions observed in the clinical trial. Included a pooled population for the safety information described in section 5.
Section 7 Drug Interactions	FDA modified this section to add a heading for the effect of Lunsumio on CYP450 substrates. Included the mechanism of the DDI with CYP450 substrates. Revised to include information about the period following CRS as a potential risk for DDI based on the mechanism of the DDI. Added recommendation for monitoring for toxicity or concentrations of drugs used concomitantly with Lunsumio that are CYP450 substrates where minimal concentration changes might result in increased serious adverse reactions.
Section 8 Use in Specific Populations	FDA modified these sections to align with current PLLR labeling practice in sections 8.1-8.3, including adding recommendations for pregnancy testing and contraception, as well as adding a statement that Lunsumio may cause fetal harm when administered to a pregnant woman.
Section 11 Description	FDA modified to add the EPC and additional information about the drug substance and drug product, as well as USP/NF monograph titles for the inactive ingredients.
Section 12 Clinical Pharmacology	FDA revised section 12.2 pharmacodynamics to include language to describe the B-cell depletion and cytokine elevations and to add information on hypogammaglobulinemia. In section 12.3 pharmacokinetics, a table to describe PK exposures (AUC, C _{max} , C _{trough}) in the first 2 cycles and at steady state was added, as was a figure to show the mosunetuzumab concentration-time profile up to steady state. Per FDA guidance Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling , immunogenicity information moved to a new section 12.6.
Section 13 Nonclinical Toxicology	FDA modified this section to align with current labeling practice.
Section 14 Clinical Studies	Included study inclusion and exclusion criteria, demographic information, and study dosage regimen for the efficacy population of 90 patients with relapsed or refractory FL who

Section	FDA's proposed Labeling
	had received at least two prior lines of systemic therapy. FDA revised to include one table for efficacy results of ORR and DOR.
Section 16 How Supplied/Storage and Handling	FDA generally agreed with the applicant's proposal but added the proper name and provided some edits to align with current labeling practice.
Section 17 Patient Counseling	FDA modified this section to align with edits made in the W&P section.

The FDA's Assessment:

FDA modified sections of the USPI as described in the table above. The Medication Guide was updated to align with changes made to the USPI.

13 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

The Division of Risk Management (DRM) in the Office of Surveillance and Epidemiology (OSE) reviewed this Application and concurs with the review team that additional risk evaluation mitigation strategies (REMS) are not required for the safe use of mosunetuzumab in the indicated population.

14 Postmarketing Requirements and Commitment

The FDA's Assessment:

The review team recommends two postmarketing requirements (PMR), an accelerated approval PMR to verify clinical benefit and a safety PMR for further characterization of safety with longer-term use of mosunetuzumab.

- 1) Conduct a randomized clinical trial in patients with relapsed or refractory follicular lymphoma, with patients randomized to receive mosunetuzumab in combination with lenalidomide or rituximab in combination with lenalidomide. The primary endpoint should be progression-free survival, with secondary endpoints that include response rate and overall survival. The trial should enroll a sufficiently representative study population to reflect the racial and ethnic diversity of the U.S. patient population with follicular lymphoma and allow for interpretation of the results in these patient populations.

Final Protocol Submission:	09/2021 (completed)
Trial Completion:	06/2025
Final Report Submission:	12/2025

- 2) Conduct an integrated safety analysis in patients with follicular lymphoma and other lymphoid malignancies to further characterize the incidence and severity of neurologic adverse reactions, hematologic adverse reactions, hemophagocytic lymphohistiocytosis, infections, and pneumonitis/interstitial lung disease, that may develop with longer term use of mosunetuzumab. Include patient-level and pooled analyses of ongoing and completed clinical trials and postmarketing reports and/or literature reports.

The timetable you submitted on November 22, 2022, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission (Analysis Plan):	03/2023
Final Protocol Submission (Analysis Plan):	06/2023
Interim Report Submission:	03/2024
Study Completion:	06/2025
Final Report Submission:	12/2025

Submit the datasets with the final report submission.

15 Division Director (DHOT) (NME ONLY)

X

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16 Division Director (OCP)

X

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17 Division Director (OB)

X

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18 Division Director (Clinical)

X

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19 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

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20 Appendices

20.1. References

The Applicant's References:

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20.2. Financial Disclosure

The Applicant's Position:

Information on financial disclosures for GO29781 is provided in Module 1.3.4 of the BLA.

The FDA's Assessment:

Covered Clinical Study (Name and/or Number):* GO29781

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>38</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>3</u>		
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: <u>0</u> Significant payments of other sorts: <u>0</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in study: <u>0</u> Sponsor of covered study: <u>Genentech, Inc.</u>		
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) <u>0</u>		
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.

20.3. Nonclinical Pharmacology/Toxicology

The Applicant's Position:

see Section 5.

The FDA's Assessment: Not applicable.

20.4. OCP Appendices (Technical documents supporting OCP recommendations)

20.4.1. Summary of Bioanalytical Method

The FDA's Assessment:

Mosunetuzumab concentrations in human serum were determined using a validated enzyme-linked immunosorbent assay (ELISA).

In the assay, a monoclonal anti-idiotypic antibody against the anti-CD20 arm of mosunetuzumab was used for capture. A biotin-conjugated monoclonal anti-idiotypic antibody against the anti-CD3 arm of mosunetuzumab was applied for detection. Streptavidin (SA)-horseradish peroxidase (HRP) and a peroxidase substrate (tetramethyl benzidine) were added sequentially for color development. The lower limit of quantification (LLOQ) of the assay is 10 ng/mL. This assay was validated at two sites for analyzing samples from Study GO29781. Results for the methods validation, cross-validation and method performance during study sample analysis are provided in Table 52 and Table 53 below.

Table 52: Methods validation and performance in study GO29781

Bioanalytical method validation report name, amendments, and hyperlinks	Genentech: ELISA for Measuring BTCT4465A (Anti-CD20/CD3 TDB) Antibody in Human Serum (B20T3.003.AVR_0) (b) (4) Partial Validation of an ELISA Method for the Quantification of Anti-CD20/CD3 TDB (BTCT4465A) in Human Serum and Addendum 1 and 2 (S84, S84-1 and S84-2)
Method description	The method for the quantification of mosunetuzumab in human serum is an ELISA. A standard curve is prepared fresh in standard diluent (2% normal human serum in sample diluent). Quality controls and unknown samples are diluted to the assay minimum required dilution of 1/50 in sample diluent. Plate is incubated with mouse anti-BTCT4465A monoclonal antibody (against to anti-CD20 Fab) in carbonate buffer and then washed and blocked with assay diluent. The calibrators, diluted quality controls, and samples are transferred to the coated and blocked plate and incubated at room temperature. Following an additional wash step, a solution of biotinylated mouse anti-BTCT4465A monoclonal antibody (against to anti-CD3 Fab) is added and incubated at room temperature. Unbound materials are removed with a wash step. Subsequently, streptavidin conjugated to HRP is added for detection and incubated. Unbound materials are removed with a wash step. Then, a peroxidase substrate TMB is added for color development before stopping with 1M phosphoric acid. The plate is read at 450 nm for detection absorbance and at 630 nm for reference absorbance. The LLOQ to ULOQ neat serum concentration range is from 10.0 to 500 ng/mL. The in-well calibration range is from 0.125 to 16.0 ng/mL. A four-parameter logistic, unweighted, least-squares regression algorithm is used to quantify unknown samples.
Materials used for calibration curve & concentration	Genentech: Anti-CD20/CD3 TDB Clinical Material, BTCT4465A, Lot: 678541; Concentration: 60.6 mg/mL; Retest date: 24 November 2015 (b) (4) BTCT4465A (Anti-CD20/CD3 TDB); Reference Standard; Lot: 638414; Concentration: 60.2 mg/mL; Retest Date: (b) (4) Lot: 3265083; Concentration: 10.0 mg/mL; Retest Date: (b) (4)
Validated assay range	LLOQ to ULOQ range is 10.0 ng/mL to 500 ng/mL in neat human serum.
Material used for QCs & concentration	Genentech: Anti-CD20/CD3 TDB Clinical Material, BTCT4465A, Lot: 678541; Concentration: 60.6 mg/mL; Retest date: 24 November 2015 (b) (4) BTCT4465A (Anti-CD20/CD3 TDB); Reference Standard; Lot: 638414; Concentration: 60.2 mg/mL; Retest Date: (b) (4) Lot: 3265083; Concentration: 10.0 mg/mL; Retest Date: (b) (4)
MRDs	1/50
Source & lot of reagents (LBA)	Capture reagent: Coat Stock I; Source: Genentech; Lot: Vua-02Mar15-58-coat; Conc: 1.00 mg/mL; Detection reagent: biotin Conjugate Stock I; Source: Genentech; Lot: Tsd-12Feb16-250; Conc: 100 µg/mL
Regression model & weighting	4-PL logistic fit, unweighted

Validation parameters	Method validation summary	Source location
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ: Mosunetuzumab	Genentech: 8 (b) (4) 8
	Cumulative accuracy (%bias) from LLOQ to ULOQ: Mosunetuzumab	Genentech: NA (b) (4) -2.91% to 6.96%
	Cumulative precision (%CV) from LLOQ to ULOQ: Mosunetuzumab	Genentech: NA (b) (4) ≤ 6.94%
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs Genentech: QCs 1-6 for Mosunetuzumab: 10.0, 12.5, 20.0, 75.0, 300, 500 ng/mL	Genentech: -7% to 16% (b) (4)
	(b) (4) QCs 1-5 for Mosunetuzumab: 10.0, 20.0, 75.0, 375, 500 ng/mL	(b) (4) -7.20% to 2.36%
	Inter-batch %CV Genentech: QCs 1-6 in Mosunetuzumab: 10.0, 12.5, 20.0, 75.0, 300, 500 ng/mL	Genentech: ≤ 11%
	(b) (4) QCs 1-5 for Mosunetuzumab: 10.0, 20.0, 75.0, 375, 500 ng/mL	(b) (4) ≤ 7.32%
Total Error (TE)	Genentech: QCs 1-6 in Mosunetuzumab: 10.0, 12.5, 20.0, 75.0, 300, 500 ng/mL	Genentech: ≤ 28%
	(b) (4) QCs 1-5 for Mosunetuzumab: 10.0, 20.0, 75.0, 375, 500 ng/mL	(b) (4) ≤ 9.87

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Validation parameters	Method validation summary	Source location
Selectivity & matrix effect	Genentech: 10 total individual human serum samples from patients with the following disease states: NHL, CLL, DLBCL, and FL. 10/10 samples fortified with mosunetuzumab at LQC (20.0 ng/mL) and 8/10 samples fortified with mosunetuzumab at HQC (300 ng/mL) quantified within ±80%-120% of nominal. 10/10 samples with no analyte spike have a signal response below the LLOQ 2 NHL lots fortified at LQC (20.0 ng/mL); mean % recovery: 97-108% 2 NHL lots fortified at HQC (300 ng/mL); median % recovery: 78-102% 2 NHL lots unfortified: 2/2 <LLOQ 2 CLL lots fortified at LQC (20.0 ng/mL); mean % recovery: 96 to 98% 2 CLL lots fortified at HQC (300 ng/mL); median % recovery: 91 to 93% 2 CLL lots unfortified: 2/2 <LLOQ 3 DLBCL lots fortified at LQC (20.0 ng/mL); mean % recovery: 89 to 100% 3 DLBCL lots fortified at HQC (300 ng/ml); median % recovery: 79 to 91% 3 DLBCL lot unfortified: 3/3 <LLOQ 3 FL lots fortified at LQC (20.0 ng/mL); median % recovery: 83 to 86% 3 FL lots fortified at HQC (300 ng/mL); median % recovery: 83 to 96% 3 FL lots unfortified: 3/3 <LLOQ	Genentech: Table 3 of B20T3.003.AVR_0
Selectivity & matrix effect (cont'd)	(b) 12 individual human serum lots (3 each) from patients with the following disease states: DLBCL, FL, NSCLC, and CLL tested at LQC (20 ng/mL) and HQC (375 ng/mL); Additional 6 individual human serum lots from patients with DLBCL tested at LQC. 18/18 samples fortified with mosunetuzumab at LQC quantified within 80%-120% of nominal value. 12/12 samples fortified with mosunetuzumab at HQC (375 ng/mL) quantified within 80.0%-120% of nominal value. 18/18 samples with no analyte spike have a signal response below the LLOQ. 9 DLBCL lots fortified at LQC (20.0 ng/mL); % bias range: -31.1 to -6.47% 3 DLBCL lots fortified at HQC (375 ng/mL); % bias range: -3.40 to 3.80% 9 DLBCL lots; 9/9 <LLOQ 3 FL lots fortified at LQC (20.0 ng/mL); % bias range: -15.1 to -9.67% 3 FL lots fortified at HQC (375 ng/mL); % bias range: 1.00 to 3.13% 3 FL lots unfortified: 3/3 <LLOQ 3 NSCLC lots fortified at LQC (20.0 ng/mL); % bias range: -13.5 to -4.23% 3 NSCLC lots fortified at HQC (375 ng/mL); % bias range: -5.27 to 3.73% 3 NSCLC lots unfortified: 3/3 <LLOQ 3 CLL lots fortified at LQC (20.0 ng/mL); % bias range: -16.0 to -6.47% 3 CLL lots fortified at HQC (375 ng/mL); % bias range: -10.9 to 1.53% 3 CLL lots unfortified: 3/3 <LLOQ	(b) Tables 6A, 6B, 6C, 6D, 6E of ICD 554 Validation Report (S84)
Interference & specificity	Genentech: Atezolizumab: Atezolizumab at 80.0 and 1000 µg/mL with mosunetuzumab at 0 ng/mL; no cross-reactivity observed Atezolizumab at 80.0 and 1000 µg/mL with mosunetuzumab at 20.0 ng/mL; % recovery range: 112 to 114% Atezolizumab at 80.0 and 1000 µg/mL with mosunetuzumab at 300.0 ng/mL; % recovery range: 108 to 124% Obinutuzumab: Obinutuzumab at 100 and 500 µg/mL with mosunetuzumab at 0 ng/mL; no cross-reactivity observed Obinutuzumab at 100 and 500 µg/mL with mosunetuzumab at 20.0 ng/mL; % recovery range: 108 to 117% Obinutuzumab at 100 and 500 µg/mL with mosunetuzumab at 300.0 ng/mL; % recovery range: 100 to 102% Rituximab: Rituximab between 0.156 and 500 µg/mL with mosunetuzumab at 0 ng/mL; no cross reactivity observed Rituximab 0.500, 5.000, 50.0, and 500 µg/mL with mosunetuzumab at 20.0 ng/mL; % recovery range: 84 to 96% Recombinant human CD20 (rhCD20) ECD: rhCD20 at 0.065, 0.65, 6.50, and 65.0 µg/mL with mosunetuzumab at 20.0 ng/mL; % recovery range: 82 to 85%	Genentech: Tables 4, 5, 6, 7, 8 of B20T3.003.AVR_0

BLA Multi-disciplinary Review and Evaluation {BLA 761263, Lunsumio (Mosunetuzumab)}

Validation parameters	Method validation summary	Source location
Interference & specificity (cont'd)	(b) (4) Atezolizumab (MPDL3280A): Atezolizumab at 1.00 and 1000 µg/mL with mosunetuzumab at 0 ng/mL, no cross-reactivity observed Atezolizumab at 1.00 and 1000 µg/mL with mosunetuzumab at 20.0 ng/mL; % difference of control range is 3.85 to 5.49%; no interference observed Atezolizumab at 1.00 and 1000 µg/mL with mosunetuzumab at 375 ng/mL; % difference of control range is 15.7 to 18.5%; no interference observed Rituximab: Rituximab at 30.0 and 600 µg/mL with mosunetuzumab at 0 ng/mL, no cross reactivity observed Rituximab at 30.0 and 600 µg/mL with mosunetuzumab at 20.0 ng/mL, % difference from control range is 5.76 to 8.38%; no interference observed Rituximab at 30.0 and 600 µg/mL with mosunetuzumab at 375 ng/mL, % difference from control range is -1.90 to -1.63%; no interference observed Polatuzumab Vedotin (Polivy): Polatuzumab Vedotin at 1.60 and 30.0 µg/mL with mosunetuzumab at 0 ng/mL, no cross reactivity observed Polatuzumab Vedotin at 1.60 and 30.0 µg/mL with mosunetuzumab at 20.0 ng/mL, % difference from control is -13.0 to 9.81%; no interference observed Polatuzumab Vedotin at 1.60 and 30.0 µg/mL with mosunetuzumab at 375 ng/mL, % difference from control is -12.6 to -0.756%; no interference observed Tocilizumab: Tocilizumab at 50.0 and 200 µg/mL with mosunetuzumab at 0 ng/mL, no cross reactivity observed Tocilizumab at 50.0 and 200 µg/mL with mosunetuzumab at 20.0 ng/mL, % difference from control is -6.73%; no interference observed Tocilizumab at 50.0 and 200 µg/mL with mosunetuzumab at 375 ng/mL, % difference from control is -7.55 to -4.58%; no interference observed	(b) (4) Table 6 of ICD 554 Validation Report (S84) (b) (4) Table 9C, 10D-E, 11 of ICD 554 Addendum 1 (S84-1)
Validation parameters	Method validation summary	Source location
Hemolysis effect	Genentech: 1 pooled normal matrix lot tested at a 2 and 10% hemolyzed serum concentration. Range of observed bias not calculated, recovery shown instead. LQC (20.0 ng/mL): 108 to 109% HQC (300 ng/mL): 102% (b) Hemolysis was validated in the original Genentech validation and was not re-evaluated by (b) (4)	Genentech: Table 9 of B20T3.003.AVR_0 NA
Lipemic effect	Genentech: 1 pooled normal matrix lot tested at a 150 and 500 mg/dL lipemic serum concentration. Range of observed bias not calculated, recovery shown instead. LQC (20.0 ng/mL): 97 to 108% HQC (300 ng/mL): 103 to 119% (b) (4) Lipemia was validated in the original Genentech validation and was not re-evaluated by (b) (4)	Genentech: Table 10 of B20T3.003.AVR_0 NA
Dilution linearity & hook effect	Genentech: Highest concentration tested was 50 µg/mL BTCT4465A diluted at the MRD followed by 7 dilutions down to 1/500,000. Range of observed bias: -8 to 7% Accuracy and linearity were acceptable for this sample. No hook effect observed. (b) (4) Highest concentration was 1.00 mg/mL BTCT4465A with 2 dilution factors above the curve, 5 dilutions on the curve, and one dilution below the curve tested. Range of observed bias: -2.16 to 18.4% No hook effect observed.	Genentech: Table 2 of B20T3.003.AVR_0 (b) (4) Tables 4A and 4B of ICD 554 Validation Report (S84)
Validation parameters	Method validation summary	Source location (hyperlinked)
Bench-top/process stability	Genentech: Mosunetuzumab in neat serum at LQC (20 ng/mL), MQC (75 ng/mL), and HQC (300 ng/mL) is stable for a combined storage of 97 hours at 2°C-8°C 30 hours at ambient temperature 10 freeze/thaw cycles at or below -60°C % Recovery range: 94 to 101% (b) (4) Bench-top/process Stability was validated as part of the original Genentech method validation and was not re-evaluated by (b) (4)	Genentech: Table 20 of B20T3.003.AVR_0 NA
Freeze-Thaw stability	Genentech: See Freeze/thaw stability above in combined storage stability. (b) (4) Freeze-Thaw Stability was validated as part of the original Genentech method validation and was not re-evaluated by (b) (4)	Genentech: Table 20 of B20T3.003.AVR_0 NA
Long-term stability	Genentech: Mosunetuzumab in neat serum at HQC (300 ng/mL) and ultra-high level (50.0 µg/mL) Stable at -20°C for 12 months, range of observed bias: -8 to -4%. Stable at -60°C for 12 months, range of observed bias: -14 to -9%. (b) (4) Mosunetuzumab in neat serum at HQC (375 ng/mL) and LOQ (20.0 ng/mL) Stable at -80°C for 722 days, range of observed bias: -11.4 to -8.36%.	Genentech: Table 22 and 23 of B20T3.003.AVR_0 (b) (4) Table 1 of ICD 554 Addendum 2 (S84-2)
Parallelism	See summary in "Dilution linearity & hook effect"	
Carry over	NA	

BLA Multi-disciplinary Review and Evaluation {BLA 761263, Lunsumio (Mosunetuzumab)}

Method performance in study GO29781 (Bioanalytical Report Number GO29781_PK_BAR_0 [Genentech])		
Materials used for calibration curve & QC	Standard Source Material: Genentech reference material BTCT4465A, Lot 678541, Conc: 60.6 mg/mL	GO29781-PK-BAR-0, Table 2
Assay passing rate	41 of 56 runs (73.2%) acceptable	GO29781-PK-BAR-0, Page 7
Standard Curve Performance	Cumulative %Difference from Theoretical Range: Not reported Cumulative Precision: Not reported	NA
QC Performance (both passing and failed runs)	Cumulative %Difference from Theoretical Range: -1 to 11% Cumulative Precision: ≤22% CV TE: ≤33%	GO29781-PK-BAR-0, Appendix 1
Method Reproducibility	Incurred sample reanalysis was performed in 10% of study samples and 94% of samples met the pre-specified criteria.	GO29781-PK-BAR-0, Appendix 3
Study Sample Analysis/Stability	Not reported	NA
Method performance in study GO29781 (Bioanalytical Report Project RHWT (b) (4))		
Materials used for calibration curve & QC	Standard Source Material: Genentech reference material BTCT4465A, Lot 638414, Conc: 60.2 mg/mL BTCT4465A, Lot 3265083, Conc: 10.0 mg/mL	Report-RHWT, Page 6
Assay passing rate	371/420 runs (88.3%) acceptable	Report-RHWT, Table 3
Standard Curve Performance	Cumulative %Difference from Theoretical Range: -0.567 to 0.970% Cumulative Precision: ≤9.15% CV	Report-RHWT, Table 5
QC Performance (both passing and failed runs)	Cumulative %Difference from Theoretical Range: -1.35 to 1.39% Cumulative Precision: ≤9.13% CV TE: ≤10.5%	Report-RHWT, Table 6
Method performance in study GO29781 (Bioanalytical Report Project RHWT (b) (4)cont'd)		
Method Reproducibility	Incurred sample reanalysis was performed in 9.01% of study samples and 94.6% of samples met the pre-specified criteria.	Report-RHWT, Amendment 1 of report, Page 10
Study Sample Analysis/Stability	Nine thousand one hundred eighty-eight (9188) of the 9197 reported study samples were analyzed within the 722 days demonstrated long-term storage stability in human serum at -80 °C. Collection dates were not provided for 9 of the 9197 reported study samples; therefore, storage duration could not be assessed for these samples.	Report-RHWT, Amendment 1 of report, Page 10

CLL = chronic lymphocytic leukemia; CV = coefficient of variation; DLBCL = diffuse large B-cell lymphoma; ECD = extracellular domain; ELISA = enzyme-linked immunofluorescence assay; FL = follicular lymphoma; HQC = higher quality control; HRP = horseradish peroxidase; LLOQ = lower limit of quantitation; LQC = lower quality control; MQC = middle quality control; MRDs = minimum required dilutions; NA = not applicable; NHL = Non-Hodgkin's lymphoma; NSCLC = non-small cell lung cancer; TE = total error; TMB = tetramethyl benzidine; ULOQ = upper limit of quantitation.

Source: Table 2a in summary of biopharmaceutical studies and associated analytical methods

Table 53: Methods for Cross validation

Bioanalytical method validation report name and hyperlink	Cross-Validation of Anti-CD20/CD3 TDB (BTCT4465A, mosunetuzumab) Pharmacokinetic ELISA Method B20T3.003 (Genentech) and ELISA Method ICD554 (b)(4) Using Incurred Samples from Clinical Study GO29781 B20T3.003.CVR_0		
Changes in method	No changes in method		
New validated assay range if any	Assay range is unchanged		
Validation parameters	Cross-validation performance	Source location	
Standard calibration curve performance during accuracy & precision	Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ	NA	NA
	Cumulative precision (%CV) from LLOQ to ULOQ	NA	NA
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs	NA	NA
	Inter-batch %CV	NA	NA
	Percent total error (TE)	NA	NA
Cross-validation	100 post-dose incurred samples from study GO29781, an open-label, multicenter, Phase 1 trial evaluating the safety and pharmacokinetics of escalating doses of BTCT4465A, with or without single-dose obinutuzumab pretreatment, in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma and chronic lymphocytic leukemia. These incurred samples were analyzed in the mosunetuzumab PK methods at (b)(4) and Genentech. The methods were found to be equivalent.	Tables 1, 2, and 3 of B20T3.003.CVR_0	
	Slope of the %Difference by mean concentration	-0.008 ± 0.007	
	%Difference of all samples (n= 100) Bias for of the 90% confidence interval lower bound	8.22%	
	Bias for of the 90% confidence interval upper bound:	11.34%	
	%Difference by Quartile Bias range of the 90% confidence interval lower bound for quartiles 1, 2 and 3 combined, and 4:	5.05 to 11.12%	
	Bias range of the 90% confidence interval upper bound for quartiles 1, 2 and 3 combined, and 4:	9.21 to 15.72%	
List other parameters	NA		

CV = coefficient of variation; CVR = cross validation report; LLOQ = lower limit of quantitation; NA = not applicable; TE = total error; ULOQ = upper limit of quantitation.

Source: Table 2b in summary of biopharmaceutic studies and associated analytical methods

20.4.2. Mosunetuzumab Pharmacokinetics

The FDA's Assessment:

Mosunetuzumab PK sampling schedules and PK results in group A and B in study GO29781 are summarized in Table 54 below.

Table 54: Schedule of PK Assessment for Mosunetuzumab in Study GO29781

	PK Sample Timepoints ^a
Group A	Cycle 1: Day 1 (predose, end of infusion, 2 h post-infusion), 24 h, 48 h, 72 h, Day 8, Day 15. Cycles 2, 3, 4, 6, and 8: Day 1 (predose, end of infusion, 2 h post-infusion), Day 8. Cycles 12 and 16: Day 1 (predose). And the follow-up visit.
Group B Dose-Escalation and Expansion (dense)	Cycle 1: Day 1 (predose, end of infusion, 2 h post-infusion), Day 2, and Day 4; Day 8 (predose, end of infusion, 2 h post-infusion), Day 9, Day 11, Day 15 (predose, end of infusion, 2 h post-infusion), Day 16, and Day 18. Cycles 2, 3, 4, 6, and 8: Day 1 (predose, end of infusion, 2 h post-infusion) and Day 8. Cycles 12 and 16: Day 1 (predose). And the follow-up visit.
Group B Dose-Escalation and Expansion (sparse)	Cycle 1: Day 1 (predose, end of infusion, 2 h post-infusion), Day 8 (predose, end of infusion) and Day 15 (predose, end of infusion). Cycles 2, 3, 4, 6, and 8: Day 1 (predose, end of infusion, 2 h post-infusion) and Day 8. Cycles 12 and 16: Day 1 (predose). And the follow-up visit.

h=hours; post-infusion= post the end of infusion; infusion duration is 4 hours for the first dose and 2 hours for the remaining doses.

^a Day 1 is considered the first day of drug administration.

Source: Table 2 in summary of clinical pharmacology.

Mosunetuzumab PK in Group A

A total of 33 patients enrolled in Group A received mosunetuzumab IV q3w treatment with the dosing range 0.05-2.8 mg. Of these, 32 patients were included in the PK analysis.

Mosunetuzumab concentrations in the only patient treated at the 0.05 mg dose were below the assay lower limit of quantification (LLOQ) of 10 ng/mL. See the summary of PK parameters in Table 55 and concentration-time profile in Figure 23 below.

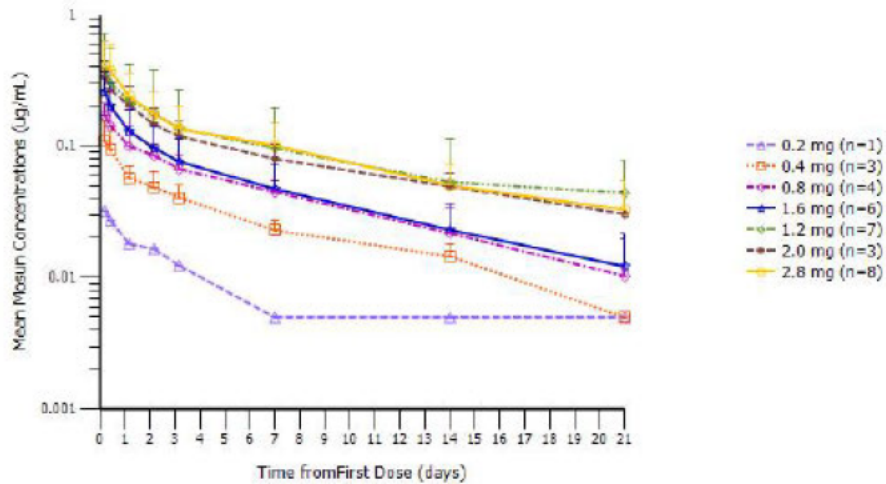
Table 55: Summary of Serum Mosunetuzumab Pharmacokinetic Parameters following Administration as IV Monotherapy in Non-Fractionated Dose Escalation Cohorts in Group A, PK-Evaluable Patients

Patient Cohort and Dose		Half-life (day)	T _{max} (day)	C _{max} (µg/mL)	AUC ₀₋₂₁ (day•µg/mL)	AUC _{inf} (day•µg/mL)	CL (L/day)	V _{ss} (L)
A2: 0.2 mg	N	1	1	1	1	1	1	1
	Mean	2.66	0.319	0.0323	0.0604	0.108	1.85	7.02
	CV%	NA	NA	NA	NA	NA	NA	NA
A3: 0.4 mg	N	3	3	3	3	3	3	3
	Mean	6.94	0.191	0.109	0.447	0.591	0.694	6.69
	CV%	9.8	5.1	40.5	21.6	19.6	18.5	26.1
A4: 0.8 mg	N	4	4	4	4	4	4	4
	Mean	6.82	0.176	0.171	0.818	0.995	0.875	7.54
	CV%	18.6	3.0	23.2	40.2	36.9	29.9	25.0
A5: 1.6 mg	N	6	6	6	6	6	6	6
	Mean	7.46	0.191	0.258	1.04	1.23	1.75	15.5
	CV%	32.8	15.1	44.0	56.4	55.6	60.3	55.4
A6: 1.2 mg	N	7	7	7	7	7	7	7
	Mean	7.77	0.174	0.385	1.85	2.32	1.01	8.13
	CV%	44.2	1.8	89.0	118	116.5	69.6	49.8
A7: 2.0 mg	N	3	3	3	3	3	3	3
	Mean	9.17	0.789	0.282	1.56	2.04	1.04	12.7
	CV%	18.1	67.7	50.0	38.6	32.0	27.0	35.6
A8: 2.8 mg	N	8	8	8	8	8	8	8
	Mean	9.69	0.258	0.402	1.99	2.53	1.16	14.4
	CV%	27.3	40.4	52.4	45.9	45.7	28.0	39.7

AUC_{inf} = area under serum concentration curve from time zero extrapolated to infinity; AUC₀₋₂₁ = area under Cycle 1 (21 days) serum concentration curve; CV = coefficient of variation; C_{max} = maximum serum concentration from 0 to 21 days; CL = total body clearance; PK=pharmacokinetic; T_{max} = time from dosing to maximum concentration; V_{ss} = volume of distribution at steady state; NA=not applicable.

Note: All data at the 0.05 mg dose group (Cohort A1, N=1) were below the assay lower limit of quantification (LLOQ) of 10 ng/mL.

Source: table 3 in summary of clinical pharmacology.



Note: All data at the 0.05 mg dose group were below the assay lower limit of quantification (LLOQ) of 10 ng/mL. For all data below the LLOQ, half LLOQ (5ng/mL) were used for plotting.

Figure 23: Cycle 1 Mean (+SD) Mosunetuzumab Concentration-Time Profiles Following Administration of a Fixed (Non-Fractionated) Dose by IV Infusion in Group A, PK-Evaluable Patients

Source: figure 2 in summary of clinical pharmacology.

Mosunetuzumab PK in Group B

Dose Escalation and Dose Expansion Cohorts (Excluding the RP2D Dose Patients)

A total of 196 PK-evaluable patients were included in 11 different dosing regimen groups at Cycle 1 step-up dose escalation and dose expansion stages in Group B, excluding patients treated at the RP2D. See the summary of PK parameters in Table 56 and concentration-time profile in Figure 24 below.

Table 56: Summary of Serum Mosunetuzumab Pharmacokinetic Parameters following Administration as IV Monotherapy in Cycle 1 Step-up Dose Escalation and Dose Expansion Cohorts in Group B (excluding the RP2D cohort), PK-Evaluable Patients

Patient Cohort and Dose		Half-life (day)	T _{max} (day)	C _{max} (µg/mL)	AUC ₀₋₂₁ (day*µg/mL)
B1 (0.4/1.0/2.8 mg)	N	6	6	6	6
	Mean	4.37	14.2	0.565	2.80
	CV%	16.1	0.3	23.9	29.0
B2 (0.8/2.0/4.2 mg)	N	14	15	15	14
	Mean	7.23	14.8	0.871	5.27
	CV%	137.7	21.7	47.0	39.8
B3 (1.0/1.0/3.0 mg)	N	1	1	1	1
	Mean	4.74	14.1	0.622	3.74
	CV%	0.00	0.00	0.00	0.00
B4 (1.0/2.0/6.0 mg)	N	5	6	6	5
	Mean	4.99	16.6	1.43	8.57
	CV%	7.6	22.9	53.4	28.1
B5 (0.8/2.0/6.0 mg)	N	25	27	27	25
	Mean	4.81	14.3	1.43	8.04
	CV%	28.8	14.0	64.6	76.0
B6 (1.0/2.0/9.0 mg)	N	5	5	5	5
	Mean	3.56	14.5	2.03	8.11
	CV%	27.5	2.0	18.1	24.2
B7 DE and expansion (1.0/2.0/13.5 mg)	N	66	73	73	68
	Mean	3.78	15.1	2.54	12.4
	CV%	32.4	17.3	36.1	42.5
B8 (1.0/2.0/20.0 mg)	N	9	10	10	9
	Mean	4.09	14.2	4.09	17.6
	CV%	28.2	5.5	29.4	27.3
B9 (1.0/2.0/27.0 mg)	N	23	24	24	23
	Mean	3.98	14.7	5.35	24.4
	CV%	46.1	11.6	25.5	43.1
B10 (1.0/2.0/40.5 mg)	N	15	15	15	15
	Mean	3.73	14.2	9.32	32.0
	CV%	20.2	2.7	29.5	24.8
B11 DE (1.0/2.0/60 mg)	N	2	3	3	2
	Mean	5.12	14.2	14.1	50.2
	CV%	3.3	0.5	20.7	9.3

CV = coefficient of variation; C_{max} = maximum serum concentration from 0 to 21 days; DE = dose escalation; T_{max} = time from dosing to maximum concentration; AUC = area under Cycle 1 (21 days) serum concentration curve.

Source: table 4 in summary of clinical pharmacology.

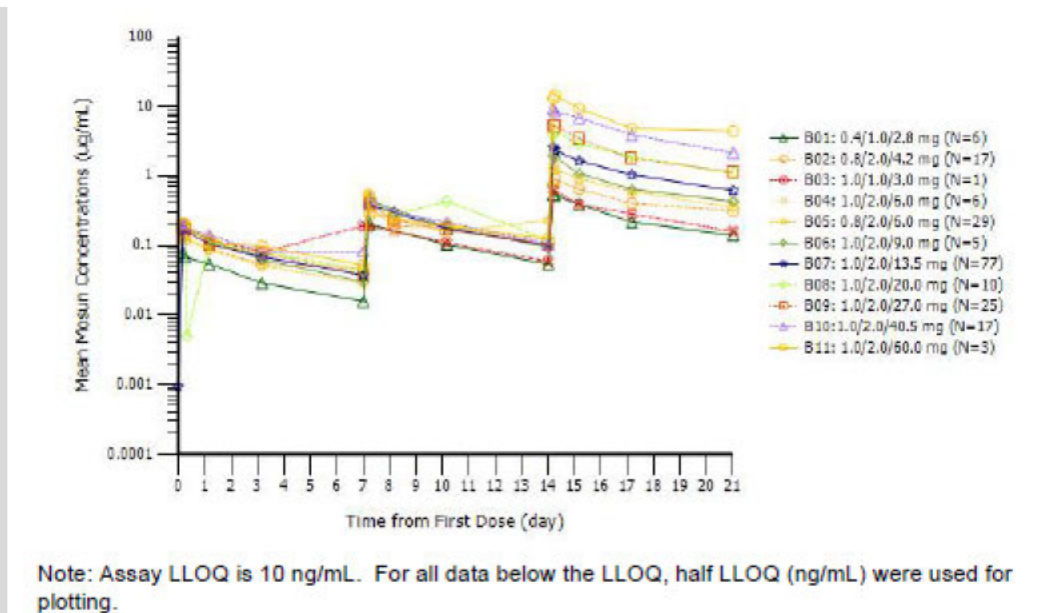


Figure 24: Cycle 1 Mean Mosunetuzumab Concentration-Time Profiles Following Administration of a Step-up Dose by IV Infusion in Group B Dose Escalation Cohorts, PK-Evaluable Patients

Source: figure 3 in summary of clinical pharmacology.

Dose Expansion Cohort at RP2D by Histologies

Among 218 patients enrolled in the B11 RP2D cohort, 211 patients were PK evaluable, which includes the 90 patients in the B11 FL RP2D cohort.

See the summary of PK parameters in Table 57 and concentration-time profile in Figure 25 below.

Table 57: Summary of Serum Mosunetuzumab Pharmacokinetic Parameters following Administration of IV Monotherapy in Patients Receiving 1/2/60/30 mg RP2D in Cycle 1 and Cycle 2 Step-up Dose Expansion in Group B, PK-Evaluable Patients

Patient Cohort and Dose ^a		Half-life (day)	T _{max} (day)	C _{max} (µg/mL)	AUC ₀₋₄₂ (day*µg/mL)
All Patients (N=211)	N	153	191	191	155
	Mean	8.58	22.3	17.9	246
	CV%	43.8	41.0	49.6	46.9
R/R FL Patients (N=90)	N	81	86	86	81
	Mean	8.38	22.1	17.9	256
	CV%	32.3	38.9	39.3	43.1

CV = coefficient of variation; C_{max}= maximum serum concentration from 0 to 42 days; T_{max}=time from dosing to maximum concentration; AUC = area under Cycle 1 and Cycle 2 (42 days) serum concentration curve.

^a The recommended Phase II dose (RP2D) of mosunetuzumab IV monotherapy was 1/2/60/30 mg.

Source: table 5 in summary of clinical pharmacology.

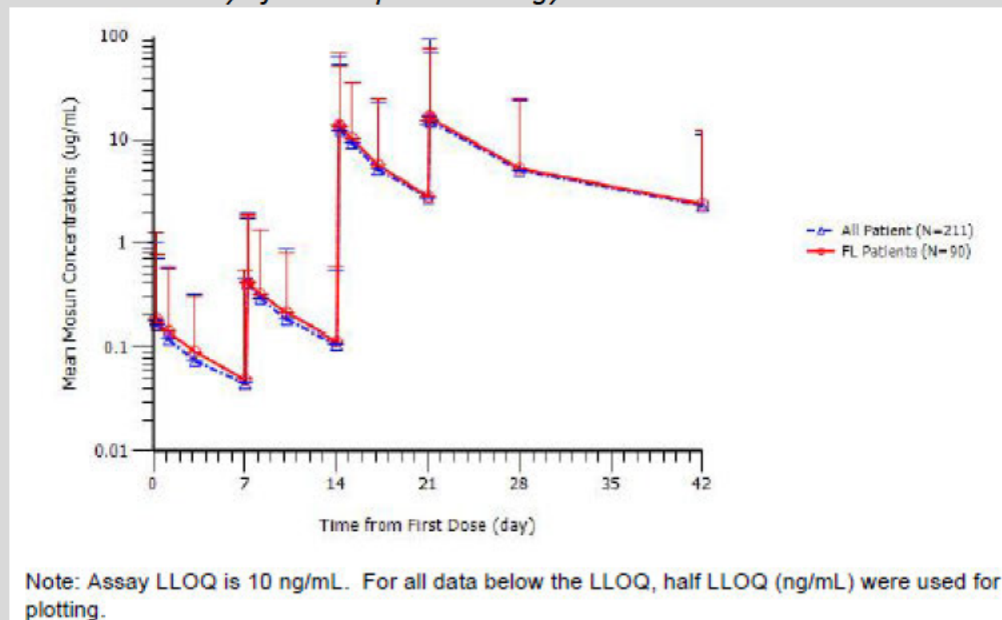


Figure 25: Cycle 1 and Cycle 2 Mean (+SD) Mosunetuzumab Concentration-Time Profiles Following Administration of Two Cycles of a Step-up Dose of 1/2/60/30 mg by IV Infusion in the RP2D Expansion Cohort in Group B, PK-Evaluable Patients

Source: figure 4 in summary of clinical pharmacology.

20.4.3. Mosunetuzumab Pharmacodynamics

The FDA's Assessment:

B-cell Depletion

To assess the magnitude and kinetics of B-cell depletion, a quantitative flow cytometry assay to detect CD19+ B cells was added to the Study Protocol (version 9 [dated 30 January 2019]). B-cell depletion was measured in 152 patients from cohort B11. A majority (110/152 patients, 72%) of patients enrolled had B-cell counts below 70 cells/ul (the lower limit of the normal range for peripheral B cell counts) at baseline, and approximately half of patients (71/152, 47%) enrolled had B-cell counts below the level of quantitation (LLOQ) for the assay (5 cells/ul) at baseline.

For patients with paired baseline and on-study samples, i.e., those having measurable B-cells (≥ 5 cells/ul) prior to mosunetuzumab dosing and at least one additional measurement post-treatment, B-cells were found to be reduced to undetectable levels in most patients within Cohort B11 as early as Cycle 2 [58/63 (92%)], and depletion was sustained at later cycles including at Cycle 4 (58/60, 97%), and Cycle 8 (45/48, 94%) (Table 58). Furthermore, 100% of these patients had B-cell depletion to < 70 cells/ul by cycle 4.

Table 58: Summary of B cell Counts at Baseline and Post-baseline

CD19+ B cells	Baseline (n=73)	Cycle 2 Day 1 (n=63)	Cycle 4 Day 1 (n=60)	Cycle 8 Day 1 (n=48)	3 Months post treatment (n=18)	6 Months post treatment (n=16)
< 70 counts/uL	35 (47.9%)	59 (93.7%)	60 (100%)	48 (100%)	18 (100%)	15 (93.8%)
< 5 counts/uL	0	58 (92.1%)	58 (96.7%)	45 (93.8%)	/	/

Source: table 3.1 in response to FDA information request received on 08/22/2022 and CSR 1111637 page 364.

IgG Levels

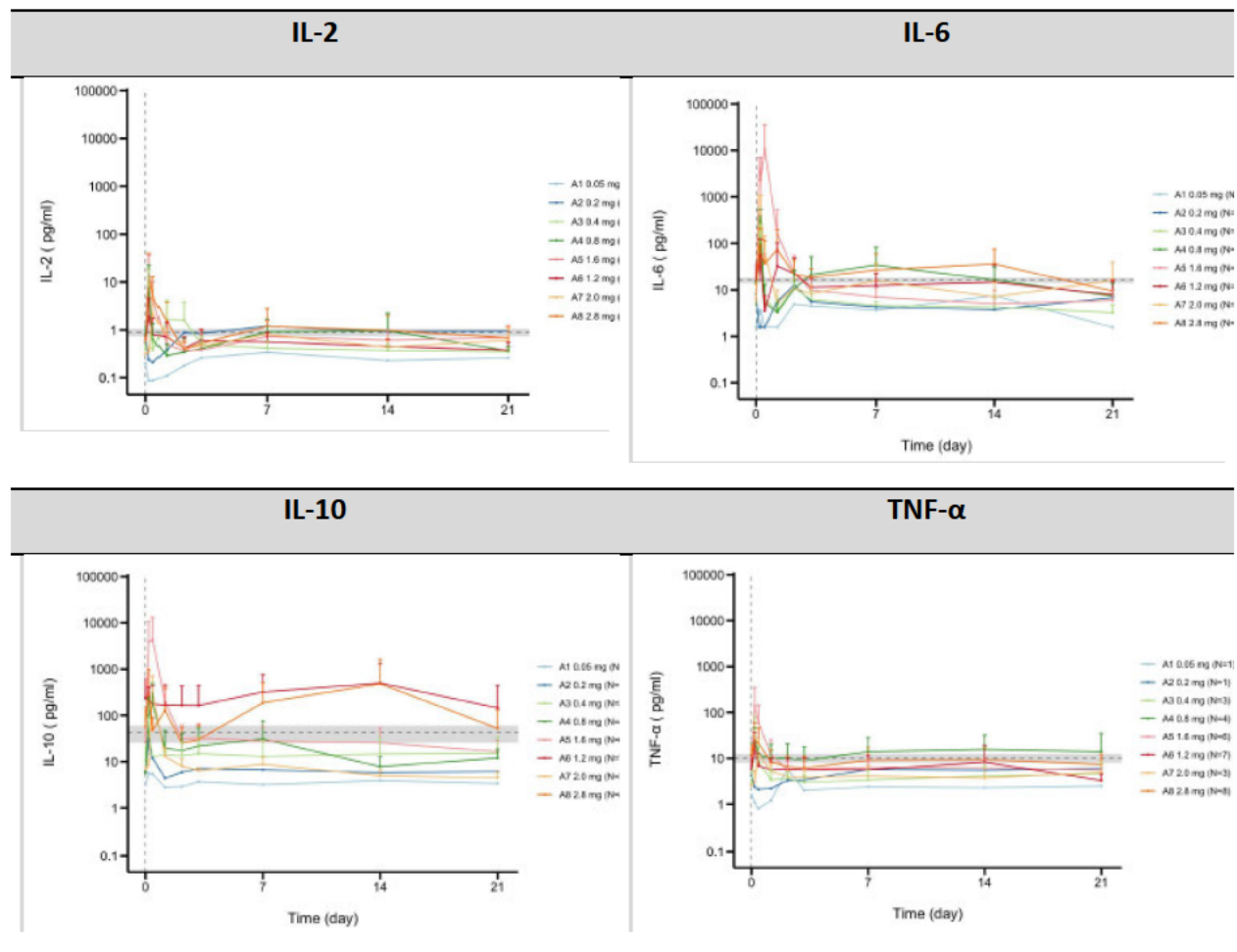
Of the 105 evaluable patients in the B11 RP2D cohort (n=218) who had a baseline IgG measurement and at least one post-baseline IgG measurement, a total of 38 patients enrolled had IgG levels < 5 g/L, the remaining 67 patients had baseline IgG levels ≥ 5 g/L.

- Among 38 patients with baseline IgG levels < 5 g/L, 78.9% (30/38) of the patients maintained post-baseline IgG levels < 5 g/L.
- Among 67 patients with baseline IgG levels ≥ 5 g/L, 59.7% (40/67) of the patients maintained post-baseline IgG levels ≥ 5 g/L, while the remaining patients (27/67; 40.3%) had the IgG values decreased to < 5 g/L.

Cytokine levels

Cytokines (IL-2, IL-6, IL-10, TNF- γ , IFN- α) were measured in clinical studies GO29781. Only IL-6 and INF γ were cytokines that were measured in all cohorts, including the Group A and B step-up dosing cohorts. For TNF- α , IL-2 and IL-10, data are only available for Group A and cohort B11 in Group B.

The general profile of all cytokines showed a consistent pattern of acute elevation after initial mosunetuzumab exposure in both Group A (fixed-dosing) and Group B (step-up-dosing) followed by a return to baseline levels later within Cycle 1. In Group A, no changes from baseline were observed in later cycles (Figure 26). In the step-up-dosing Group B, a first cytokine peak was observed after the first step dose on Cycle 1 Day 1, and a second cytokine peak was observed with the first loading dose on Cycle 1 Day 15. However, two peaks were not found to be proportional to mosunetuzumab dose (Figure 27). Limited data are available in later cycles. This repeat dose and time-related decrease observed within tested cytokines that coincide with CRS occurrence reflect the outcome of effective CRS mitigation by the proposed step-up dosing regimen of 1/2/60/30 mg.



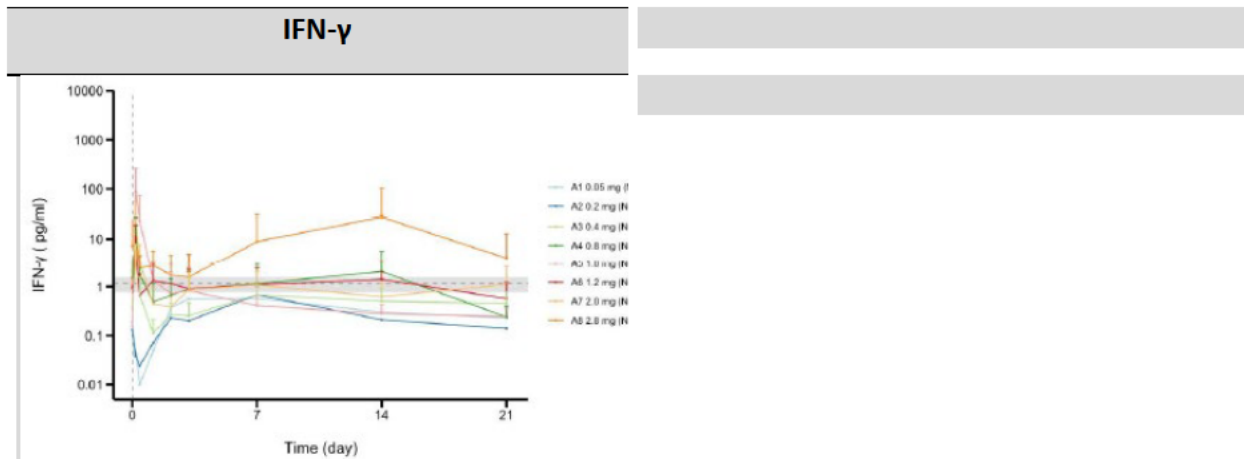
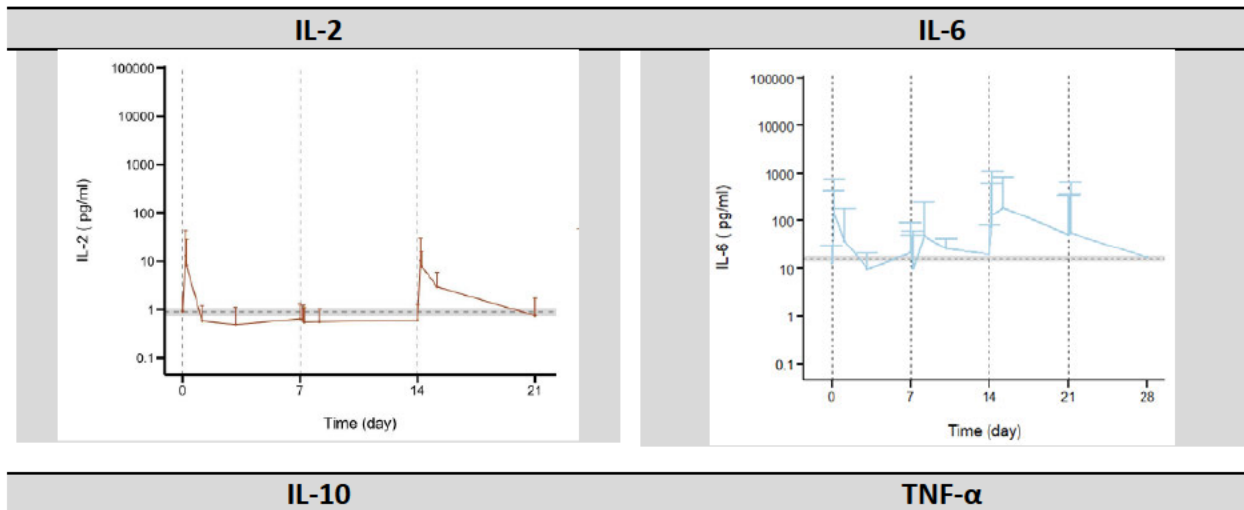


Figure 26: Arithmetic Mean (+SD) of Plasma Cytokine Concentration vs. Nominal Time Following IV Administrations of Mosunetuzumab in R/R NHL Patients (Group A, Fixed Dosing from 0.05 mg to 2.8 mg)

Source: figure 8 in response to FDA information request received on 08/22/2022 and figure 1 in exposure response for biomarker report 1112127.



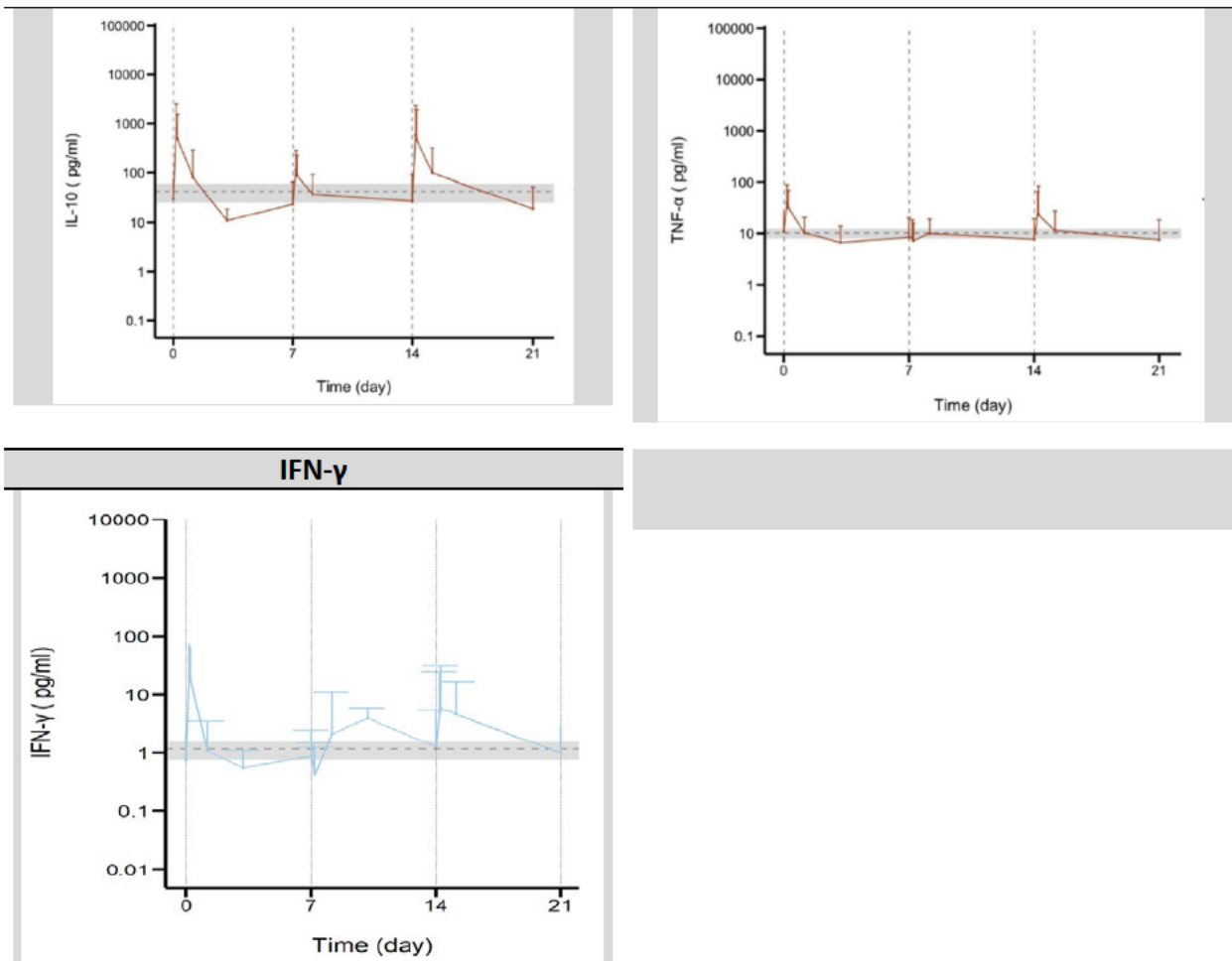


Figure 27: Arithmetic Mean (+SD) of Plasma Cytokine Concentration vs. Nominal Time Following IV Administrations of Mosunetuzumab in R/R NHL Patients (Group B11, 1.0/2.0/60.0/30.0 mg)

Source: Figure 8 in response to FDA information request received on 08/22/2022 and figure 2 in exposure response for biomarker report 1112127.

20.4.4. Population PK Analysis for Mosunetuzumab

20.4.4.1. Executive Summary

The FDA's Assessment:

In support of the proposed dosing regimen of mosunetuzumab in adult patients with relapsed or refractory (R/R) follicular lymphoma (FL) who have received at least two prior systemic therapies, the Applicant submitted the Population Pharmacokinetic (PopPK) report from the IV monotherapy cohorts of Study GO29781, including the fixed dosing group (Group A; 0.05-2.8 mg IV q3w) and the step-up dosing group (Group B; 0.4/1/2.8-1/2/60 mg IV q3w) in patients

with R/R NHL. The Applicant's final PopPK models of mosunetuzumab is characterized as 2-compartment PPK model with time varying clearance, which is adequate to describe the mosunetuzumab serum concentration-time profiles of R/R FL patients, following the IV administration of mosunetuzumab with 1/2/60/30 mg Q3W. The shrinkage value of the Applicant's mosunetuzumab PopPK model was 6.69% for IIV on CL, 6.64% for IIV on V1, 22.8% for V2, and 32.1% for distributional clearance Q, Inter-individual variabilities (IIV) were estimated to be higher for CL_{base} (63%) and half-life HL_{trans} (86%) versus CL_{ss} (18%), V1 (31%), and V2 (25%); Shrinkage was relatively low on CL_{base} , V1, and CL_{ss} , supporting a robust covariate analysis on these parameters, and indicating there was no obvious bias in the parameter estimates for mosunetuzumab.

Covariate analysis results showed the statistically significant covariates e.g., body weight, tumor burden, albumin, baseline anti-CD20 drug concentrations (specifically residual rituximab [R] or Gazyva [G]), and sex had a marginal impact on mosunetuzumab pharmacokinetics when assessing the influence of extreme values. In addition, neither patient age, renal impairment status, hepatic impairment status, drug material used, histology (i.e., FL vs. DLBCL vs. other), nor race (Asian vs. non-Asian) were identified as covariates influencing mosunetuzumab PK.

Given the unique step-up dose regimen, and time dependent clearance, additional simulations including PopPK model-predicted mosunetuzumab concentration-time profiles, receptor occupancy (RO)-time (%), and CL-time (L/day) profiles based on the 1/2/60/30 mg dose regimen were performed to support the AUC endpoints selected, and E-R analysis for CRS. The final PK model is acceptable for simulating post-hoc exposure metrics of mosunetuzumab (AUC_{0-42} , AUC_{0-63} , AUC_{0-84}) and RO(%) used for subsequent E-R analyses for efficacy and safety measurements.

In general, the Applicant's PopPK analysis for mosunetuzumab is considered acceptable for the purpose of supporting analyses objectives. The Applicant's analyses were verified by the reviewer, with no significant discordance identified. More specifically, the developed model is acceptable to be used to derive exposure metrics for E-R analysis, and to support the Applicant's proposed labeling statements about general PK information including intrinsic and extrinsic factors in the current submission.

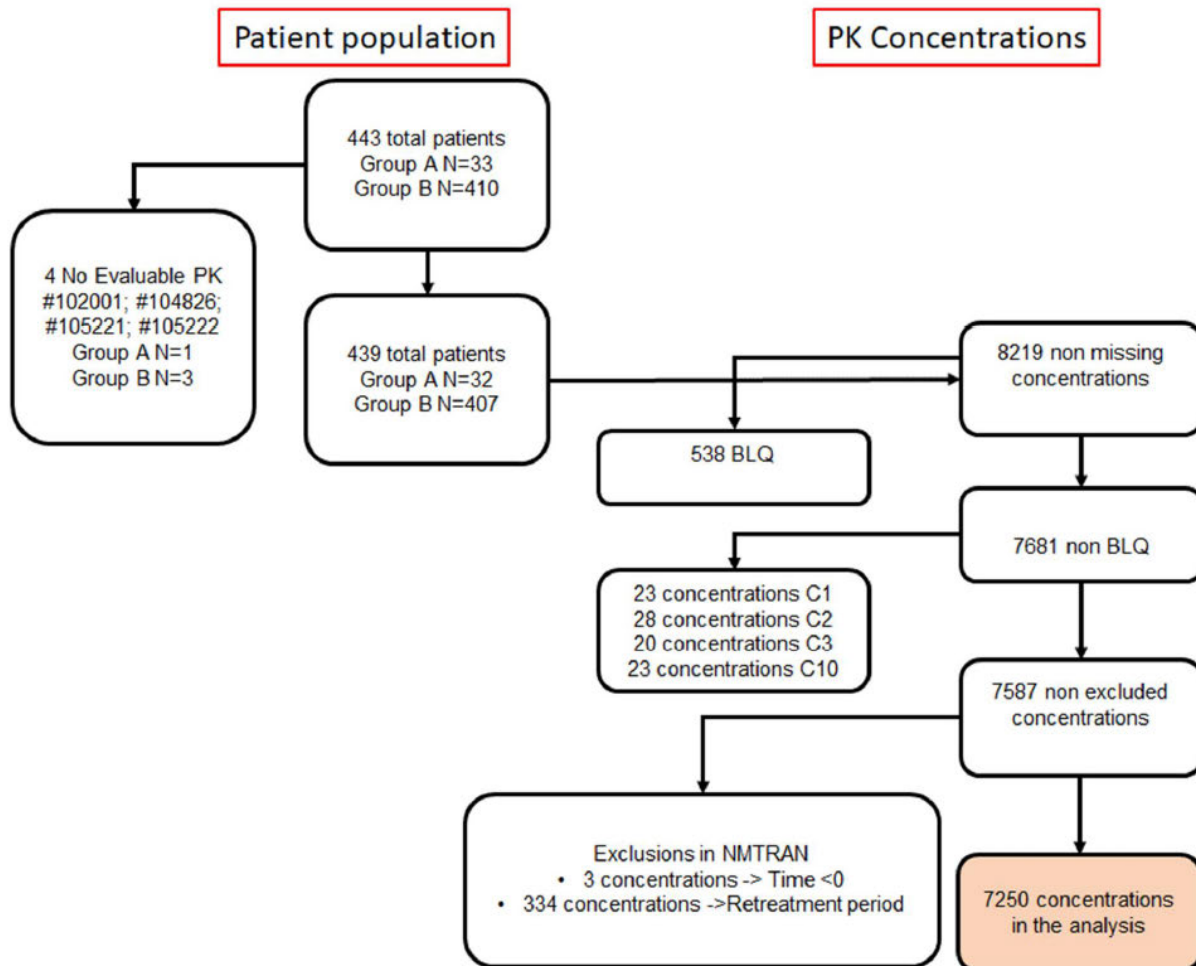
20.4.4.2. PPK Assessment Summary

The Applicant's Position:

Population PK (PopPK) analysis for mosunetuzumab was conducted using 7250 PK samples from 439 subjects across mosunetuzumab intravenous (IV) doses ranging with varying administration schedules: Group A (dose ranging from 0.05-2.8 mg) and Group B (dose ranging from 0.4/1.0/2.8 mg to 1.0/2.0/60 mg, including 1.0/2.0/60/30 mg). A brief overview of the data used for Mosunetuzumab PopPK analysis was listed in Figure 28. Summary statistics of the

continuous and categorical covariates that were evaluated in the PopPK analysis are shown in Table 59 and Table 60, respectively.

Figure 28: Data Used for PopPK Analyses



BLQ= below the lower limit of quantification; N=number of patients; NMTRAN= NONMEM translator; PK=pharmacokinetic.

Source: Applicant's Population PK Report (poppk-1112117), Figure 2.

Table 59: Summary of Continuous Covariates in the Population PK Analysis, Stratified by Study Groups

	Group A (N=32)	Group B (N=407)	Overall (N=439)
Age (y)			
Median [Min, Max]	64.0 [30.0, 84.0]	63.0 [19.0, 96.0]	63.0 [19.0, 96.0]
Mean (CV%)	62.6 (17.4%)	61.9 (20.8%)	62.0 (20.6%)
Body Weight (kg)			
Median [Min, Max]	76.2 [45.9, 111]	78.0 [37.1, 163]	77.9 [37.1, 163]
Mean (CV%)	78.2 (22.2%)	78.6 (23.6%)	78.5 (23.4%)
Missing	0 (0%)	7.00 (1.7%)	7.00 (1.6%)
Body Mass Index (kg/cm²)			
Median [Min, Max]	27.0 [17.1, 37.9]	26.4 [14.9, 52.2]	26.4 [14.9, 52.2]
Mean (CV%)	27.3 (16.5%)	27.1 (19.4%)	27.1 (19.2%)
Missing	2.00 (6.3%)	27.0 (6.6%)	29.0 (6.6%)
Albumin (g/L)			
Median [Min, Max]	37.0 [29.0, 44.0]	39.0 [19.0, 480]	39.0 [19.0, 480]
Mean (CV%)	37.2 (9.1%)	43.4 (103.7%)	43.0 (101.0%)
Missing	0 (0%)	1.00 (0.2%)	1.00 (0.2%)
Alanine aminotransferase (U/L)			
Median [Min, Max]	20.5 [7.00, 68.0]	19.0 [3.00, 119]	19.0 [3.00, 119]
Mean (CV%)	23.5 (55.0%)	22.9 (67.7%)	22.9 (66.8%)
Aspartate aminotransferase (U/L)			
Median [Min, Max]	26.5 [13.0, 71.0]	23.0 [7.00, 96.0]	23.0 [7.00, 96.0]
Mean (CV%)	29.5 (48.0%)	26.4 (50.5%)	26.6 (50.3%)

Total Bilirubin (µmol/L)			
Median [Min, Max]	8.55 [5.13, 25.7]	8.55 [1.14, 54.0]	8.55 [1.14, 54.0]
Mean (CV%)	9.79 (43.7%)	9.25 (59.0%)	9.29 (57.9%)
Creatinine (µmol/L)			
Median [Min, Max]	78.7 [34.5, 129]	76.9 [30.0, 158]	77.0 [30.0, 158]
Mean (CV%)	80.3 (28.1%)	79.7 (26.3%)	79.7 (26.4%)
Creatinine Clearance (mL/min)			
Median [Min, Max]	88.6 [48.6, 179]	86.9 [27.4, 247]	87.1 [27.4, 247]
Mean (CV%)	90.8 (31.1%)	94.1 (37.1%)	93.9 (36.7%)
Missing	0 (0%)	7.00 (1.7%)	7.00 (1.6%)
Lactate Dehydrogenase (U/L)			
Median [Min, Max]	306 [123, 1600]	270 [100, 6480]	271 [100, 6480]
Mean (CV%)	454 (85.7%)	389 (114.8%)	394 (112.4%)
B Cell Count (count/µL)			
Median [Min, Max]	NA	9.50 [0, 23400]	9.50 [0, 23400]
Mean (CV%)	NA	528 (518.5%)	528 (518.5%)
Missing	32.0 (100%)	261 (64.1%)	293 (66.7%)
T Cell Count (count/µL)			
Median [Min, Max]	NA	718 [40.0, 4910]	718 [40.0, 4910]
Mean (CV%)	NA	820 (80.5%)	820 (80.5%)
Missing	32.0 (100%)	261 (64.1%)	293 (66.7%)

Rituximab Conc (µg/mL)			
Median [Min, Max]	0.500 [0.500, 62.4]	0.500 [0.500, 151]	0.500 [0.500, 151]
Mean (CV%)	11.8 (151.7%)	10.1 (204.7%)	10.2 (200.2%)
Missing	1.00 (3.1%)	19.0 (4.7%)	20.0 (4.6%)
Obinutuzumab Conc (µg/mL)			
Median [Min, Max]	0.000000100 [0.000000100, 24.7]	0.000000100 [0.000000100, 305]	0.000000100 [0.000000100, 305]
Mean (CV%)	1.08 (429.5%)	2.92 (744.8%)	2.79 (753.0%)
Tumor Burden (mm²)			
Median [Min, Max]	2130 [216, 11900]	3070 [96.0, 70900]	2970 [96.0, 70900]
Mean (CV%)	3300 (92.9%)	4710 (125.4%)	4610 (125.0%)
SQR Tumor Burden (mm)			
Median [Min, Max]	46.2 [14.7, 109]	55.4 [9.80, 266]	54.5 [9.80, 266]
Mean (CV%)	51.8 (48.6%)	60.6 (53.2%)	59.9 (53.1%)
Time Since Last aCD20 trt (day)			
Median [Min, Max]	139 [27.0, 3100]	213 [18.0, 4430]	211 [18.0, 4430]
Mean (CV%)	448 (142.6%)	477 (139.5%)	475 (139.6%)
Missing	0 (0%)	3.00 (0.7%)	3.00 (0.7%)

Source: Applicant's Population PK Report (poppk-1112117), Appendix 3.

Table 60: Summary Statistics for the Categorical Covariates in the Population PK Analysis, Stratified by Study Groups

	Group A (N=32)	Group B (N=407)	Overall (N=439)
Sex			
Female	13.0 (40.6%)	142 (34.9%)	155 (35.3%)
Male	19.0 (59.4%)	265 (65.1%)	284 (64.7%)
Race			
American Indian Alaskan Native	0 (0%)	2.00 (0.5%)	2.00 (0.5%)
Asian	10.0 (31.3%)	67.0 (16.5%)	77.0 (17.5%)
Black	1.00 (3.1%)	11.0 (2.7%)	12.0 (2.7%)
Multiple	1.00 (3.1%)	1.00 (0.2%)	2.00 (0.5%)
Unknown	1.00 (3.1%)	12.0 (2.9%)	13.0 (3.0%)
White	19.0 (59.4%)	314 (77.1%)	333 (75.9%)
Asian			
Asian	10.0 (31.3%)	67.0 (16.5%)	77.0 (17.5%)
Non-Asian	22.0 (68.8%)	340 (83.5%)	362 (82.5%)
Performance Status			
ECOG0	11.0 (34.4%)	176 (43.2%)	187 (42.6%)
ECOG1	21.0 (65.6%)	230 (56.5%)	251 (57.2%)
ECOG2	0 (0%)	1.00 (0.2%)	1.00 (0.2%)
Ethnicity			
Hispanic or Latino	1.00 (3.1%)	26.0 (6.4%)	27.0 (6.2%)
Not Hispanic or Latino	31.0 (96.9%)	370 (90.9%)	401 (91.3%)
Not reported	0 (0%)	7.00 (1.7%)	7.00 (1.6%)
Unknown	0 (0%)	4.00 (1.0%)	4.00 (0.9%)
Country			
Australia	0 (0%)	75.0 (18.4%)	75.0 (17.1%)
Canada	1.00 (3.1%)	59.0 (14.5%)	60.0 (13.7%)
Germany	0 (0%)	7.00 (1.7%)	7.00 (1.6%)
Great Britain	0 (0%)	4.00 (1.0%)	4.00 (0.9%)
South Korea	7.00 (21.9%)	50.0 (12.3%)	57.0 (13.0%)
Spain	0 (0%)	29.0 (7.1%)	29.0 (6.6%)
USA	24.0 (75.0%)	183 (45.0%)	207 (47.2%)

Histology			
DLBCL	13.0 (40.6%)	144 (35.4%)	157 (35.8%)
DLBCL /MCL	0 (0%)	1.00 (0.2%)	1.00 (0.2%)
FL	9.00 (28.1%)	154 (37.8%)	163 (37.1%)
FL3B	0 (0%)	1.00 (0.2%)	1.00 (0.2%)
MCL	2.00 (6.3%)	37.0 (9.1%)	39.0 (8.9%)
MEL	0 (0%)	1.00 (0.2%)	1.00 (0.2%)
MZL	1.00 (3.1%)	2.00 (0.5%)	3.00 (0.7%)
RS	1.00 (3.1%)	13.0 (3.2%)	14.0 (3.2%)
SLL	1.00 (3.1%)	1.00 (0.2%)	2.00 (0.5%)
trFL	5.00 (15.6%)	52.0 (12.8%)	57.0 (13.0%)
trMZL	0 (0%)	1.00 (0.2%)	1.00 (0.2%)
NHL Type			
aNHL	21.0 (65.6%)	249 (61.2%)	270 (61.5%)
iNHL	11.0 (34.4%)	157 (38.6%)	168 (38.3%)
missing	0 (0%)	1.00 (0.2%)	1.00 (0.2%)
Drug Material			
Phase 1 material	32.0 (100%)	41.0 (10.1%)	73.0 (16.6%)
Phase 3 material	0 (0%)	366 (89.9%)	366 (83.4%)
Numb. of Prior Therapies			
1	2.00 (6.3%)	11.0 (2.7%)	13.0 (3.0%)
2	12.0 (37.5%)	140 (34.4%)	152 (34.6%)
3	8.00 (25.0%)	111 (27.3%)	119 (27.1%)
4	4.00 (12.5%)	66.0 (16.2%)	70.0 (15.9%)
5	2.00 (6.3%)	40.0 (9.8%)	42.0 (9.6%)
6	2.00 (6.3%)	23.0 (5.7%)	25.0 (5.7%)
7	1.00 (3.1%)	2.00 (0.5%)	3.00 (0.7%)
8	0 (0%)	5.00 (1.2%)	5.00 (1.1%)
9	1.00 (3.1%)	4.00 (1.0%)	5.00 (1.1%)
10	0 (0%)	3.00 (0.7%)	3.00 (0.7%)
13	0 (0%)	1.00 (0.2%)	1.00 (0.2%)
14	0 (0%)	1.00 (0.2%)	1.00 (0.2%)

Prior Therapies >2			
prior ther. =2	14.0 (43.8%)	151 (37.1%)	165 (37.6%)
prior ther. =3	18.0 (56.3%)	256 (62.9%)	274 (62.4%)
Renal Impairment			
Mild	14.0 (43.8%)	164 (40.3%)	178 (40.5%)
missing	0 (0%)	7.00 (1.7%)	7.00 (1.6%)
Moderate	3.00 (9.4%)	50.0 (12.3%)	53.0 (12.1%)
Normal	15.0 (46.9%)	185 (45.5%)	200 (45.6%)
Severe	0 (0%)	1.00 (0.2%)	1.00 (0.2%)
Hepatic Impairment			
Mild	5.00 (15.6%)	48.0 (11.8%)	53.0 (12.1%)
Moderate	0 (0%)	2.00 (0.5%)	2.00 (0.5%)
Normal	27.0 (84.4%)	357 (87.7%)	384 (87.5%)
Cell of Origin (COO1)			
GCB	12.0 (37.5%)	109 (26.8%)	121 (27.6%)
missing	14.0 (43.8%)	193 (47.4%)	207 (47.2%)
non-GCB	5.00 (15.6%)	81.0 (19.9%)	86.0 (19.6%)
unknown	1.00 (3.1%)	24.0 (5.9%)	25.0 (5.7%)

CV= coefficient of variation; DLBCL= diffuse large B-cell lymphoma; ECOG= Eastern Co-operative Oncology Group (performance status); FL= follicular lymphoma; GCB= germinal center B-cell-like; MCL=mantle cell lymphoma; MEL=melanoma; MZL=marginal zone lymphoma; NHL=non-Hodgkin's lymphoma; aNHL= aggressive NHL; iNHL= indolent NHL; RS= Richter's Syndrome; SLL=small lymphocytic lymphoma; SQR= succinate quinone reductase; trFL=transformed follicular lymphoma; trMCL=transformed mantle cell lymphoma; trt= treatment.

Source: Applicant's Population PK Report (poppk-1112117), Appendix 3.

The Applicant claimed that a 2-compartment PopPK model with a time-varying clearance (CL) parameterized as an initial baseline clearance (CL_{base}) that transitions to a CL_{ss} according to a transition time half-life (HL_{trans}) as described in the following equation:

$$CL = CL_{base} + (CL_{ss} - CL_{base}) \cdot \left\{ 1 - \exp \left[- \left(\frac{\ln(2)}{HL_{trans}} \right) \cdot t \right] \right\}$$

The final PK model parameter estimates and the corresponding 95% confidence intervals (CIs) from Bootstrap for mosunetuzumab are presented in Table 61. The goodness-of-fit plots for the final PK model are presented in Figure 29. The prediction corrected visual predictive check

(pcVPC) based on all data (Figure 30) illustrated the prediction percentiles and corresponding 95% CI of simulated concentrations overlaid on the observed mosunetuzumab concentrations and the corresponding 5th and 95th percentiles.

Table 61: Population PK Parameters of Mosunetuzumab From the Applicant’s Final PK Model

Parameter	Estimate	% RSE	95% CI	Shrinkage (%)
CL _{base} (L/day)	1.08	5.6	[0.962;- 1.20]	–
V ₁ (L)	5.49	2.5	[5.221 ; 5.76]	–
CL _{ss} (L/day)	0.584	2.0	[0.561 ; 0.607]	–
HL _{trans} (day)	16.3	7.1	[14.026 ; 18.6]	–
V ₂ (L)	6.17	3.6	[5.729 ; 6.61]	–
Q (L/day)	1.46	3.7	[1.354 ; 1.57]	–
Body weight on CL _{ss}	0.549	10.5	[0.436 ; 0.662]	–
Body weight on V ₁	0.433	13.4	[0.319 ; 0.547]	–
Body weight on V ₂	0.737	15.9	[0.508 ; 0.966]	–
Albumin on CL _{base}	-1.51	19.1	[-2.074 ; -0.946]	–
aCD20 drug on CL _{base}	-0.573	20.2	[-0.8 ; -0.346]	–
Sex (female) on CL _{ss}	-0.128	18.8	[-0.175 ; -0.081]	–
Albumin on V ₁	-0.481	23.3	[-0.701 ; -0.261]	–
Sex on V ₁	-0.126	18.9	[-0.173 ; -0.079]	–
Tumor burden on CL _{ss}	0.0935	26.6	[0.045 ; 0.142]	–
IIV on CL _{base} ($\omega_{CL_{base}}^2$, variance)	0.426	8.4	[0.356 ; 0.496]	4.8
CL _{base} -V ₁ covariance (ω_{CL_{base},V_1})	0.180 [¥]	7.3	[0.169 ; 0.191]	–
IIV on V ₁ ($\omega_{V_1}^2$, variance)	0.0981	5.8	[0.0722 ; 0.124]	4.6
IIV on CL _{ss} ($\omega_{CL_{ss}}^2$, variance)	0.0343	11.5	[0.0266 ; 0.0420]	33.8
CL _{ss} -HL _{trans} covariance ($\omega_{CL_{ss},HL_{trans}}$)	-0.0892 [¥]	24.8	[-0.133 ; -0.0459]	–
IIV on HL _{trans} ($\omega_{HL_{trans}}^2$, variance)	0.739	15.8	[0.510 ; 0.968]	40.9
IIV on V ₂ ($\omega_{V_2}^2$, variance)	0.0621	16.7	[0.0417 ; 0.0825]	49.9
Residual variability (additive on log scale)**	0.259	0.257	[0.258 ; 0.260]	–
Objective function value	-9853.132			

CL_{base} = clearance at baseline; CL_{ss} =clearance at steady state; HL_{trans} = transition half-life for CL_{base} to CL_{ss}; IIV = interindividual variability; Q= intercompartmental clearance; V₁= central volume of distribution; V₂=peripheral volume of distribution.

*Calculated asymptotically from NONMEM-provided standard errors.

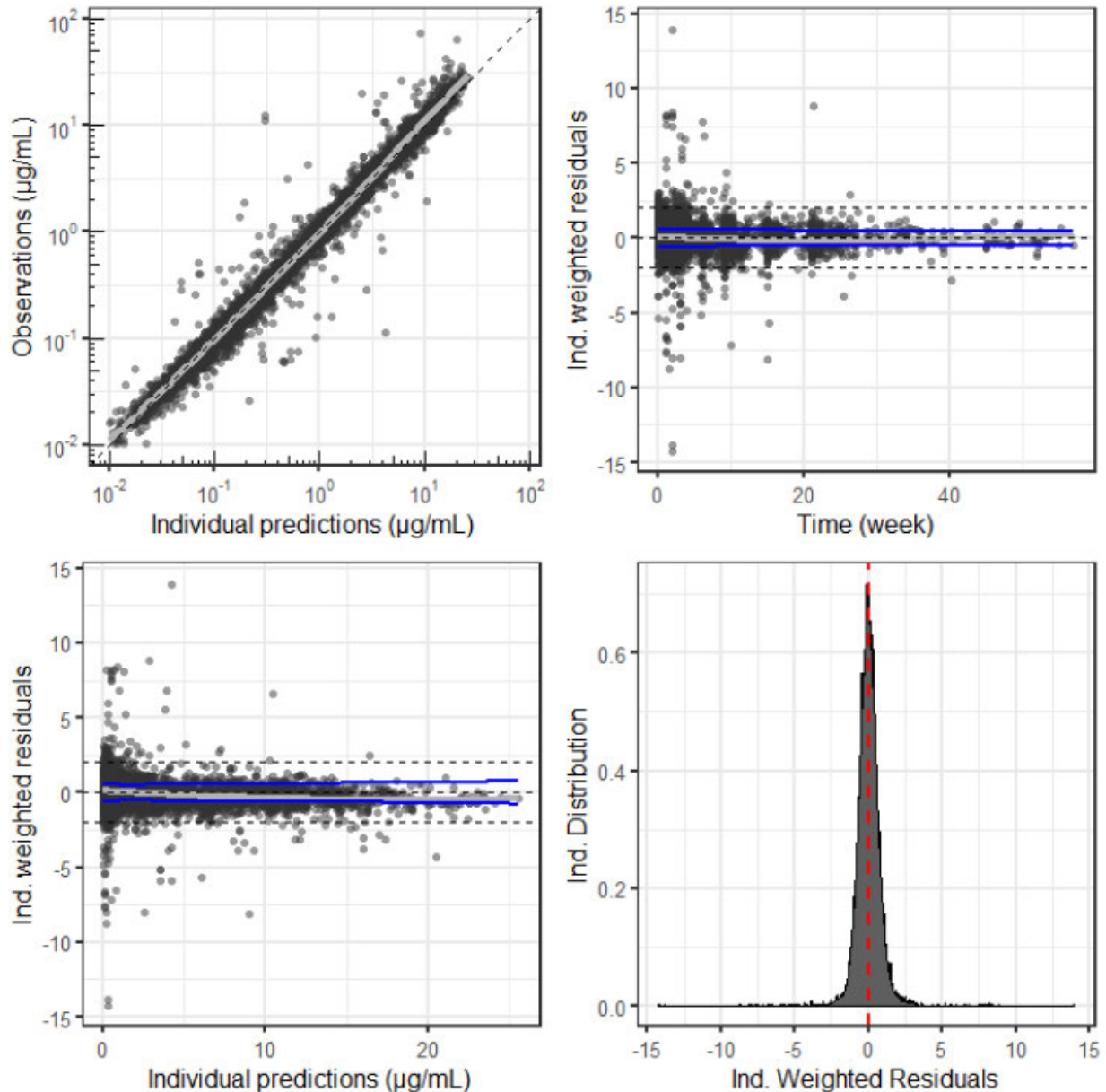
**Corresponds to proportional on normal scale.

[¥] correlation is 0.882.

[¥] correlation is -0.560.

Source: Applicant’s Population PK Report (poppk-1112117), Table 7.

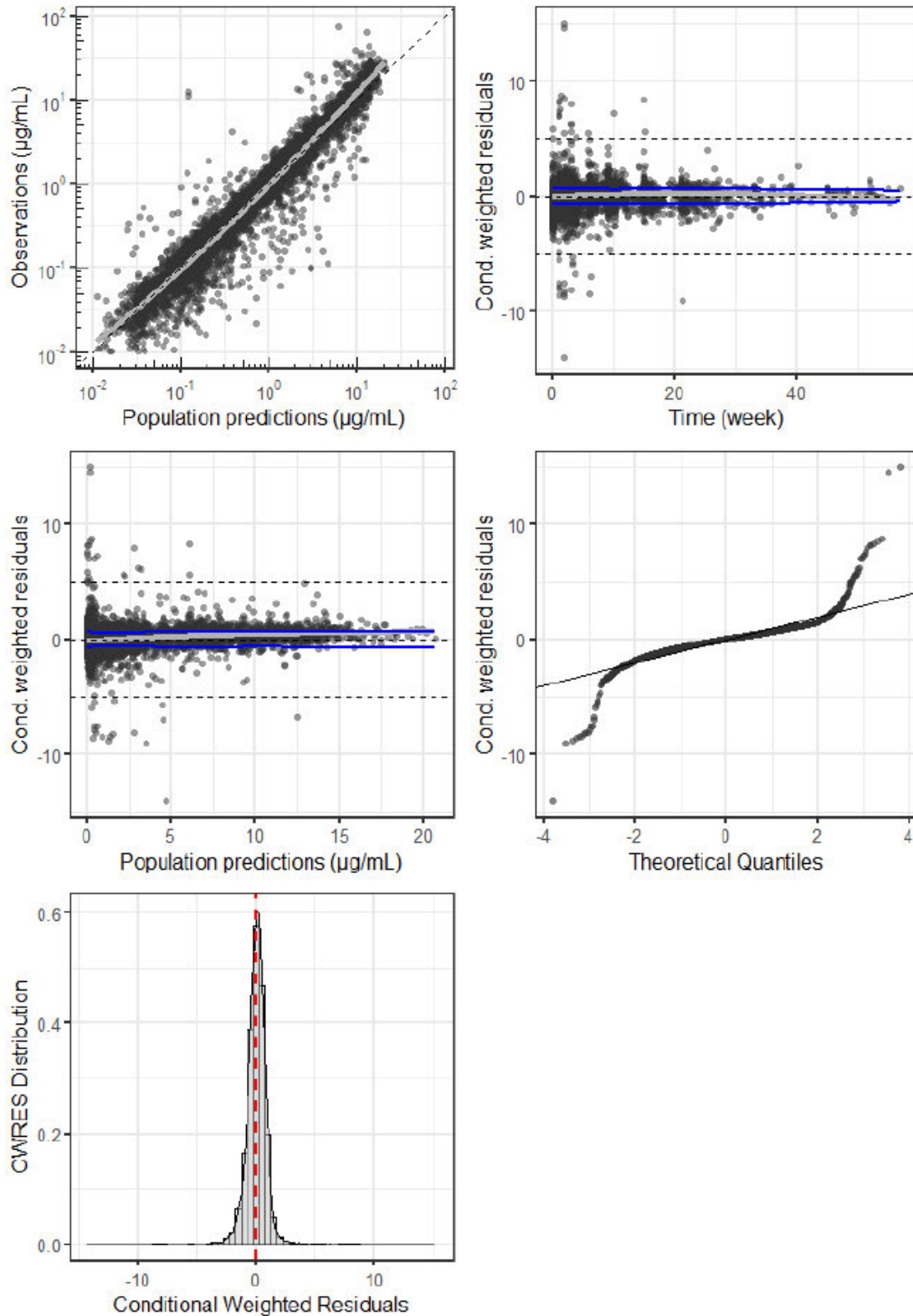
Figure 29: Goodness-of-fit Plots for the Applicant's Final Population PK Model for Mosunetuzumab



Ind. = Individual; PK=pharmacokinetic.

Scatterplots: grey points are observations, and blue and grey lines are LOESS smooths.

Histogram: bars represent observed residuals distribution, red line represents median.



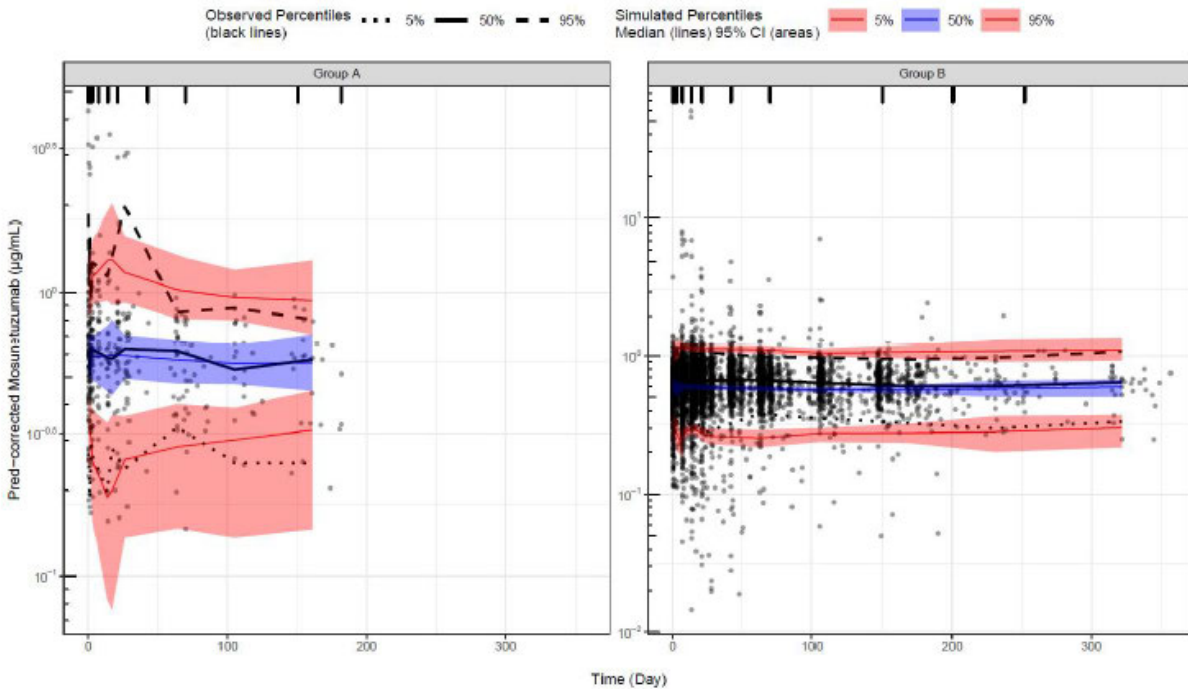
CWRES=conditional weighted residuals. Scatterplots: grey points are observations, and blue and grey lines are LOESS smooths. Histogram: bars represent observed CWRES distribution, shaded area represents theoretical CWRES distribution, and red line represents median.

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.

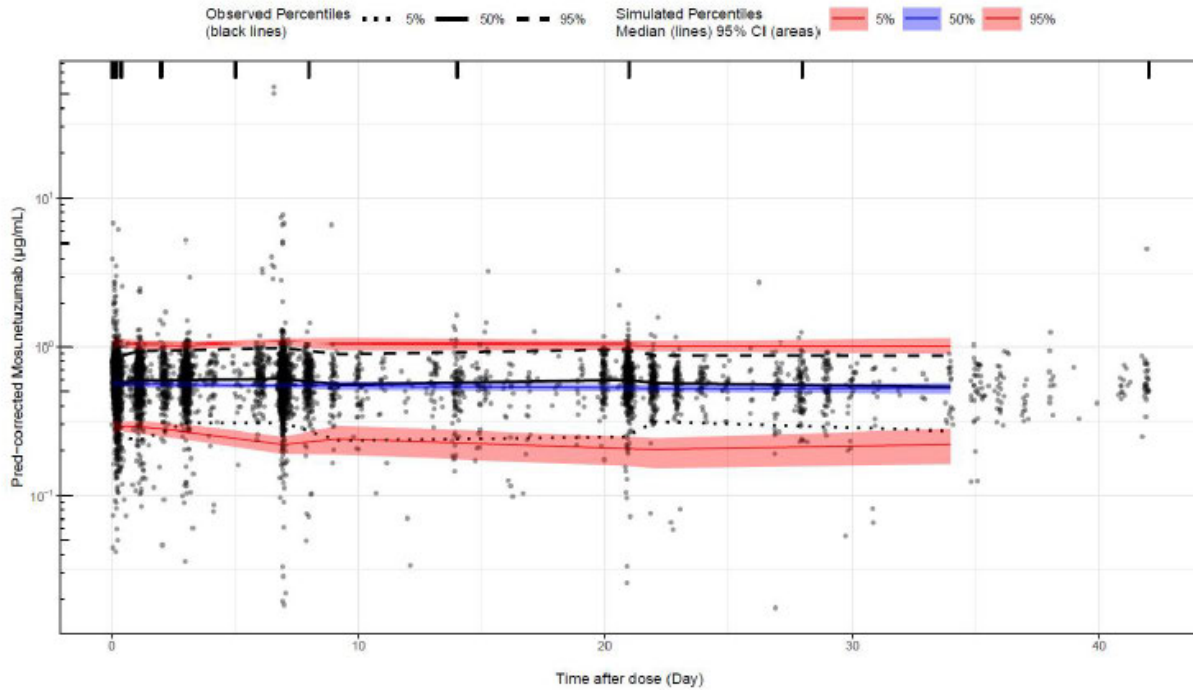
Note: The circles represent observations, the black dashed lines represent identity lines, and gray curves represent loess smoothers.

Source: Applicant's Population PK Report (popk-1112117), Figure 11.

Figure 30: Prediction-corrected VPC for the final PopPK model



Points are observations. Solid red lines are medians of observations (by bin). Dashed and dotted red lines are upper and lower limits of the 95% intervals for the observations (by bin). Shaded red area in the 95% CI for the simulated median (by bin). Shaded red areas are 95% CIs for the upper and lower limits of the 95% prediction interval for the simulations (by bin).

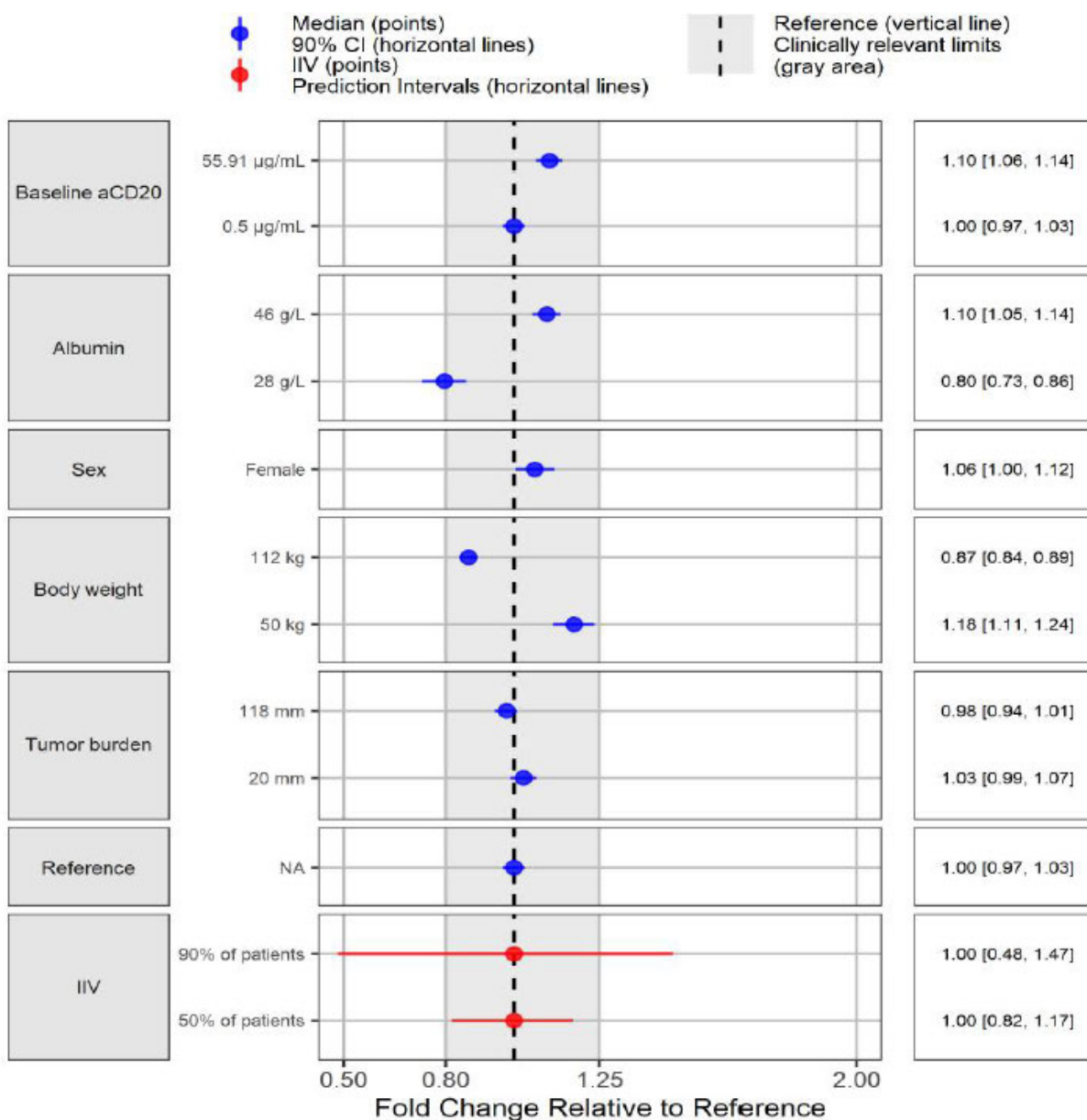


Points are observations. Solid black lines are medians of observations (by bin). Dashed and dotted black lines are upper and lower limits of the 95% intervals for the observations (by bin). Solid blue lines are medians of simulations (by bin). Solid red lines are upper and lower limits of the 95% intervals for the simulations (by bin). Shaded blue area in the 95% CI for the simulated median (by bin). Shaded red areas are 95% CIs for the upper and lower limits of the 95% prediction interval for the simulations (by bin).

Source: Applicant's Population PK Report (poppk-1112117), Figure 15&16.

Among the covariates evaluated, body weight (with median 77.9 kg, range from 37.1 to 163 kg), tumor burden (with median 2970 mm², range from 96.0 to 70900 mm²), albumin (with median 39.0 g/L, range from 19.0 to 480 g/L), baseline residual anti-CD20 drug concentrations, and sex (Female 155 [35.3%] and Male 284 [64.7%]) were found to be statistically significant covariates on mosunetuzumab PK with marginal impact on drug exposures. There were no clinically significant differences in the PK of mosunetuzumab based on age (19 to 96 years), sex, race (Asian [17.5%] and Non-Asian [82.5%]), ethnicity (Hispanic/Latino [6.2%] and not Hispanic/Latino [91.3%]), mild or moderate renal impairment (estimated Creatinine clearance [CrCL] by Cockcroft-Gault formula: 30 to 89 mL/min), or mild hepatic impairment (total bilirubin less than or equal to upper limit of normal [ULN] with AST greater than ULN or total bilirubin greater than 1 to 1.5 times ULN with any AST). The relative importance of covariate effects included in the final mosunetuzumab model was evaluated with a forest plot of relative changes in exposure (AUC₀₋₄₂) in the Figure 31.

Figure 31: Forest Plots of Covariates Effects on AUC₀₋₄₂

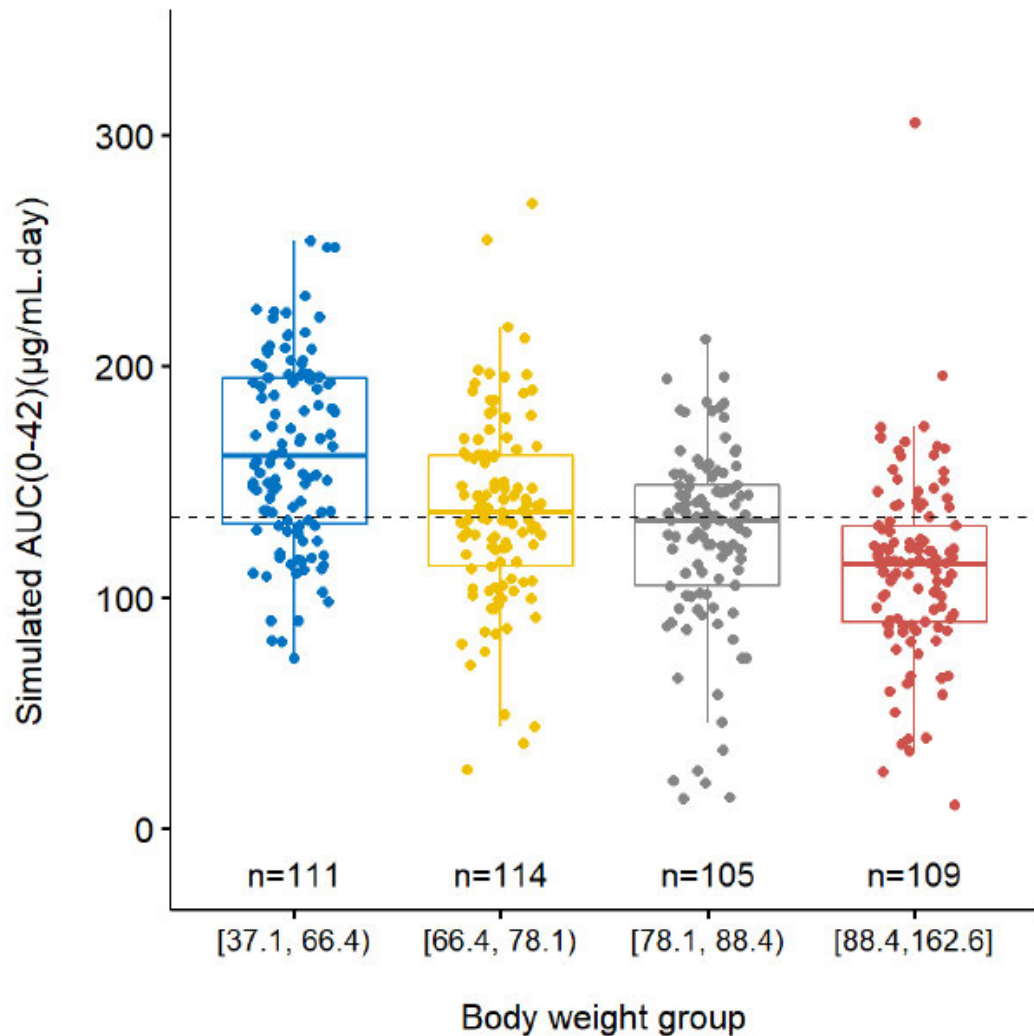


aCD20= prior anti-CD20 drug treatment concentrations, specifically Rituximab (R) and Obinutuzumab (G) in this popPK analysis; IIV= interindividual variability.

Source: Applicant's Population PK Report (popk-1112117), Figure 17.

The impact of body weight was found statistically significant, as shown in Figure 32. Exposure (AUC_{0-42}) decreases as body weight increases. However, the exposure changes had a marginal impact when assessing the influence of extreme values of these covariates on drug exposures.

Figure 32: Comparison of AUC₀₋₄₂ in Body Weight Quartiles at 1/2/60/30 mg



AUC₀₋₄₂= cumulative area under the curve from Day 0 to Day 42; n=number of patients.

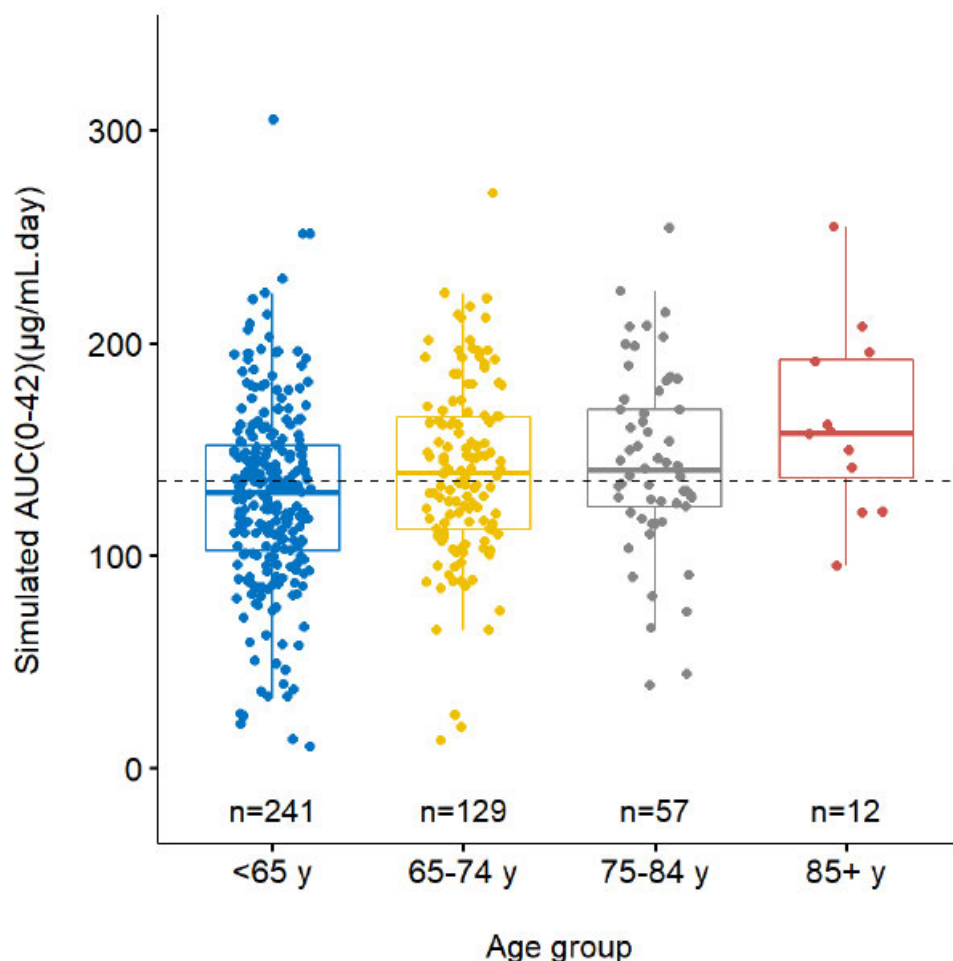
Dotted line= mean of simulated AUC₀₋₄₂ across all the patients.

Boxplots represent medians (central horizontal lines), 50% ranges (box hinges), and whiskers extend from the hinge to the largest or smallest values no further than 1.5 * the interquartile range from the hinges.

Source: Applicant's Population PK Report (popk-1112117), Figure 20.

Among the 439 patients included in the analysis, 241 patients (54.9%) were below 65 years, 129 patients (29.4%) were between 65 and 74 years, 57 patients (12.9%) were between 75 and 84 years, and 12 patients (2.7%) >85 years. As shown in Figure 33, exposure (AUC₀₋₄₂) is comparable across age groups.

Figure 33: Comparison of AUC₀₋₄₂ in Age Groups at 1/2/60/30 mg



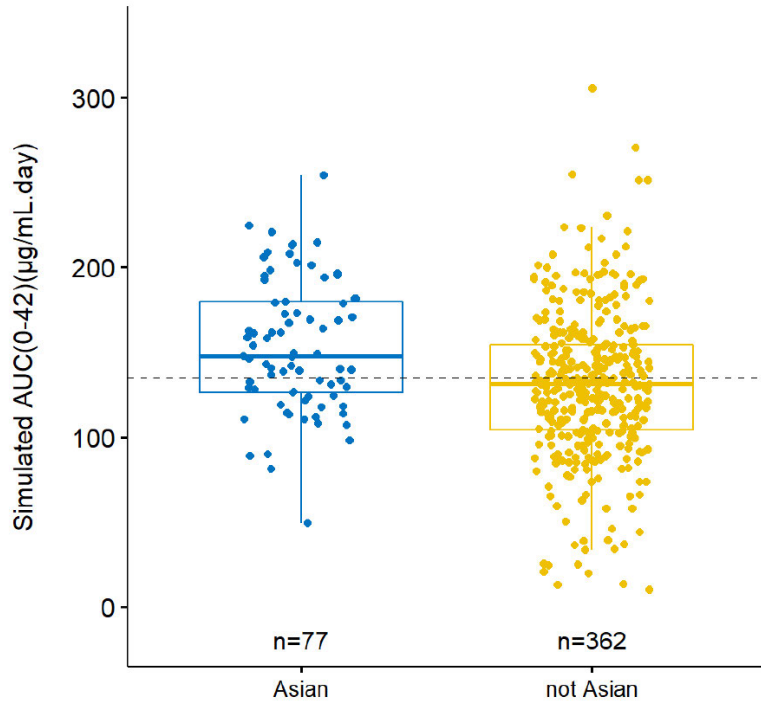
AUC_{0-42} = cumulative area under the curve from Day 0 to Day 42; n=number of patients; y=years.
Dotted line= mean of simulated AUC_{0-42} across all the patients.

Boxplots represent medians (central horizontal lines), 50% ranges (box hinges), and whiskers extend from the hinge to the largest or smallest values no further than $1.5 \times$ the interquartile range from the hinges.

Source: Applicant's Population PK Report ((poppk-1112117), Figure 17).

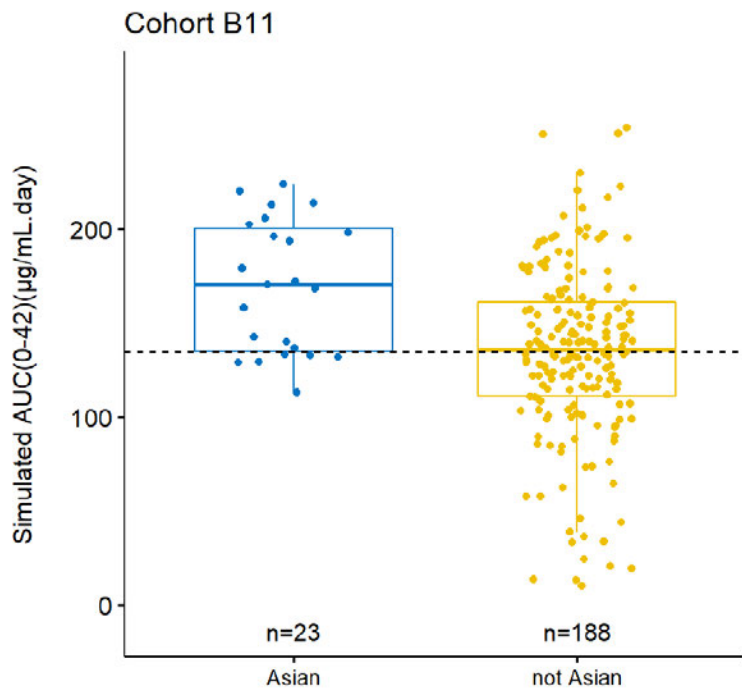
The impact of Race (Asian vs. Non-Asian population) on mosunetuzumab PK was also assessed by the Applicant. As shown in Figure 34 and Figure 35 for Cohort B11, exposure (AUC_{0-42}) is comparable between the two groups, Asian and non-Asian. At the clinical dose of 1/2/60/30 mg, the simulated PK exposures (median (95%CI)) over the first 2 cycles (AUC_{0-42}) were 148 $\mu\text{g}/\text{mL}\cdot\text{day}$ (88.3-221), 131 $\mu\text{g}/\text{mL}\cdot\text{day}$ (34.0-217), for Asian (N=77), and non-Asian (N=362), respectively.

Figure 34: Comparison of AUC0-42 by Asian Population at 1/2/60/30 mg



Source: Applicant's Population PK Report ((poppk-1112117), Figure 22.

Figure 35: Comparison of AUC0-42 by Asian Population for Cohort B11



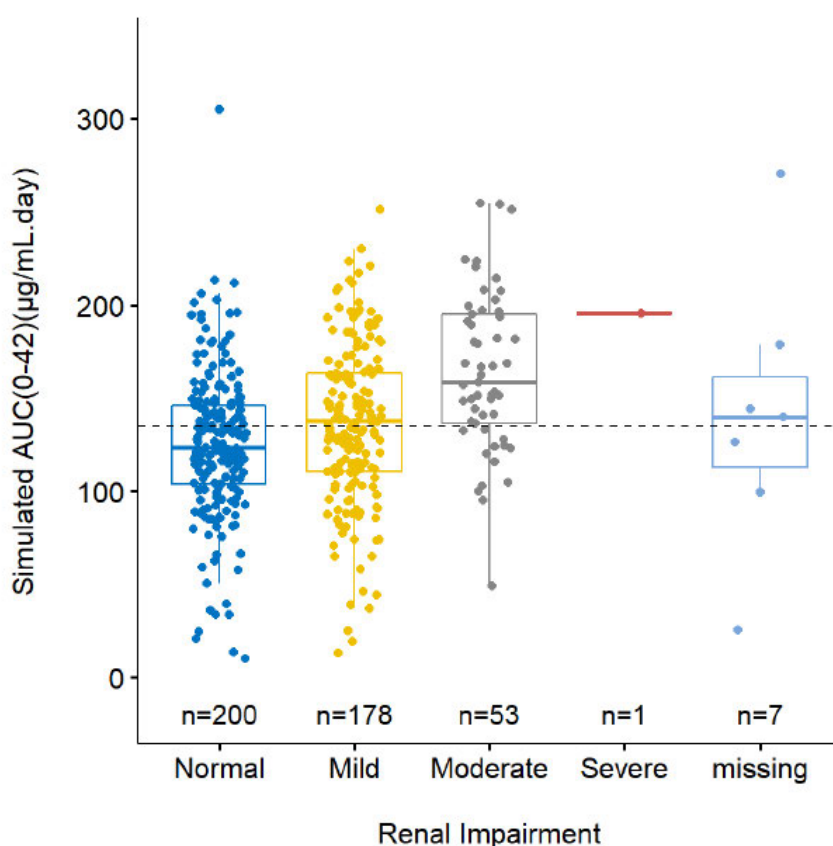
Source: Applicant's Population PK Report ((poppk-1112117), Figure 17.

Special Population

Renal impairment

The covariate analysis results showed that CrCL was not statistically significant covariates on mosunetuzumab CL. The impact of the degree of renal impairment on mosunetuzumab CL was further assessed by categorizing patients with varying degrees of renal impairment into 4 categories based on their estimated CrCL (Normal: CrCL $\geq$ 90 mL/min, Mild: 60 to < 90 mL/min, Moderate: 30 to < 60 mL/min, and Severe: CrCL < 30 mL/min). There is marginally increased AUC in patients with moderate and severe renal impairment compared to mild renal impairment and normal renal function (Figure 36). The Applicant claimed that the PK exposure is not expected to be impacted by renal impairment.

Figure 36: Comparison of AUC₀₋₄₂ in Renal Function Groups at 1/2/60/30 mg



AUC₀₋₄₂=cumulative area under the curve from Day 0 to Day 42; n=number of patients.

Dotted line= mean of simulated AUC₀₋₄₂ across all the patients.

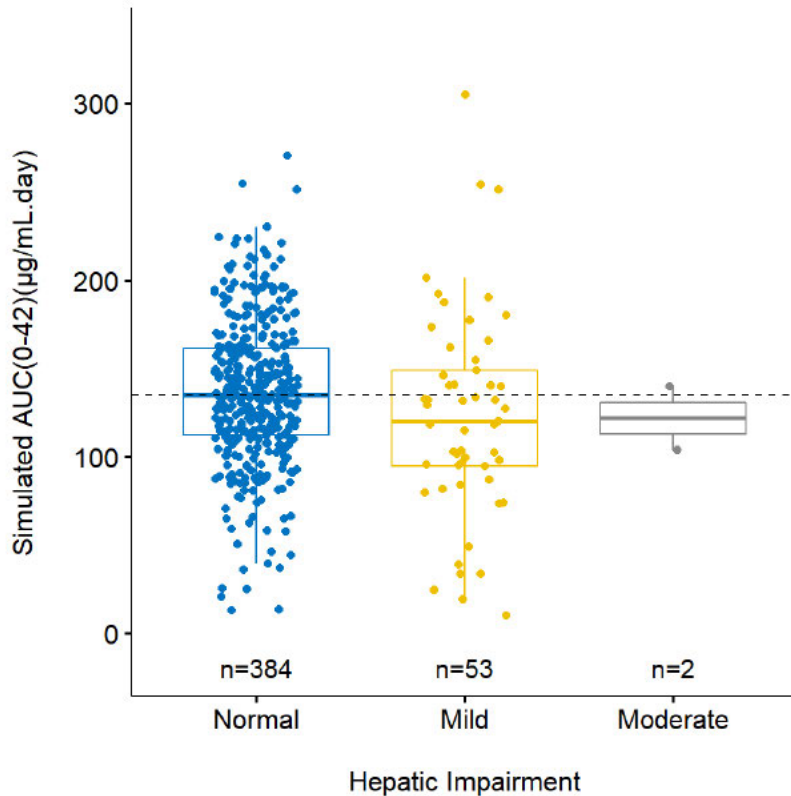
Boxplots represent medians (central horizontal lines), 50% ranges (box hinges), and whiskers extend from the hinge to the largest or smallest values no further than 1.5 * the interquartile range from the hinges.

Source: Applicant's Population PK Report (poppk-1112117), Figure 24.

Hepatic impairment

The PK of mosunetuzumab is not expected to be impacted by hepatic impairment (Figure 37). Mosunetuzumab has not been investigated in subjects with severe hepatic impairment and the data from subjects with moderate hepatic impairment (Figure 37) are limited (n=2).

Figure 37: Comparison of AUC₀₋₄₂ in Hepatic Function Groups at 1/2/60/30 mg



AUC₀₋₄₂= cumulative area under the curve from Day 0 to Day 42; n=number of patients.

Dotted line= mean of simulated AUC₀₋₄₂ across all the patients.

Boxplots represent medians (central horizontal lines), 50% ranges (box hinges), and whiskers extend from the hinge to the largest or smallest values no further than 1.5 * the interquartile range from the hinges.

Source: Applicant's Population PK Report (poppk-1112117), Figure 27.

Receptor Occupancy (RO) for Mosunetuzumab

Due to varying levels of residual rituximab and/or obinutuzumab, especially in patients with aNHL, the mosunetuzumab receptor occupancy (%RO) has been used to address the confounding effect of the ER relationship for efficacy and cytokine release syndrome (CRS). The observed mosunetuzumab CD20 %RO time-course was calculated within the NONMEM using Equation below:

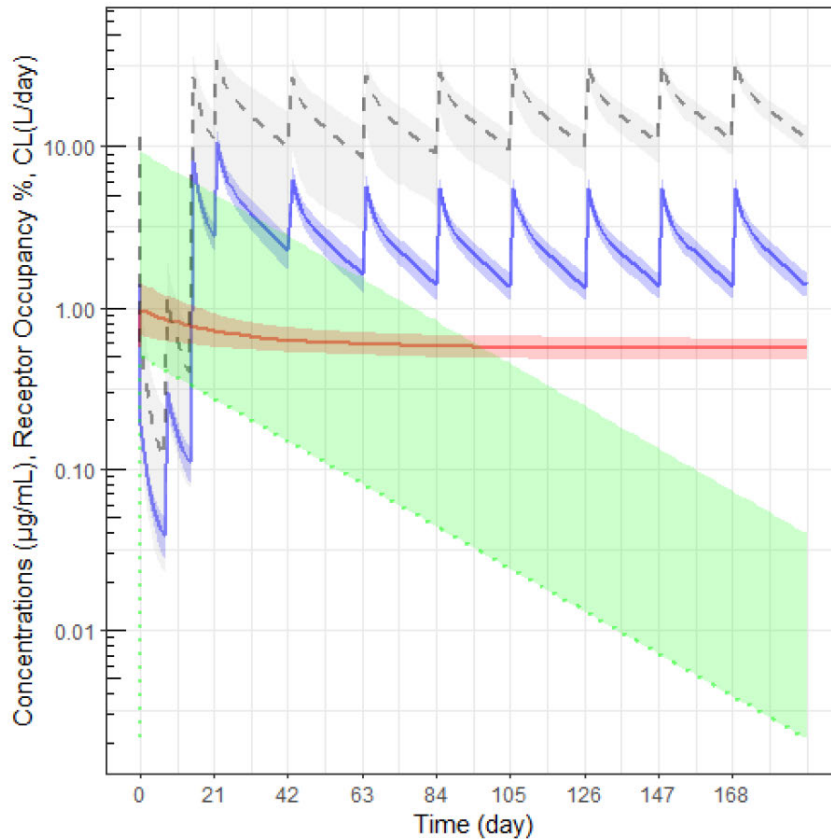
$$\%RO(t) = 100 \cdot \frac{100 \cdot \text{Mosun}(t)}{\text{Mosun}(t) + K_{D,\text{Mosun}} + \left(\frac{K_{D,\text{Mosun}}}{K_{D,\text{Ritux}}}\right) \cdot \text{Ritux}(t) + \left(\frac{K_{D,\text{Mosun}}}{K_{D,\text{Obinut}}}\right) \cdot \text{Obinut}(t)}$$

Here, $\text{Mosun}(t)$, $\text{Ritux}(t)$, and $\text{Obinut}(t)$ are the model-predicted time-courses (ng/mL) for mosunetuzumab, rituximab, and obinutuzumab, respectively. $K_{D,\text{Mosun}}$ (10200 ng/mL), $K_{D,\text{Ritux}}$ (675 ng/mL), and $K_{D,\text{Obinut}}$ (600 ng/mL) are the equilibrium dissociation constants for mosunetuzumab, rituximab and obinutuzumab, respectively, per Scatchard assay data on file.

The observed average mosunetuzumab CD20 receptor occupancy over 42 days (ROavg0-42) was calculated within the NONMEM code by implementing a reservoir compartment in which receptor occupancy accumulated over time, denoted by the cumulative area under the receptor occupancy time curve (AUC_RO). The average %RO was then calculated by AUC_RO/time for any selected time point.

The PopPK model-predicted mosunetuzumab concentration-time (ug/mL), receptor occupancy (RO)-time (%), and CL-time (L/day) profiles based on the cohort B11 (N=214) from the popPK model estimates for the 1/2/60/30 mg dose regimen together with model-predicted rituximab concentration-time (ug/mL) profiles are shown in Figure 38. Given the unique step-up dosing regimen, and time dependent clearance, these figures were provided to illustrate the complexities of this PK system, and to support the AUC endpoints selected. As shown, CL decreases with time, from a typical CL_{base} of ~1.08 L/day to a CL_{ss} of ~0.584 L/day. Given the typical HL_{trans} of 16.3 days, 90% of steady state will be reached after approximately 3.3 half-lives, i.e., 54 days; this is confirmed by the blue line representing the typical mosunetuzumab concentration for the dosing regimen of 1/2/60/30 mg.

Figure 38: Model-Predicted Mosunetuzumab Concentration- (blue), RO-(grey), CL- (red), and Rituximab Concentration-Time (green) Profiles for 1/2/60/30 mg Dosing Regimen Based on Cohort B11 Patient EBEs (N=214)



CL= clearance at steady state.

Shaded regions for each curve represent the 25th and 75th percentiles. Solid or stippled lines represent the median value. For the rituximab time-course (green), the lower bound is set by the BLQ concentration of 0.5 µg/mL, which is the median for the FL patient population.

Source: Applicant's Population PK Report (poppk-1112117), Figure 32.

The FDA's Assessment:

In general, the Applicant's PopPK analysis is considered acceptable.

20.4.5. Exposure-Response Analysis

20.4.5.1. ER (efficacy) Executive Summary

The FDA's Assessment:

In support of the current BLA application, the Applicant submitted exposure-response (E-R) for efficacy analysis including complete response rate (CRR), objective response rate (ORR) and PFS with R/R NHL patients from Studies GO29781 to characterize E-R for efficacy relationships. Under the proposed dosage of 1/2/60/30 mg, the E-R efficacy analysis indicated that clinical responses (CR, ORR) increased with increasing mosunetuzumab exposure (AUC₀₋₄₂) and approached a plateau. Further ER analysis showed a longer median PFS with increased

mosunetuzumab exposure (AUC_{0-42}), and a longer median PFS at the 1/2/60/30 mg dose (B11 cohort, RP2D) compared to the 1/2/13.5 mg dose (B7 cohort). Loading doses of 60 mg on Cycle 1 Day 15 and Cycle 2 Day 1 were predicted by E-R analysis to achieve a plateau for clinical endpoints ORR and CR .

Overall, the Applicant's E-R analysis for efficacy appear adequate. The E-R relationship for efficacy endpoints may imply that the effectiveness of mosunetuzumab reached a plateau at the proposed dosing regimen of 1/2/60/30 mg, which supports the proposed dosage.

20.4.5.2. ER (efficacy) Assessment Summary

The Applicant's Position:

The Applicant's E-R for efficacy analysis of Mosunetuzumab were conducted in 159 patients with relapsed or refractory B-cell Follicular Lymphoma (R/R FL) patients with ≥ 2 Prior Therapies in Study GO29781 in one of the following two dosing regimens: 1) every 3 weeks (q3w) fixed dosing schedule (Group A) or 2) on a Cycle 1 step-up dosing regimen (Group B), followed by a once every 3 weeks (q3w) fixed dosing schedule. The dose range for these patients was from 0.2 mg to 1/2/60/30 mg; specifically, 7 patients from Group A cohorts received doses ranging from 0.2 to 2.8 mg q3w, and 152 patients from Group B step-up dosing cohorts received doses ranging from 0.4/1.0/2.8 mg to 1.0/2.0/60/30 mg.

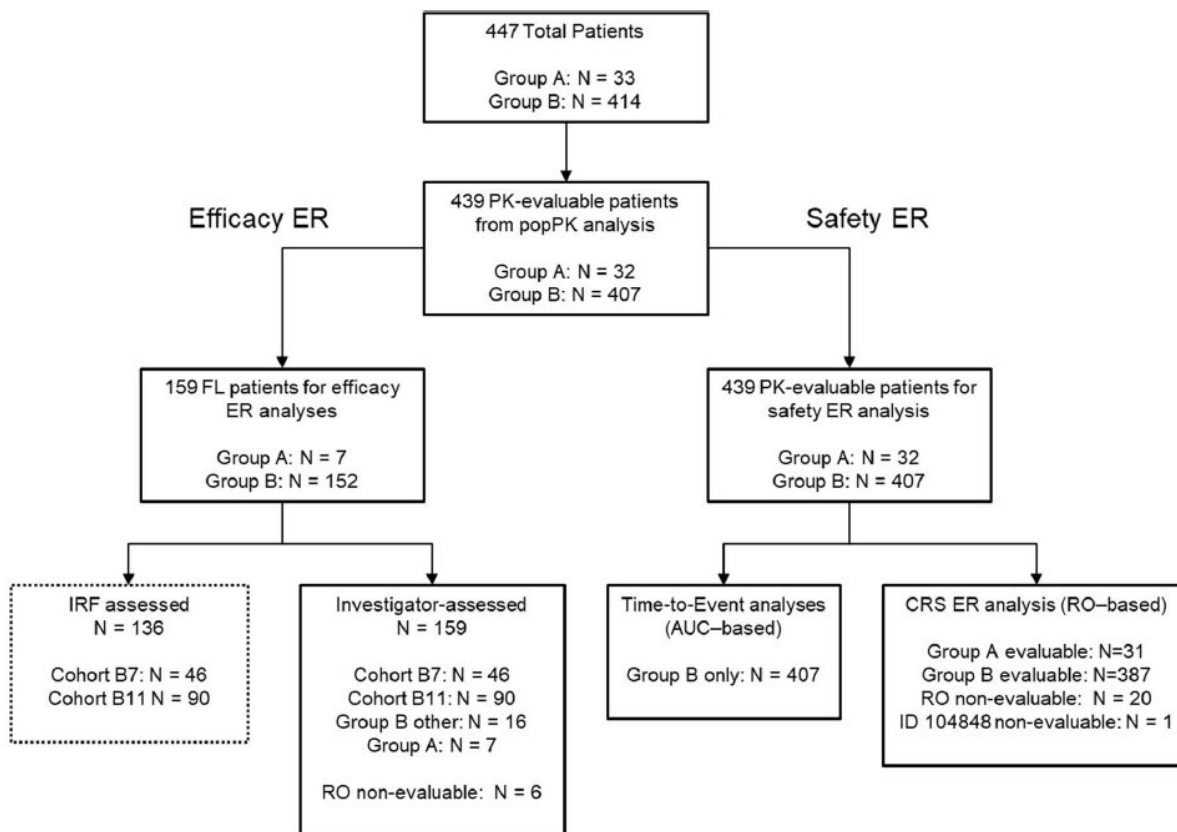
A brief overview of E-R analysis for Mosunetuzumab is listed in the Table 62: and Figure 39. The efficacy endpoints for E-R analyses primarily included CR, OR, PFS, DOCR, and DOR in R/R FL patients with ≥ 2 Prior Therapies. The E-R analysis for R/R FL covered age ranging from 27 to 90 years with a median of 60 years, body weight ranging from 42 to 140 kg with a median of 80.4 kg, and albumin ranging from 20 to 480 g/L with a median of 41 g/L. Table 63: shows statistical summaries of continuous and categorical covariates for the efficacy E-R population.

Table 62: Investigator–Response Assessment of Patients with R/R FL $\geq$ 2 Prior Therapies by Dose Cohort (N=159)

Cohort	Dose Level (mg)	Total (N)	CR (N)	PR (N)	SD (N)	PD (N)	Other ¹ (N)
A2	0.2 mg	1	0	0	0	1	0
A5	1.6 mg	1	0	0	1	0	0
A6	1.2 mg	2	1	0	0	1	0
A8	2.8 mg	3	1	0	1	1	0
B1	1 / 2 / 2.8 mg	1	0	0	1	0	0
B2	1 / 2 / 4.2 mg	3	2	0	1	0	0
B4	1 / 2 / 6.0 mg	1	1	0	0	0	0
B5	0.8 / 2 / 6.0 mg	9	4	3	1	1	0
B6	1 / 2 / 9.0 mg	2	1	1	0	0	0
B7	1 / 2 / 13.5 mg	46	22	7	5	9	3
B11	1 / 2 / 60 / 30 mg	90	54	16	8	9	3
Total		159	86	27	18	22	6
CR = complete response; N = number of patients; PD = progressive disease; PR = partial response; SE = stable disease.							
¹ "Other" refers to investigator assessments of ND = not determined, NE = not evaluable and -99 = missing.							

Source: Applicant's Exposure Response Analysis Report (ER-1112149), Appendix 6.

Figure 39: Data Used for ER Analyses



AUC= area under the concentration–time curve; CRS= cytokine release syndrome; ER=exposure–response; IRF= Independent Review Facility; N=number of patients; PK=pharmacokinetic; RO= receptor occupancy.

Group A= q3w dosing; Dose range from 0.05–2.8 mg.

Group B= Step-up Cycle 1 dosing; Dose range from 0.4/1/2.8–1/2/60 mg, including 1/2/60/30 mg.

Source: Applicant’s Exposure Response Analysis Report (ER-1112149), Figure 2.

Table 63: Baseline Patient Characteristics for the R/R FL ≥ 2 Prior Therapies Efficacy ER Population (N=159).

BLA Multi-disciplinary Review and Evaluation {BLA 761263, Lunsumio (Mosunetuzumab)}

Variable	Cohort			Total
	A	B1-B10	B11	
N	7	62	90	159
Mosunetuzumab AUC (42 day, day•µg/mL)	3.25 (3.81) [0.4 ; 9.2]	24.2 (26.9) [4.89 ; 54.7]	145 (141) [1.59 ; 251]	85.9 (90.3) [0.4 ; 251]
Average receptor occupancy (42 day, %)	0.483 (0.379) [0.0107 ; 0.754]	3 (3.01) [0.0624 ; 9.95]	14.8 (12.7) [0.222 ; 30.5]	5.13 (8.38) [0.0107 ; 30.5]
Baseline age (y)	63 (61.7) [57 ; 65]	59 (58.1) [27 ; 85]	60 (60) [29 ; 90]	60 (59.3) [27 ; 90]
Baseline height (cm)	173 (170) [150 ; 186]	171 (171) [150 ; 198] {4}	171 (170) [138 ; 193] {8}	172 (170) [138 ; 198] {12}
Baseline weight (kg)	69.1 (79.2) [64.6 ; 100]	77.4 (81) [51.2 ; 128] {2}	83 (81.4) [42 ; 140] {1}	80.4 (81.2) [42 ; 140] {3}
Baseline BMI (kg/m ²)	29 (27.3) [20.6 ; 32.6]	26.4 (27.8) [19.7 ; 40.8] {4}	27.5 (28.2) [17 ; 45.2] {8}	27.3 (28) [17 ; 45.2] {12}
Race				
- Black or African American	0 (0.00%)	4 (6.45%)	4 (4.44%)	8 (5.03%)
- White	6 (85.7%)	41 (66.1%)	74 (82.2%)	121 (76.1%)
- Asian	1 (14.3%)	15 (24.2%)	8 (8.89%)	24 (15.1%)
- American Indian or Alaska Native	0 (0.00%)	0 (0.00%)	1 (1.11%)	1 (0.629%)
- Unknown	0 (0.00%)	2 (3.23%)	3 (3.33%)	5 (3.14%)
Sex				
- Female	4 (57.1%)	22 (35.5%)	35 (38.9%)	61 (38.4%)
- Male	3 (42.9%)	40 (64.5%)	55 (61.1%)	98 (61.6%)
Baseline ECOG				
- 0	3 (42.9%)	37 (59.7%)	53 (58.9%)	93 (58.5%)
- 1	4 (57.1%)	25 (40.3%)	37 (41.1%)	66 (41.5%)
Baseline albumin (g/L)	41 (39.7) [35 ; 42]	41 (40) [21 ; 49]	41 (54) [20 ; 480] {1}	41 (47.9) [20 ; 480] {1}

BLA Multi-disciplinary Review and Evaluation {BLA 761263, Lunsumio (Mosunetuzumab)}

Variable	Cohort			Total
	A	B1-B10	B11	
Baseline ALT (U/L)	24 (21.9) [11 ; 29]	18.5 (22.2) [3 ; 119]	19 (21.3) [7 ; 69]	19 (21.7) [3 ; 119]
Baseline AST (U/L)	27 (26) [13 ; 36]	22 (24.4) [10 ; 78]	21.5 (24) [12 ; 65]	22 (24.2) [10 ; 78]
Baseline bilirubin (μmol/L)	8.55 (8.55) [5.13 ; 12]	8.55 (9.22) [2.56 ; 23.9]	7 (8.57) [2 ; 29.1]	8.55 (8.82) [2 ; 29.1]
Baseline serum creatinine (umol/L)	78.7 (81.9) [58.4 ; 115]	82.7 (82.4) [42.4 ; 131]	76 (79.6) [41.6 ; 143]	80 (80.8) [41.6 ; 143]
Baseline creatinine clearance (mL/min)	92 (87.2) [54.6 ; 109]	91.7 (96.7) [45.7 ; 189]	89.9 (98.9) [39.4 ; 208]	91.1 (97.5) [39.4 ; 208]
Number of prior systemic therapies	4 (3.86) [2 ; 6]	3 (3.48) [2 ; 9]	3 (3.33) [2 ; 10]	3 (3.42) [2 ; 10]
Baseline tumor burden (square root of sum of the product of perpendicular diameters, mm)	45.8 (47.9) [26 ; 65.7]	58.9 (61.4) [15 ; 149]	54.9 (57.2) [15.3 ; 126]	55.4 (58.5) [15 ; 149]
Baseline B cell count (/μL)	- {7}	- {62}	31 (837.55) [0 ; 23359] {16}	31 (837.55) [0 ; 23359] {85}
Baseline T cell count (/μL)	- {7}	- {62}	809.5 (905) [141 ; 4911] {16}	809.5 (905) [141 ; 4911] {85}
Baseline LDH (U/L)	217 (265) [123 ; 613]	228 (281) [129 ; 990]	211 (239) [113 ; 727]	217 (257) [113 ; 990]
Baseline rituximab (ng/mL)	500 (3750) [500 ; 14000]	500 (6190.45) [500 ; 96300] {2}	500 (6484.86) [500 ; 102000] {4}	500 (6244.28) [500 ; 102000] {6}
Baseline Gazyva (ng/mL)	1e-04 (1428.57) [1e-04 ; 10000]	1e-04 (5593.03) [1e-04 ; 124000]	1e-04 (6934.86) [1e-04 ; 305000]	1e-04 (6169.21) [1e-04 ; 305000]
Time since last CD20 treatment (days)	558 (633.1) [78 ; 1594]	196 (452.5) [26 ; 2420] {1}	406 (595) [26 ; 3032]	299.5 (541.6) [26 ; 3032] {1}
Time since last prior therapy (days)	128 (396.1) [78 ; 1390]	96.5 (313.9) [8 ; 1851]	203.5 (433.3) [15 ; 2717]	151 (385.1) [8 ; 2717]

BLA Multi-disciplinary Review and Evaluation {BLA 761263, Lunsumio (Mosunetuzumab)}

Variable	Cohort			Total
	A	B1-B10	B11	
Baseline renal function				
- Normal (CrCL $\geq$ 90 mL/min)	4 (57.1%)	33 (53.2%)	44 (48.9%)	81 (50.9%)
- Mild (CrCL 60 to <90 mL/min)	2 (28.6%)	17 (27.4%)	37 (41.1%)	56 (35.2%)
- Moderate (CrCL 30 to <60 mL/min)	1 (14.3%)	10 (16.1%)	8 (8.89%)	19 (11.9%)
- Missing	0 (0.00%)	2 (3.23%)	1 (1.11%)	3 (1.89%)
Baseline hepatic function				
- Normal (BIL & AST $\leq$ ULN)	7 (100%)	59 (95.2%)	81 (90.0%)	147 (92.5%)
- Mild (BIL >ULN to 1.5 $\times$ ULN or AST >ULN)	0 (0.00%)	3 (4.84%)	8 (8.89%)	11 (6.92%)
- Moderate (BIL >1.5–3 $\times$ ULN, any AST)	0 (0.00%)	0 (0.00%)	1 (1.11%)	1 (0.629%)
Refractory to any prior CD20 treatment				
- Relapse to any	1 (14.3%)	8 (12.9%)	19 (21.1%)	28 (17.6%)
- Refractory to any	6 (85.7%)	54 (87.1%)	71 (78.9%)	131 (82.4%)
Refractory to last prior therapy				
- Relapse or unknown	2 (28.6%)	14 (22.6%)	28 (31.1%)	44 (27.7%)
- Refractory	5 (71.4%)	48 (77.4%)	62 (68.9%)	115 (72.3%)
Double refractory				
- No	3 (42.9%)	23 (37.1%)	42 (46.7%)	68 (42.8%)
- Yes	4 (57.1%)	39 (62.9%)	48 (53.3%)	91 (57.2%)
Start systemic therapy <24 months to PD				
- No	4 (57.1%)	32 (51.6%)	43 (47.8%)	79 (49.7%)
- Yes	3 (42.9%)	30 (48.4%)	47 (52.2%)	80 (50.3%)
Bulky disease (>6 cm)				
- No	7 (100%)	38 (61.3%)	59 (65.6%)	104 (65.4%)
- Yes	0 (0.00%)	24 (38.7%)	31 (34.4%)	55 (34.6%)

Variable	Cohort			Total
	A	B1-B10	B11	
FLIPI score				
- 0	0 (0.00%)	1 (1.61%)	3 (3.33%)	4 (2.52%)
- 1	0 (0.00%)	11 (17.7%)	23 (25.6%)	34 (21.4%)
- 2	3 (42.9%)	20 (32.3%)	24 (26.7%)	47 (29.6%)
- 3	1 (14.3%)	17 (27.4%)	21 (23.3%)	39 (24.5%)
- 4	2 (28.6%)	10 (16.1%)	18 (20.0%)	30 (18.9%)
- 5	1 (14.3%)	2 (3.23%)	1 (1.11%)	4 (2.52%)
- Missing	0 (0.00%)	1 (1.61%)	0 (0.00%)	1 (0.629%)
Ann Arbor Stage at study entry				
- Stage I	0 (0.00%)	1 (1.61%)	5 (5.56%)	6 (3.77%)
- Stage II	0 (0.00%)	8 (12.9%)	16 (17.8%)	24 (15.1%)
- Stage III	1 (14.3%)	23 (37.1%)	25 (27.8%)	49 (30.8%)
- Stage IV	6 (85.7%)	30 (48.4%)	44 (48.9%)	80 (50.3%)
Continuous variables are expressed as median (geometric mean) [range] {missing/LLOQ}. Categorical variables are expressed as count (percentage).				

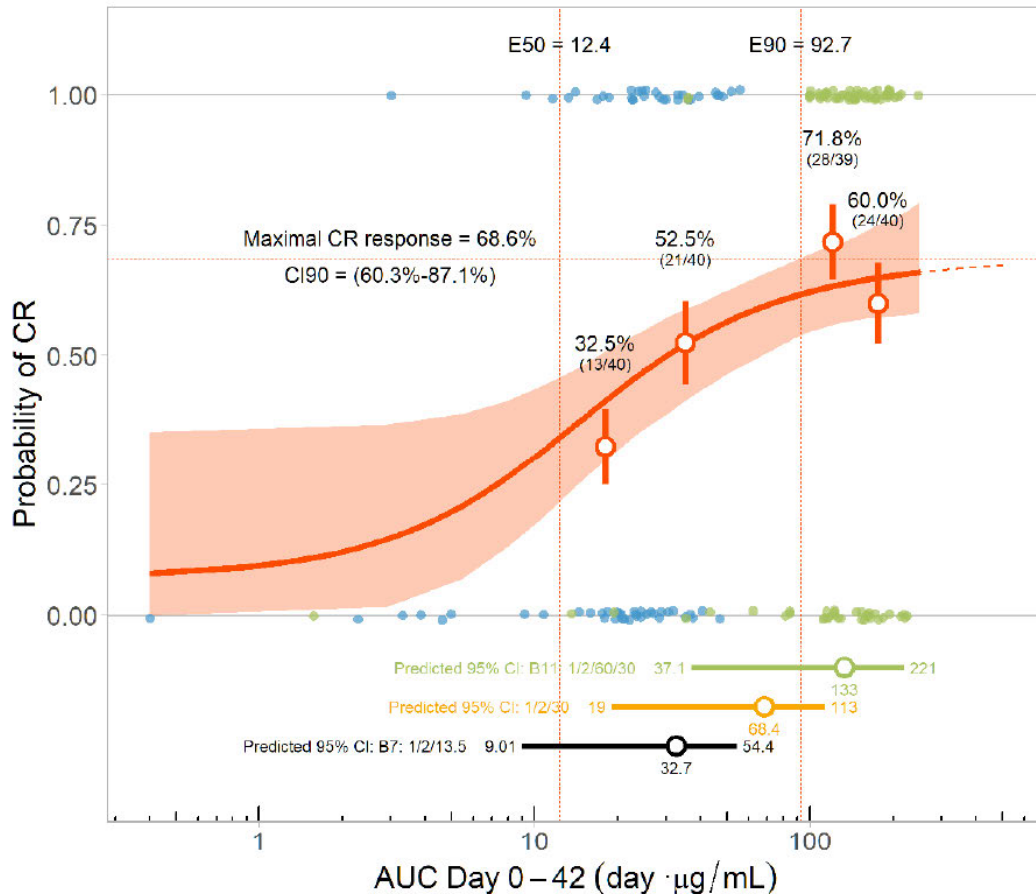
Source: Applicant's Exposure Response Analysis Report (ER-1112149), Appendix 8.

Logistic regression with Emax models well described the observed CR and OR data using AUC_{0-42} as the primary exposure endpoint. As shown in Figure 40 and Figure 41, results indicated maximal CR and OR rates of 68.6% [60.3–87.1%; 90% CI] and 81.4% [75.6–91.5%; 90% CI], respectively, in R/R FL patients with ≥ 2 Prior Therapies.

Figure 40: Observed and Predicted Relationships between CR and AUC_{0-42}

FL: CR ~ AUC₀₋₄₂

85.4% of simulated B11 AUC above E90 (87.8% observed)



159 Obs • 1/2/60/30 mg (90 Obs) • Lower Cohorts (69 Obs)

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AUC₀₋₄₂ = AUC from time equal to 0 to 42 days post-dose; CI=confidence interval; CI90=90% confidence interval; CR=complete response; E50=AUC₀₋₄₂ at 50% of maximal response; E90=AUC₀₋₄₂ at 90% of maximal response; FL=Follicular Lymphoma.

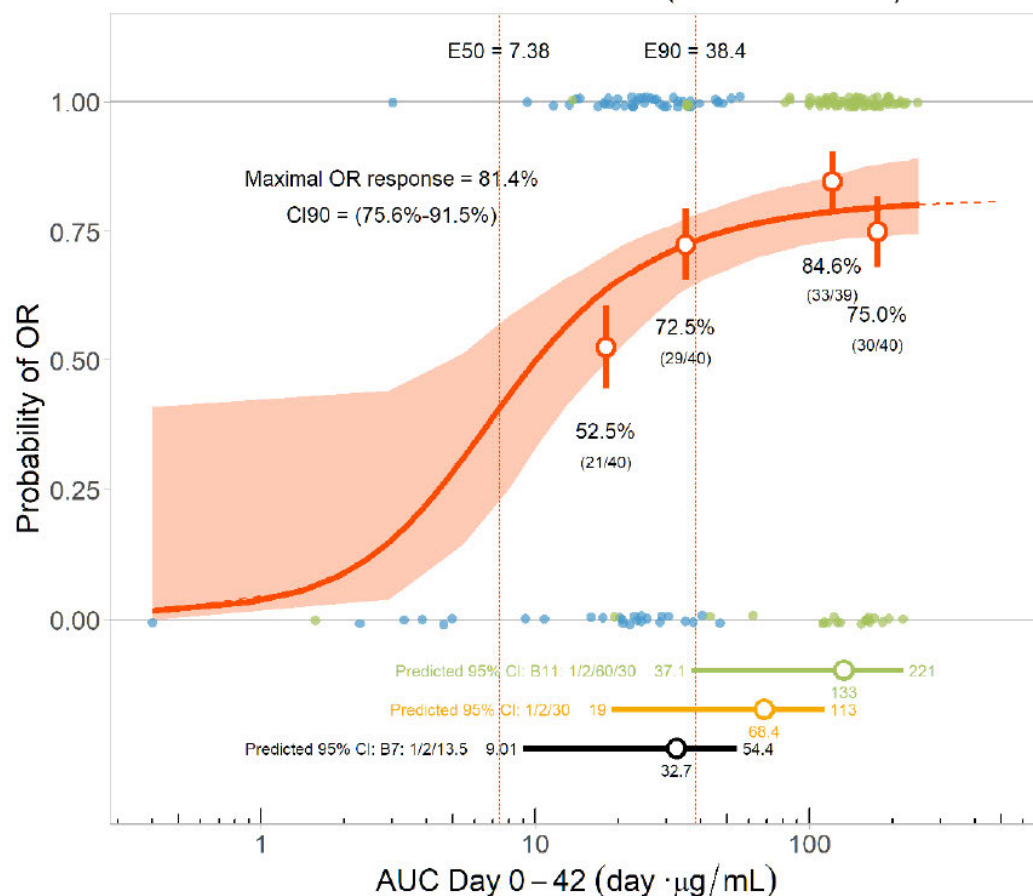
Filled circles represent the individual patient AUC₀₋₄₂ (green=1/2/60/30 mg; blue=lower dose cohorts) and response assessment (0=no event, 1=event); orange solid line represents the ER curve based on the final parameter estimates; orange shaded area represents the ER model-estimated 90% CI. Percentages indicate the observed response rate (%); (x/y=x responders out of y patients) within each exposure quartile. Open circles are the observed median probability of patients having a clinical response; error bars are the SE [sqrt(P*(1-P)/N)] at each exposure quartile. Horizontal lines at the bottom represent simulated AUC distributions (median with 95% CI) at selected dose levels (green=1/2/60/30 mg; yellow=1/2/30 mg; black=1/2/13.5 mg); simulations are based on the popPK model EBEs.

Source: Applicant's Exposure Response Analysis Report (ER-1112149), Figure 7.

Figure 41: Observed and Predicted Relationships between OR and AUC₀₋₄₂

FL: OR ~ AUC₀₋₄₂

97.3% of simulated B11 AUC above E90 (93.3% observed)



159 Obs • 1/2/60/30 mg (90 Obs) • Lower Cohorts (69 Obs)

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AUC₀₋₄₂ = AUC from time equal to 0 to 42 days post-dose; CI=confidence interval; CI90=90% confidence interval; E50=AUC₀₋₄₂ at 50% of maximal response; E90=AUC₀₋₄₂ at 90% of maximal response; FL=Follicular Lymphoma; OR = objective response.

Filled circles represent the individual patient AUC₀₋₄₂ (green=1/2/60/30 mg; blue=lower dose cohorts) and response assessment (0=no event, 1=event); orange solid line represents the ER curve based on the final parameter estimates; orange shaded area represents the ER model-estimated 90% CI. Percentages indicate the observed response rate (%; (x/y=x responders out of y patients) within each exposure quartile. Open circles are the observed median probability of patients having a clinical response; error bars are the SE [sqrt(P*(1-P)/N)] at each exposure quartile. Horizontal lines at the bottom represent simulated AUC distributions (median with 95% CI) at selected dose levels (green = 1/2/60/30 mg; yellow=1/2/30 mg; black=1/2/13.5 mg); simulations are based on the popPK model EBEs.

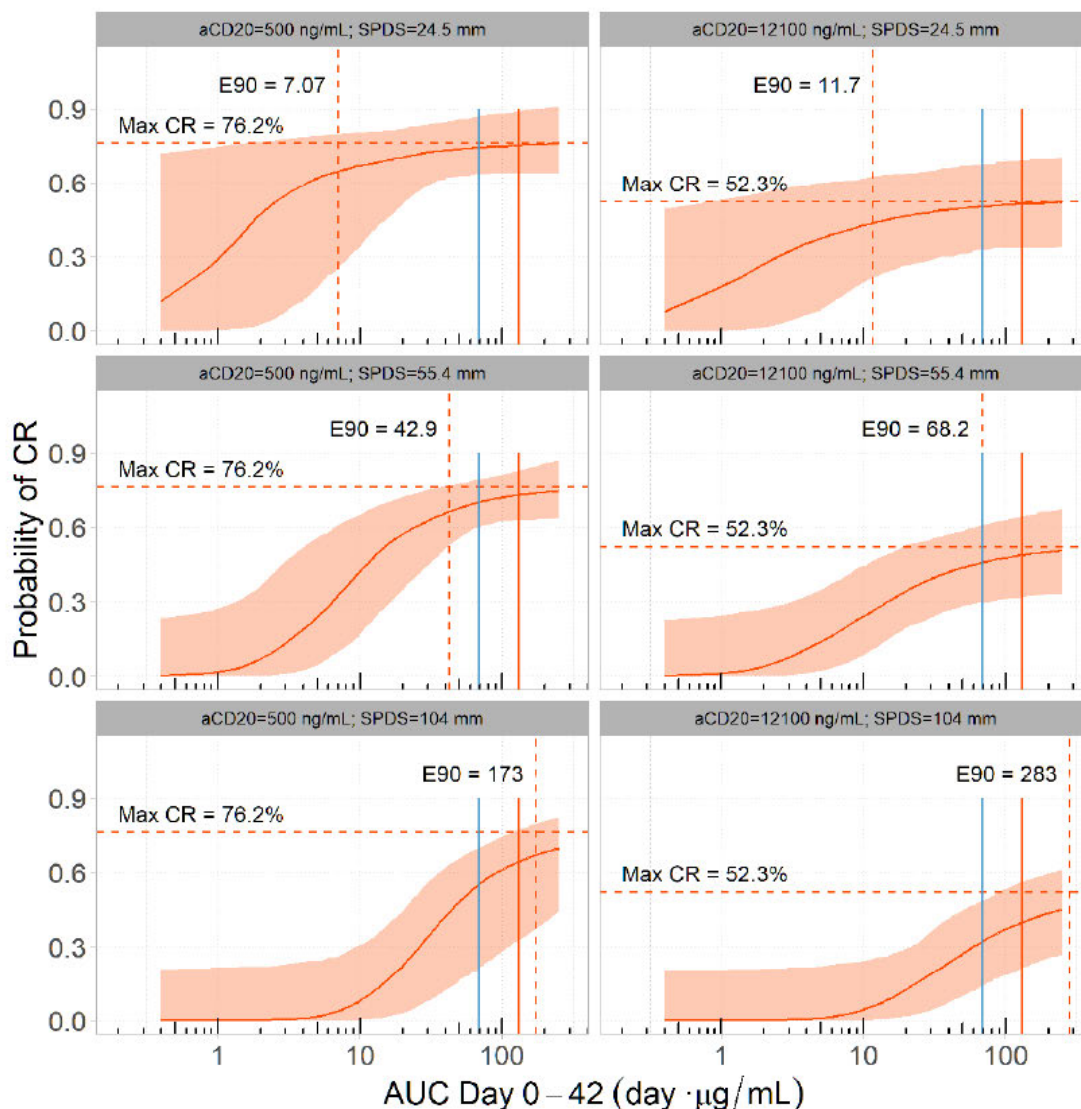
Source: Applicant's Exposure Response Analysis Report (ER-1112149), Figure 8.

At the proposed dose of 1/2/60/30 mg, the ER model–predicted probabilities for CRR and ORR were 63.1% [49.7–75.0%; 95% PI] and 79.1% [69.1–87.7%; 95% PI], respectively. When compared to the maximal CR and OR rates, the model predictions for the proposed 1/2/60/30 mg regimen are at the plateau of the logistic regression Emax ER curves.

The covariate analysis indicated that baseline tumor size and predose anti-CD20 drug concentrations were predictors for E50 and Emax, respectively; patients with larger tumors or with high predose aCD20 concentrations are predicted to have a lower probability to attain CR, though still expected to be higher than 50% CR rate (Figure 42).

Figure 42: Effect of Baseline Tumor Size (SPDS) and aCD20 Baseline Concentration on the Exposure (AUC_{0-42}) - Response Analyses for Investigator-Assessed Complete Response

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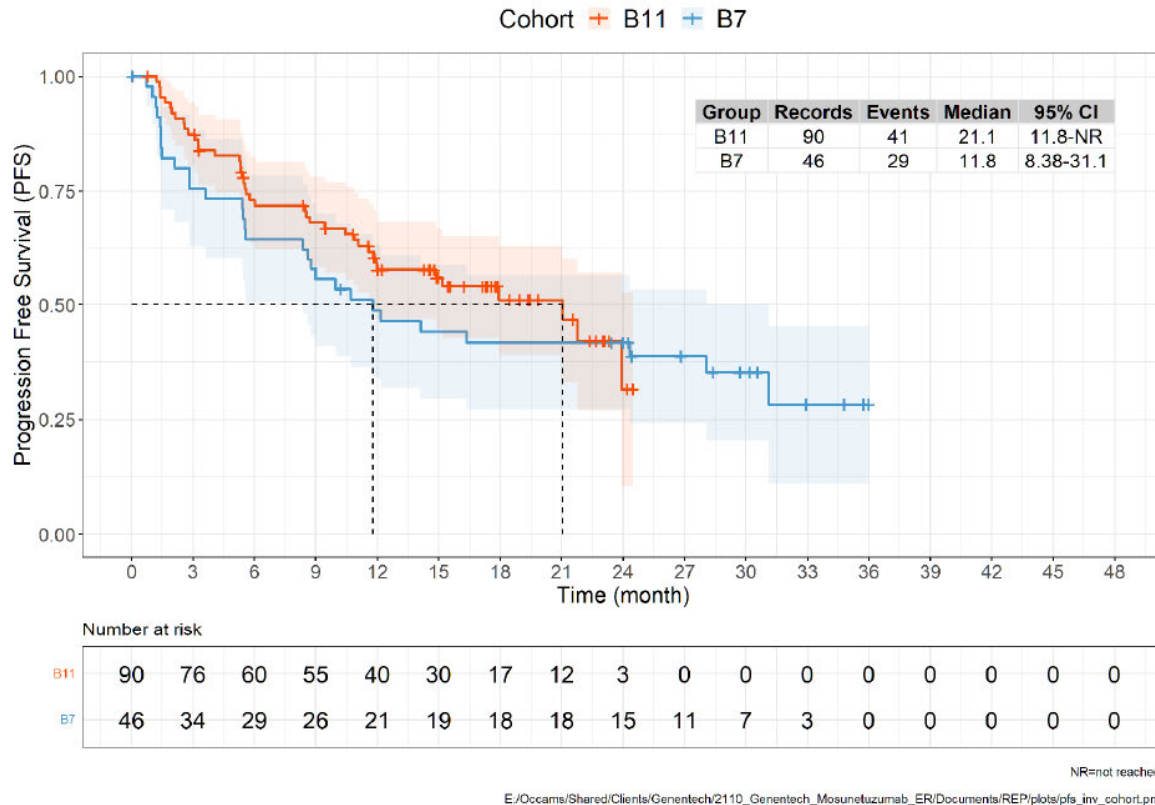
Figure 9 (left panels) represent the majority (~65%) of R/R FL patients, who do not have measurable aCD20 concentrations at baseline (LLOQ = 500 ng/mL); Figure 9 (right panels) represent the subset (~35%) of patients who have a median level of 12100 ng/ml of aCD20 at baseline (12100 ng/mL is at the 82nd percentile of the overall R/R FL ≥2 Prior Therapies patient population); Panels from top to bottom represents the 5th, 50th, and 95th percentile splits used for square root of SPD (mm); shaded region reflects ER model uncertainty; Vertical solid lines represent the median AUC₀₋₄₂ at simulated dose levels of 1/2/30 mg (blue) and 1/2/60/30 mg (red); Vertical dashed lines represent E90.

Source: Applicant's Exposure Response Analysis Report (ER-1112149), Figure 9.

The PFS analysis showed a longer median PFS at the 1/2/60/30 mg dose (B11 cohort, RP2D) compared to the 1/2/13.5 mg dose (B7 cohort) in Figure 43; further E-R analysis showed a

longer median PFS with increased mosunetuzumab exposure (AUC_{0-42}) in Figure 44. The duration of complete response (DOCR) and durations of objective response (DOR) were similar at the 1/2/60/30 mg dose compared to the 1/2/13.5 mg dose; further E-R analysis showed a trend of longer duration of response (for both CR and OR) with increasing mosunetuzumab exposure (AUC_{0-42}).

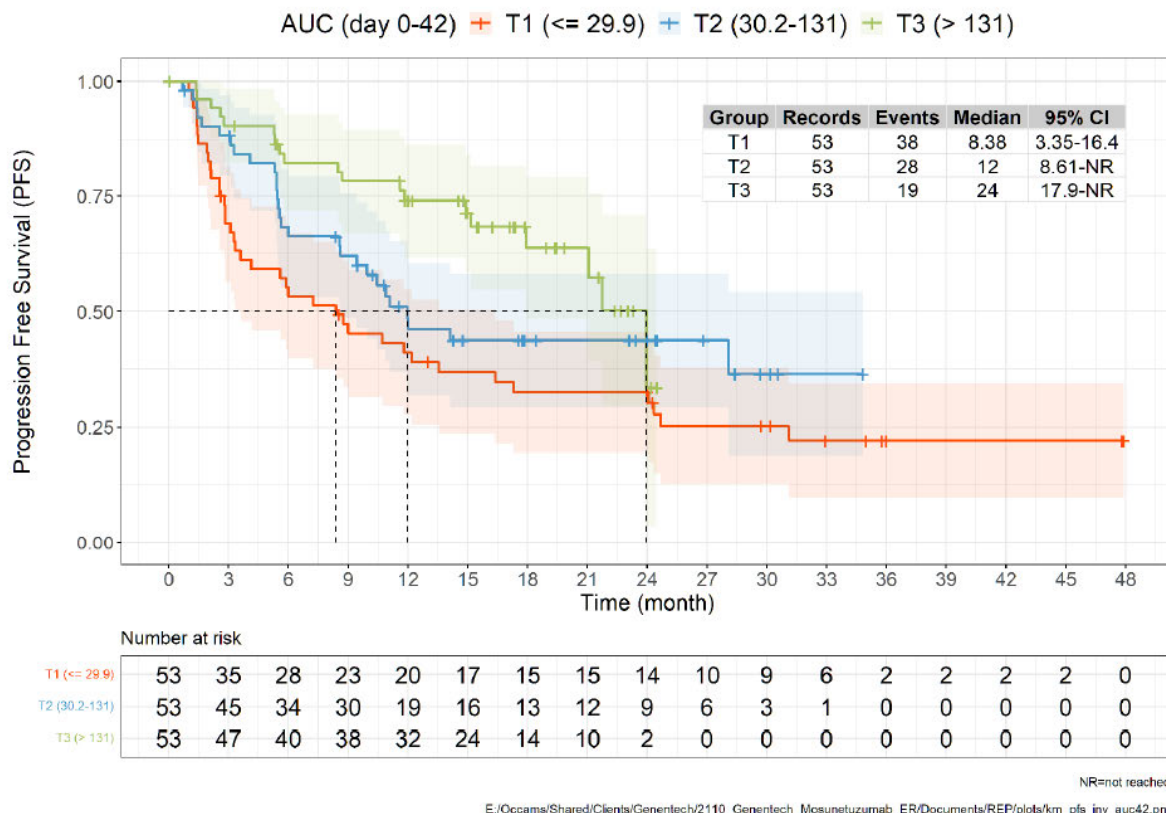
Figure 43: Investigator-Assessed PFS for the R/R FL Population Stratified by Cohorts B11 (1/2/60/30 mg) and B7 (1/2/13.5 mg)



CI=confidence interval; NR=not reached.

Source: Applicant’s Exposure Response Analysis Report (ER-1112149), Figure 11.

Figure 44: Investigator-Assessed PFS for the R/R FL Population Stratified by Tertiles of Mosunetuzumab AUC_{0-42}



AUC₀₋₄₂=AUC from time 0 to 42 days; CI=confidence interval; NR=not reached.

T1 = tertile 1 of mosunetuzumab AUC₀₋₄₂ exposure (≤ 29.9 day $\cdot\mu\text{g/mL}$).

T2 = tertile 2 of mosunetuzumab AUC₀₋₄₂ exposure >30.2 day $\cdot\mu\text{g/mL}$ and ≤ 131 day $\cdot\mu\text{g/mL}$.

T3 = tertile 3 of mosunetuzumab AUC₀₋₄₂ exposure (>131 day $\cdot\mu\text{g/mL}$).

Source: Applicant's Exposure Response Analysis Report (ER-1112149), Figure 12.

20.4.5.3. ER (safety) Executive Summary

The FDA's Assessment:

In support of the dosage recommendations for this BLA, the Applicant also submitted reports of exposure-response (E-R) for safety analysis from patients with R/R NHL from Studies GO29781 to characterize E-R for safety relationships. The E-R for safety results indicated that the no positive E-R relationship for any AEs Grade ≥ 3 and any serious AE with PK exposure to the time of event in the pooled population across all evaluated doses. The Applicant's E-R for safety analysis results using R_{0max} % supports the step-up dosing regimen at 1/2/60/30 mg with observed low frequency of Grade >2 CRS. Following the step-up dosing regimen did not lead to exposure-related increases in rates and onset time of Grade >3 neutropenia, Grade ≥ 3 infections or infestations, any Grade ≥ 3 AEs, or any Grade >1 AEs.

In addition, the Applicant also conducted E-R analysis to support neurological AE (NAE) risk mitigation through step-up dosing regimens where there was a lack of ER relationships for frequency or onset of NAE despite dose escalation of the target doses administered on Cycle 1 Day 15, Cycle 2 Day 1, and every 3 weeks thereafter. No exposure-dependency for DI-CCNAE (driving-impacting cognition or consciousness neurologic adverse event) in R/R NHL was observed across the dose range tested (i.e., 0.4/1/2.8 mg to 1/2/60/30 mg) using the step-up dosing regimen. The Applicant's E-R for NAE analysis appear reasonable.

Overall, the Applicant's E-R for safety analysis appear adequate to support the proposed dosing regimen (1/2/60/30 mg).

20.4.5.4. ER (safety) Assessment Summary

The Applicant's Position:

The Applicant's E-R for safety analysis of Mosunetuzumab (Mosunetuzumab) was conducted with 439 patients with relapsed or refractory B-cell non-Hodgkin's lymphoma (NHL) patients in Study GO29781. A brief overview of E-R analysis for Mosunetuzumab is listed in the Table 62: and Figure 39. The dose range for these patients was from 0.05 mg to 1/2/60 mg, including 1/2/60/30 mg. Adverse Events Grade ≥ 2 CRS, Grade ≥ 3 neutropenia, Grade ≥ 3 infections and infestations, any Grade ≥ 3 event, and any Grade ≥ 1 event in R/R NHL patients were included in E-R for safety analysis. The data included 32 patients from Group A cohorts receiving doses ranging from 0.05 to 2.8 mg every three weeks (q3w), and 407 patients from Group B step-up dosing cohorts receiving doses ranging from 0.4/1.0/2.8 mg to 1.0/2.0/60 mg, including 1.0/2.0/60/30 mg.

The E-R safety analysis for R/R NHL covered age ranging from 19 to 96 years with a median of 63 years, body weight ranging from 37.1 to 163 kg with a median 77.9 kg, and albumin ranging from 20 to 480 g/L with a median of 41 g/L. Table 64: shows statistical summaries of baseline continuous and categorical covariates for the evaluable patients in the E-R for safety (E-S) analysis.

For safety E-R of CRS, a mosunetuzumab receptor occupancy (RO)-based exposure endpoint - a ROmax% metric (instead of AUC or Cmax) was used to address the confounding issue of the ER relationship for CRS incidence from varying levels of anti-CD20 drug concentrations (specifically residual rituximab [R] or Gazyva [G]).

Table 64: Baseline Patient Characteristics for the Safety ER Population (PK evaluable; N=439)

BLA Multi-disciplinary Review and Evaluation {BLA 761263, Lunsumio (Mosunetuzumab)}

Variable	Cohort			Total
	A2-A8	B1-B10	B11	
N	32	193	214	439
Maximal receptor occupancy (day 0-42, %)	0.809 (1.08) [0.032 ; 3.43] {1}	7.5 (11.1) [0.0294 ; 54.4] {4}	36 (31.1) [0.0482 ; 64.3] {15}	12.9 (19.9) [0.0294 ; 64.3] {20}
Baseline age (y)	64 (62.6) [30 ; 84]	61 (60.8) [19 ; 91]	64 (63) [24 ; 96]	63 (62) [19 ; 96]
Baseline height (cm)	172 (169) [138 ; 188] {2}	169 (169) [142 ; 198] {7}	171 (171) [138 ; 195] {17}	170 (170) [138 ; 198] {26}
Baseline weight (kg)	76.2 (78.2) [45.9 ; 111]	74.8 (76.1) [38.7 ; 128] {6}	80.3 (80.7) [37.1 ; 163] {1}	77.9 (78.5) [37.1 ; 163] {7}
Baseline BMI (kg/m ²)	27 (27.3) [17.1 ; 37.9] {2}	26.2 (26.6) [17.3 ; 40.8] {10}	26.7 (27.5) [14.9 ; 52.2] {17}	26.4 (27.1) [14.9 ; 52.2] {29}
Race				
- Black or African American	1 (3.23%)	5 (2.60%)	6 (2.80%)	12 (2.75%)
- White	19 (61.3%)	139 (72.4%)	175 (81.8%)	333 (76.2%)
- Asian	10 (32.3%)	43 (22.4%)	24 (11.2%)	77 (17.6%)
- American Indian or Alaska Native	0 (0.00%)	1 (0.521%)	1 (0.467%)	2 (0.458%)
- Unknown	1 (3.23%)	4 (2.08%)	8 (3.74%)	13 (2.97%)
Sex				
- Female	13 (40.6%)	71 (36.8%)	71 (33.2%)	155 (35.3%)
- Male	19 (59.4%)	122 (63.2%)	143 (66.8%)	284 (64.7%)
Baseline ECOG				
- 0	11 (34.4%)	76 (39.4%)	100 (46.7%)	187 (42.6%)

BLA Multi-disciplinary Review and Evaluation {BLA 761263, Lunsumio (Mosunetuzumab)}

Variable	Cohort			Total
	A2-A8	B1-B10	B11	
- 1	21 (65.6%)	116 (60.1%)	114 (53.3%)	251 (57.2%)
- 2	0 (0.00%)	1 (0.518%)	0 (0.00%)	1 (0.228%)
Ann Arbor Stage at study entry				
- 1	0 (0.00%)	5 (2.59%)	9 (4.21%)	14 (3.19%)
- 2	4 (12.5%)	23 (11.9%)	26 (12.1%)	53 (12.1%)
- 3	12 (37.5%)	52 (26.9%)	49 (22.9%)	113 (25.7%)
- 4	16 (50.0%)	113 (58.5%)	130 (60.7%)	259 (59.0%)
Ann Arbor (dichotomized)				
- 1	4 (12.5%)	28 (14.5%)	35 (16.4%)	67 (15.3%)
- 2	28 (87.5%)	165 (85.5%)	179 (83.6%)	372 (84.7%)
Baseline LDH	305.5 (454.2) [123 ; 1596]	306 (436.9) [100 ; 2992]	252.5 (345.7) [113 ; 6480]	271 (393.7) [100 ; 6480]
Baseline tumor burden (INV, mm ²)	2133.2 (3301.5) [216 ; 11933]	3356.3 (5333.4) [160 ; 70931]	2851.5 (4158.9) [96 ; 33072]	2968 (4612.8) [96 ; 70931]
Baseline tumor burden (IRF, mm ²)	1214.5 (2308.2) [126 ; 10916]	2045 (3520.7) [162 ; 28272] {2}	1425.5 (2380.5) [144 ; 25202] {2}	1630 (2875.8) [126 ; 28272] {4}
Histology				
- DLBCL	13 (40.6%)	77 (39.9%)	67 (31.3%)	157 (35.8%)
- DLBCL/MCL	0 (0.00%)	1 (0.518%)	0 (0.00%)	1 (0.228%)
- FL	9 (28.1%)	64 (33.2%)	90 (42.1%)	163 (37.1%)
- FL3B	0 (0.00%)	1 (0.518%)	0 (0.00%)	1 (0.228%)
- MCL	2 (6.25%)	13 (6.74%)	24 (11.2%)	39 (8.88%)
- MEL	0 (0.00%)	0 (0.00%)	1 (0.467%)	1 (0.228%)
- MZL	1 (3.12%)	2 (1.04%)	0 (0.00%)	3 (0.683%)

BLA Multi-disciplinary Review and Evaluation {BLA 761263, Lunsumio (Mosunetuzumab)}

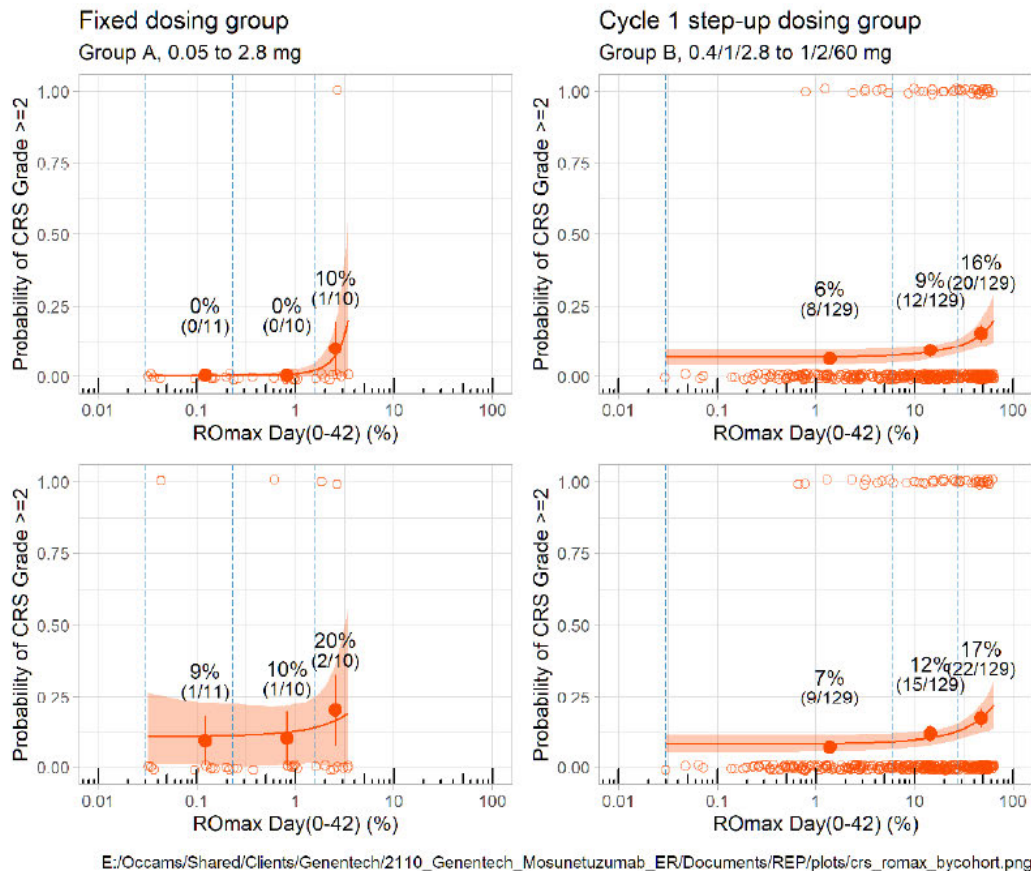
Variable	Cohort			Total
	A2-A8	B1-B10	B11	
- RS	1 (3.12%)	5 (2.59%)	8 (3.74%)	14 (3.19%)
- SLL	1 (3.12%)	1 (0.518%)	0 (0.00%)	2 (0.456%)
- trFL	5 (15.6%)	28 (14.5%)	24 (11.2%)	57 (13.0%)
- trMZL	0 (0.00%)	1 (0.518%)	0 (0.00%)	1 (0.228%)
Baseline age (y)				
- <=64	18 (56.2%)	110 (57.0%)	113 (52.8%)	241 (54.9%)
- >64	14 (43.8%)	83 (43.0%)	101 (47.2%)	198 (45.1%)
Baseline WBC (•1000/ μ L)	4.2 (4.84) [2.07 ; 12]	5.2 (6.4) [1.3 ; 71.5]	5.3 (6.6) [0.9 ; 61.7]	5.2 (6.38) [0.9 ; 71.5]
Bone marrow involvement				
- No	20 (62.5%)	122 (63.2%)	110 (51.4%)	252 (57.4%)
- Missing	6 (18.8%)	45 (23.3%)	56 (26.2%)	107 (24.4%)
- Yes	6 (18.8%)	26 (13.5%)	48 (22.4%)	80 (18.2%)
Baseline marrow mmt	0 (0.0625) [0 ; 0.3] {24}	0.2 (0.25) [0 ; 0.9] {170}	0.15 (0.258) [0 ; 0.9] {172}	0.1 (0.234) [0 ; 0.9] {366}
Prior CAR-T therapy				
- No	32 (100.%)	175 (90.7%)	184 (86.0%)	391 (89.1%)
- Yes	0 (0.00%)	18 (9.33%)	30 (14.0%)	48 (10.9%)
Prior CAR-T therapy within 6 months				
- No	0 (0.00%)	8 (4.15%)	16 (7.48%)	24 (5.47%)
- Missing	32 (100.%)	175 (90.7%)	184 (86.0%)	391 (89.1%)
- Yes	0 (0.00%)	10 (5.18%)	14 (6.54%)	24 (5.47%)
Continuous variables are expressed as median (geometric mean) [range] {missing/LLOQ}. Categorical variables are expressed as count (percentage).				

Source: Applicant's Exposure Response Analysis Report (ER-1112149), Appendix 8 Table 21.

A linear logistic regression model was used to describe the observed Grade ≥ 2 CRS over the first 2 dose cycles (ROmax₀₋₄₂), and indicated a slight increase in the probability of Grade ≥ 2 CRS as

doses increased (Figure 45). The covariate analysis indicated that histology and patient baseline age were predictors for CRS; patients with histologies other than DLBCL, transformed follicular lymphoma (trFL), or FL, and patients ≤ 64 years old, are predicted to have a higher probability of Grade ≥ 2 CRS.

Figure 45: ER for CRS Grade ≥ 2 by Grading Criteria and Dose Group



ASTCT=American Society for Transplantation and Cellular Therapy;

Top row: ASTCT grading criteria; bottom row: Lee et al. (2014) grading criteria.

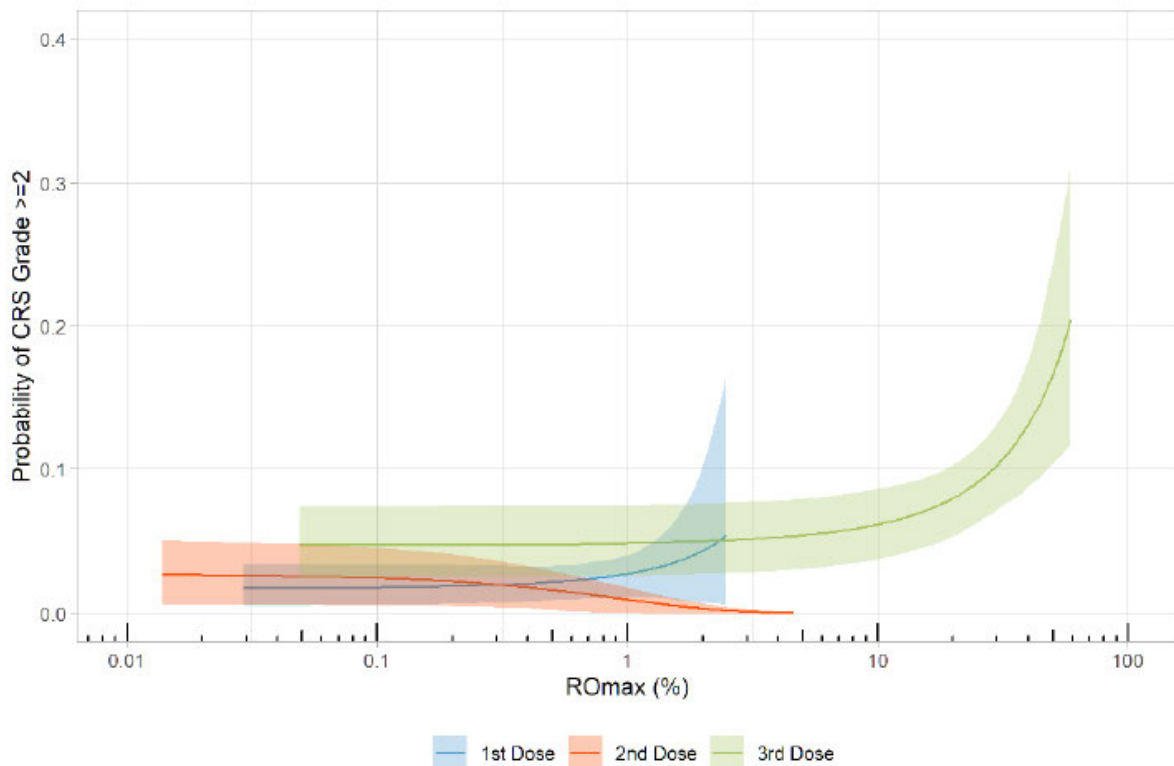
Open circles represent the individual patient $R_{0max_{0-42}}$; orange solid line represents the ER curve based on the final parameter estimates; orange shaded area represents the ER model-estimated 90% CI.

Percentages indicate the observed response rate (%; $x/y=x$ responders out of y patients) within each exposure tertile. Solid circles are the observed median probability of patients having a clinical response; error bars are the SE $[\sqrt{P*(1-P)/N}]$ at each exposure tertile.

Source: Applicant's Exposure Response Analysis Report (ER-1112149), Figure 16.

A subgroup CRS analysis in Figure 46 stratified by mosunetuzumab Cycle 1 Day 1 dose, Day 8 dose, and Day 15 dose supported the mitigation strategy of the Cycle 1 step-up dose regimen versus a standard q3w regimen.

Figure 46: Overlay ER Plot for Grade ≥ 2 CRS following Cycle 1 Doses on Day 1 (1st Dose), Day 8 (2nd Dose), and Day 15 (3rd Dose)



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CRS= cytokine release syndrome; R0max (%) = model-predicted maximum CD20 receptor occupancy (RO%) for each dose interval. Solid lines represent the model fit; shaded regions represent the 90% prediction intervals. Note that the x-axis range of each curve represents the available data range as a result of the dose ranging tested (i.e., Cycle 1 Day 1 dose from 0.4 to 1 mg; Day 8 dose from 1 to 2 mg; Day 15 dose from 2.8 to 60 mg).

Source: Applicant's Exposure Response Analysis Report (ER-1112149), Figure 21.

At the proposed dosage of 1/2/60/30 mg, the E-R model-predicted probability for Grade ≥ 2 CRS (over the first two cycles) was 11.8% [5.27–23.2%; 95% CI].

The relationships between mosunetuzumab exposure (AUC_{0-42}) and the time to event (TTE) for the selected key Grade ≥ 3 AEs (e.g., neutropenia/neutrophil count decreased, infections and infestations, and any Grade ≥ 3 AEs) were evaluated, as were any AEs of Grade ≥ 1 . Data were

from 407 PK-evaluable R/R NHL patients from Group B step-up dosing cohorts receiving doses ranging from 0.4/1.0/2.8 mg to 1.0/2.0/60 mg including 1.0/2.0/60/30 mg. As shown in Table 65, by TTE analysis, increased mosunetuzumab exposure (stratified by tertiles of AUC₀₋₄₂), was not correlated with an increased rate of Grade ≥ 3 neutropenia, Grade ≥ 3 infections and infestations, any Grade ≥ 3 adverse events, or any Grade ≥ 1 adverse events.

Table 65: Observed AE Counts Stratified by AUC₀₋₄₂ Tertiles

AUC ₀₋₄₂ (day·µg/mL)	Grade ≥ 3 Neutropenia	Grade ≥ 3 Infections and infestations (SOC)	Any Grade ≥ 3 AEs	Any Grade ≥ 1 AEs
Tertile 1 [0.177,28.5]	21.3% (N=29/136)	20.6% (N=28/136)	75.7% (N=103/136)	97.8% (N=133/136)
Tertile 2 [28.5,121]	29.6% (N=40/135)	16.3% (N=22/135)	74.8% (N=101/135)	99.3% (N=134/135)
Tertile 3 [121,254]	23.5% (N=32/136)	9.56% (N=13/136)	61.8% (N=84/136)	98.5% (N=134/136)

AE = adverse event; AUC₀₋₄₂= AUC from time 0 to 42 days; N=number of patients; SOC=System Organ Class.

Source: Applicant's Exposure Response Analysis Report (ER-1112149), Table 15.

Exposure Response for Neurological Adverse Events (NAEs)

The applicant also conducted the mosunetuzumab exposure-response (ER) analyses (including logistic regression and TTE analyses) for NAEs (defined as adverse events reported as any primary or secondary Preferred Terms [PT] in either the System Organ Class [SOC] "Nervous system disorders" or SOC "Psychiatric disorders") based on a more recent clinical dataset (clinical cutoff date [CCOD] of 27 Aug 2021) and DI-CCNAE (driving-impacting cognition or consciousness neurologic adverse event), including 439 pharmacokinetic-evaluable patients (438 non-Hodgkin's lymphoma [NHL] patients).

The exposure metrics evaluated included area under the mosunetuzumab concentration-time curve (AUC) and CD20 receptor occupancy (RO) based metrics over pre-defined time windows of 0-7 days, 0-14 days, and 0-42 days. A summary of common NAEs ($\geq 2\%$) by preferred term is summarized in Table 66. Overall results of the ER analyses for NAE patients in the safety evaluable population are shown in Figure 47. For Kaplan-Meier analyses, exposures were stratified by tertiles of observed values, the TTE analyses of any-grade NAE onset are shown in Figure 48. The logistic regression ER analyses indicate a slightly positive ER slope for increased

NAEs that occurs with AUC_{0-42} and $RO_{max0-42}$ ($p>0.05$). And Kaplan-Meier analyses showed similar trend with a visual separation occurring near the timing of the higher 60 mg loading dose (day 15); however, overall log-rank tests for time-to-event analyses showed non-significant p-values for both metrics. A flat E-R relationship for NAE was observed following the Cycle 1 Day 1 (C1D1) doses of 0.05 to 2.8 mg when mosunetuzumab was administered as fixed q3w doses (i.e., Group A).

The E-R relationships with DI-CCNAE were mostly flat across the exposure range tested (Figure 49). In summary, the overall E-R data support that neurological events are mostly lower grade and have, at worst, a modest exposure-dependency for NAE and no exposure-dependency for DI-CCNAE in R/R NHL across the dose range tested (i.e., 0.4/1/2.8 mg to 1/2/60/30 mg) using the step-up dosing regimen.

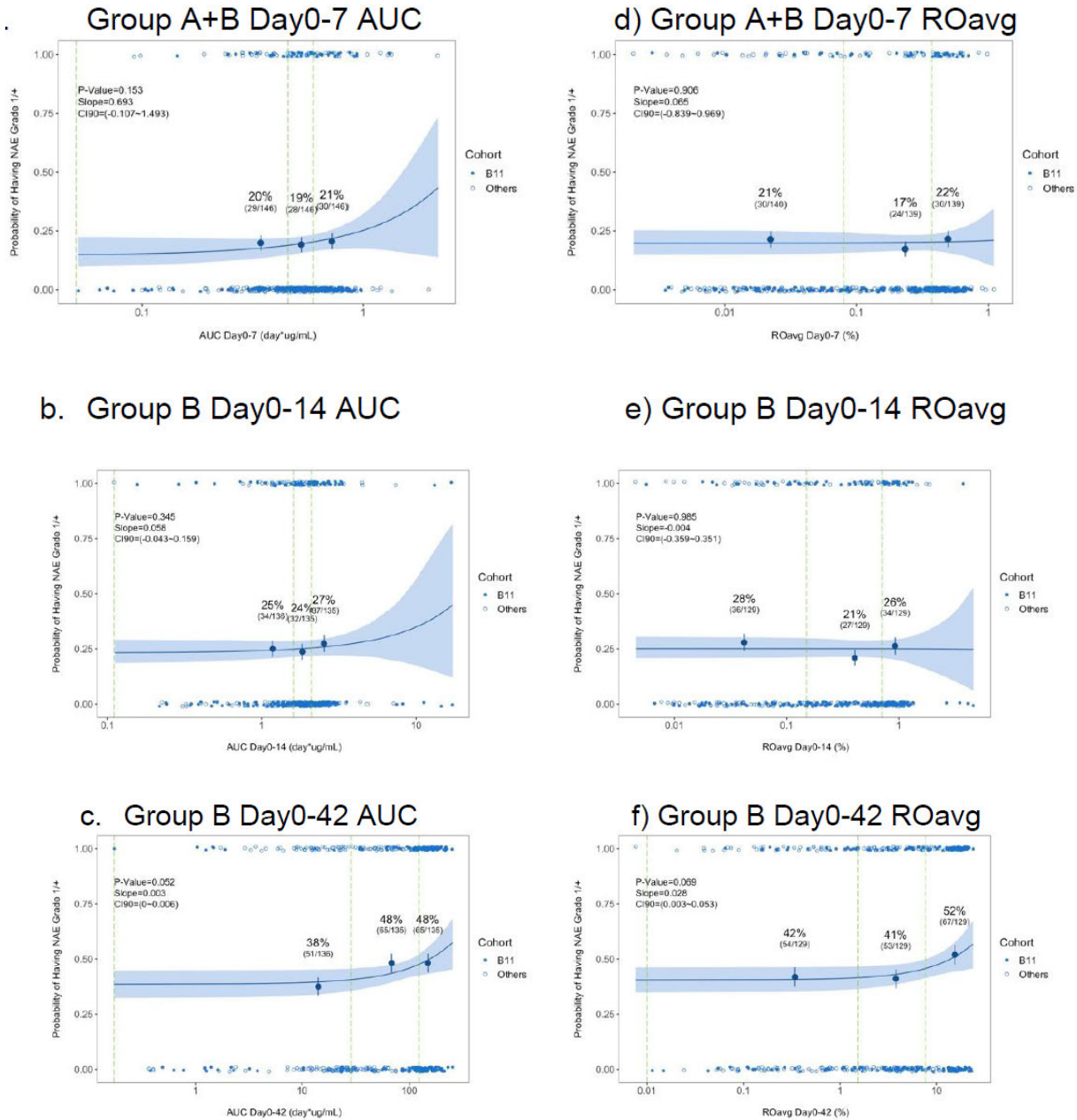
Table 66: Summary of Common NAEs ($\geq 2\%$) by Preferred Term (CCOD: 27 Aug 2021), Safety-Evaluable Patients

	Group A N=33	Group B N=414	B11 RP2D Cohort N=218	B11 FL RP2D Cohort N=90
No. of patients with at least one NAE, n (%)				
Headache	6 (18.2)	78 (18.8)	44 (20.2)	28 (31.1)
Insomnia	5 (15.2)	44 (10.6)	23 (10.6)	11 (12.2)
Dizziness	5 (15.2)	41 (9.9)	21 (9.6)	9 (10.0)
Confusional state	0	18 (4.3)	8 (3.7)	3 (3.3)
Paresthesia	1 (3.0)	10 (2.4)	8 (3.7)	5 (5.6)
Anxiety	0	11 (2.7)	7 (3.2)	4 (4.4)
Peripheral sensory neuropathy	1 (3.0)	10 (2.4)	7 (3.2)	5 (5.6)
Neuropathy peripheral	2 (6.1)	9 (2.2)	7 (3.2)	5 (5.6)
Vision blurred	0	8 (1.9)	7 (3.2)	2 (2.2)
Herpes zoster	0	14 (3.4)	7 (3.2)	3 (3.3)
Tremor	1 (3.0)	9 (2.2)	5 (2.3)	1 (1.1)

Source: 2.7.4 Summary of Clinical Safety, Table 17.

Source: Response to FDA request for information, SN#0039, Table 4.1

Figure 47: E-R Analyses for Occurrence of Any-grade NAE Based on Specified Time Intervals of AUC or ROavg Following Mosunetuzumab IV Treatment in R/R NHL Patients



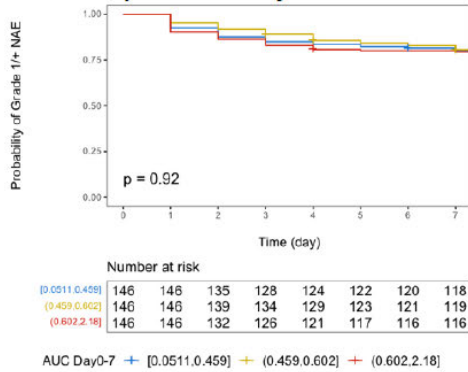
(Subplots a, b and c describe AUC-based E-R analyses; and subplots d, e and f describe ROavg-based E-R analyses) AUC = model-predicted area under the curve; ROavg (%) = model-predicted averaged CD20 receptor occupancy (RO%); Probability of NAE (clinical NAE event (0=No, 1=Yes)) are represented by blue circles; stippled green vertical lines represent tertiles of AUC or ROavg; solid blue line represents the model fit; shaded regions represent the 90% prediction intervals; blue filled circles at each quartile indicate the observed median AUC or ROavg and observed median probability of NAE; blue vertical lines represent the standard error.

Source: Response to FDA request for information, SN#0039, Figure 4.1

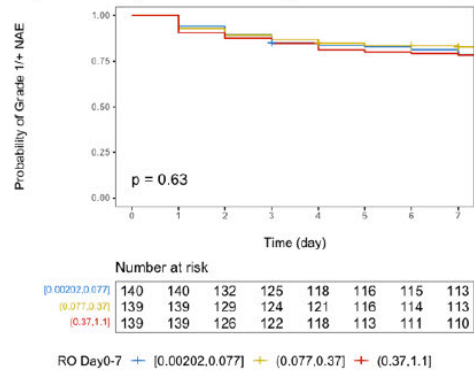
Figure 48: TTE Analyses for any-Grade NAE Onset, Grouped by AUC or ROavg Tertiles Over Specified Time Intervals

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.

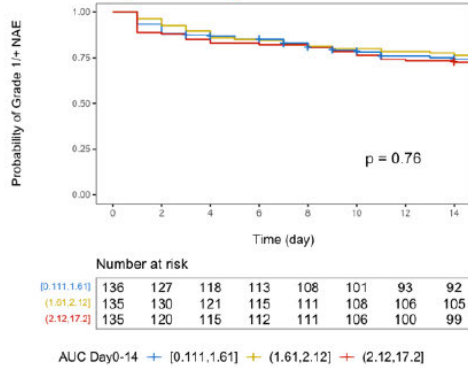
a. Group A+B Day0-7 AUC



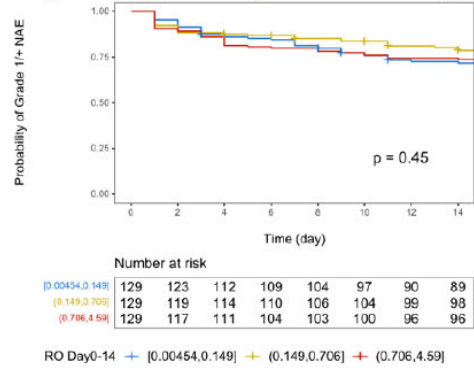
d) Group A+B Day0-7 ROavg



b. Group B Day0-14 AUC



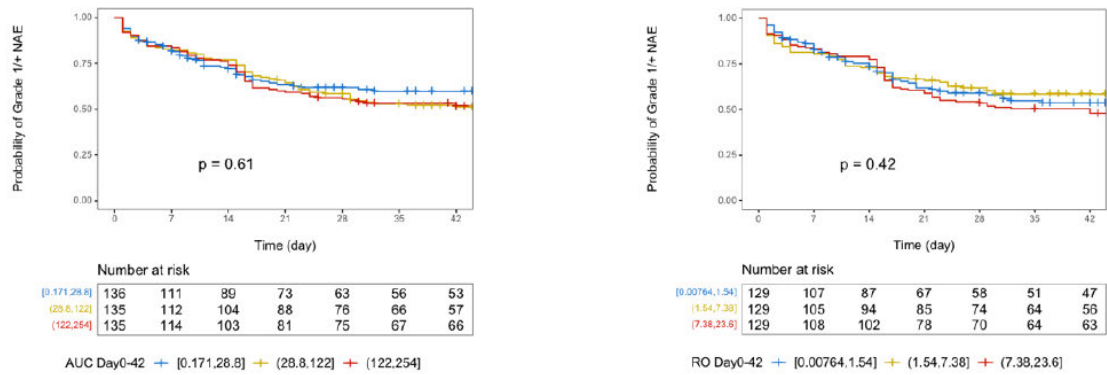
e) Group B Day0-14 ROavg



c. Group B Day0-42 AUC

f) Group B Day0-42 ROavg

BLA Multi-disciplinary Review and Evaluation {BLA 761263, Lunsumio (Mosunetuzumab)}



AUC0-7, AUC0-14, AUC0-42 tertiles in ug/ml*day, respectively:

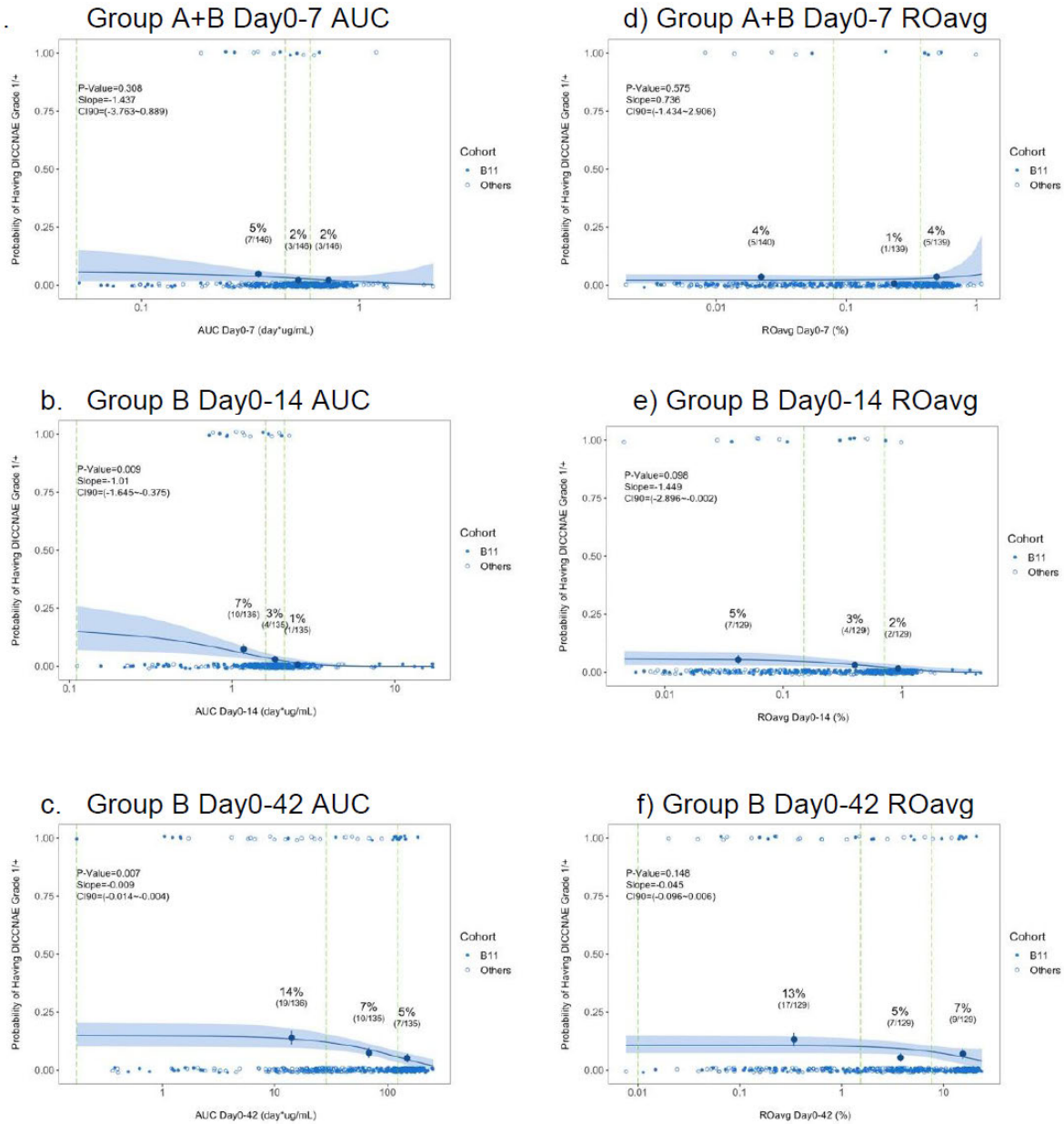
- [0.0511, 0.459], (0.459, 0.602], (0.602, 2.18]
- [0.111, 1.61], (1.61, 2.12], (2.12, 17.2]
- [0.171, 28.8], (28.8, 122), (122, 254]

ROavg0-7, ROavg 0-14, ROavg 0-42 tertiles in %, respectively:

- [0.00202, 0.077], (0.077, 0.37], (0.37, 1.1]
- [0.00454, 0.149], (0.149, 0.706], (0.706, 4.59]
- [0.00764, 1.54], (1.54, 7.38], (7.38, 23.6].

Source: Response to FDA request for information, SN#0039, Figure 4.3

Figure 49: E-R Analyses for Occurrence of Any-grade DI-CCNAE Based on Specified Time Intervals of AUC or ROavg Following Mosunetuzumab IV Treatment in R/R NHL Patients



(Subplots a, b and c describe AUC-based E-R analyses; and subplots d, e and f describe ROavg-based E-R analyses) AUC = model-predicted area under the curve; ROavg (%)= model-predicted averaged CD20 receptor occupancy (RO%); Probability of NAE (clinical NAE event (0=No, 1=Yes)) are represented by blue circles; stippled green vertical lines represent tertiles of AUC or ROavg; solid blue line represents the model fit; shaded regions represent the 90% prediction intervals; blue filled circles at each quartile indicate the observed median AUC or ROavg and observed median probability of NAE; blue vertical lines represent the standard error.

Source: Response to FDA re quest for information, SN#0039, Figure 4.2

The FDA’s Assessment:

In general, the Applicant’s E-R analyses for mosunetuzumab are considered acceptable for the purpose of supporting analyses objectives. The Applicant’s analyses were verified by the

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.

reviewer, with no significant discordance identified.

20.4.5.5. Exposure Response Analyses for Pharmacodynamic Biomarkers

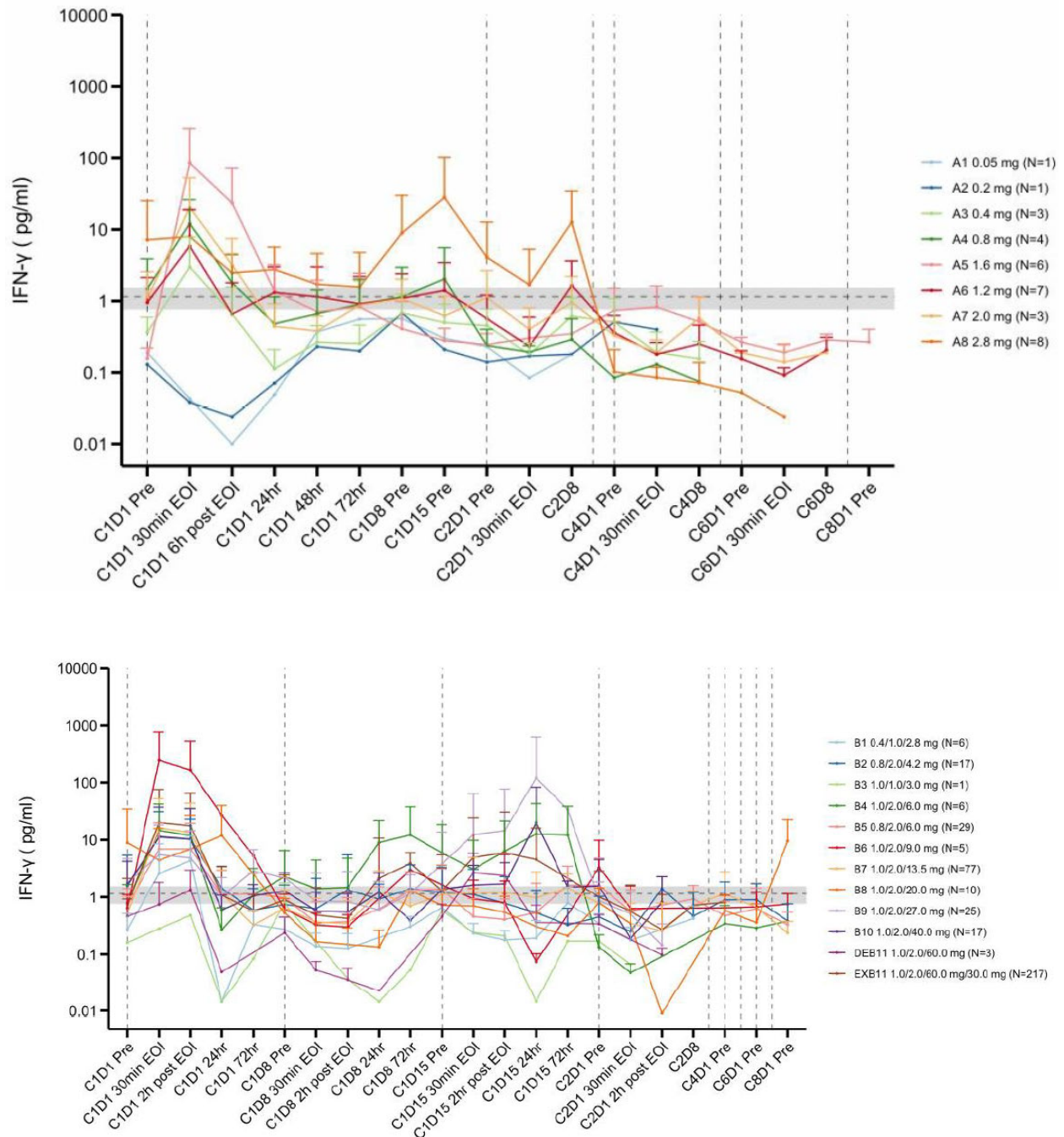
Applicant's Position

To support dosing recommendation for this BLA, the Applicant also developed the exposure-response (ER) relationship for pharmacodynamic biomarkers such as interferon-gamma (IFN- γ) and IL-6 in study GO29781. The IFN- γ and IL-6 were selected as the primary pharmacodynamic (PD) biomarkers of interest for the purpose of E-R characterization as a proximal marker for target engagement as it is produced by T-cells upon activation. As shown in Figure 50, a rapid but transient increase in IFN- γ was observed early after the initial drug administration (i.e., within 30 minutes after the end of infusion) and elevated IFN- γ levels were detected up to 6 hours post end of infusion but then returned to baseline levels by 24 hours. Similar trend was also observed for IL-6 (Figure 53).

As shown in Figure 51 and Figure 52, there is no apparent dose-response relationship between ROmax and PD biomarker- interferon-gamma (IFN- γ). No exposure-dependent increases were observed following later cycles of dose administration. Similar to ER analysis for IFN- γ , the ER relationship highlighted in Figure 54 and Figure 55 for IL-6 demonstrates that maximum change in the Log₂-transformed IL-6 concentration (Log₂-IL-6,CFBLmax) tended to increase modestly with increasing ROmax within the mosunetuzumab dose range evaluated following a Cycle 1, Day 1 dose. However, the E-R relationship following the Cycle 1, Day 15 loading dose ("3rd Dose") remained relatively flat, even with higher exposures achieved with the 60 mg loading dose. Beyond the third dose in later cycles, no apparent exposure-dependent IL-6 increases were observed following mosunetuzumab administration.

This time- and repeat dose-dependent shift (i.e., reduction) in IFN- γ / IL-6 ER relationship was consistent with the clinical mitigation of acute cytokine release from T cells upon repeated ascending dosing of mosunetuzumab. IL-6 is an established and generally recognized upstream marker of CRS. Hence, interpretations of IL-6 E-R data in this response continue to support the effectiveness of the proposed registration 1/2/60/30 mg mosunetuzumab Cycle 1 step-up dosing for mitigating acute cytokine-driven toxicities, where mosunetuzumab IV monotherapy is administered with escalating Cycle 1 Day 1 (C1D1), C1D8, and C1D15 dose levels, followed by 30 mg q3w dosing on Day 1 of subsequent cycles.

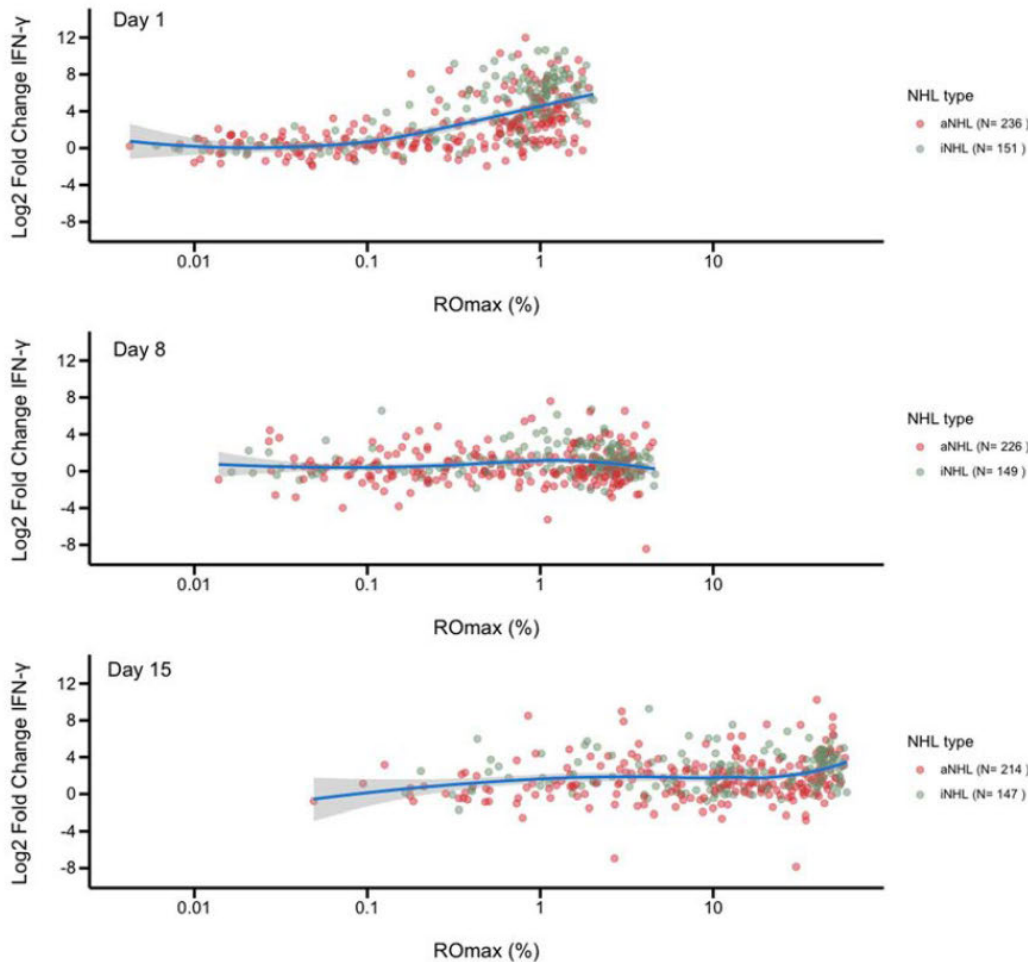
Figure 50: Arithmetic Mean (+SD) of Plasma IFN- γ Concentration vs. Nominal Time and Categorical Time Texts Following IV Administrations of Mosunetuzumab in R/R NHL



Source: Applicant's Exposure Response Analysis Report (ER-1112127), Figure 1 and Figure 2.

Figure 51: Exposure-Response Relationships Between Mosunetuzumab ROmax and Plasma IFN-r (Log2-IFN-γ,CFBLmax) Modulations Following Cycle 1 Step-up Dose Administrations on

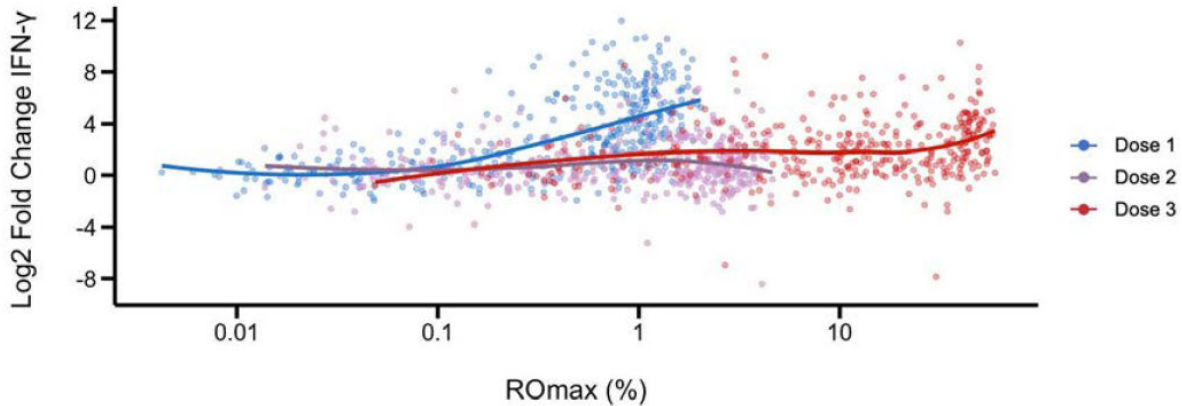
Day 1 (1st Dose), Day 8 (2nd Dose), and Day 15 (3rd Dose) in R/R NHL Patients (GO29781; Group B; Colored by Histology)



aNHL = aggressive Non-Hodgkin Lymphoma histologies (e.g., Diffused Large B-Cell Lymphoma [DLBCL], transformed follicular lymphoma [trFL], Mantle Cell Lymphoma [MCL], Richter's Transformation, transformed Marginal Zone Lymphoma [trMZL]); iNHL = indolent Non-Hodgkin Lymphoma histologies (e.g., Follicular Lymphoma, Marginal Zone Lymphoma [MZL], Small Lymphocytic Lymphoma [SLL]); RO_{max} (%) = model-predicted maximum CD20 receptor occupancy ($RO\%$) for the dose interval; Solid blue lines represent the LOESS regression; Gray shaded area represent 90% confidence interval; Red circles represent the Log2 maximal fold change IFN- γ at corresponding RO_{max} level for aNHL patients; Green circles represent the Log2 maximal fold change IFN- γ at corresponding RO_{max} level for iNHL patients; Note that the x-range of each curve represents the available data range as a result of 1) the underlying R and/or G level and 2) the dose range tested (i.e., Day 1 dose from 0.4 to 1 mg; Day 8 dose from 1 to 2 mg; Day 15 dose from 2.8 to 60 mg).

Source: Applicant's Exposure Response Analysis Report (ER-1112127), Figure 4.

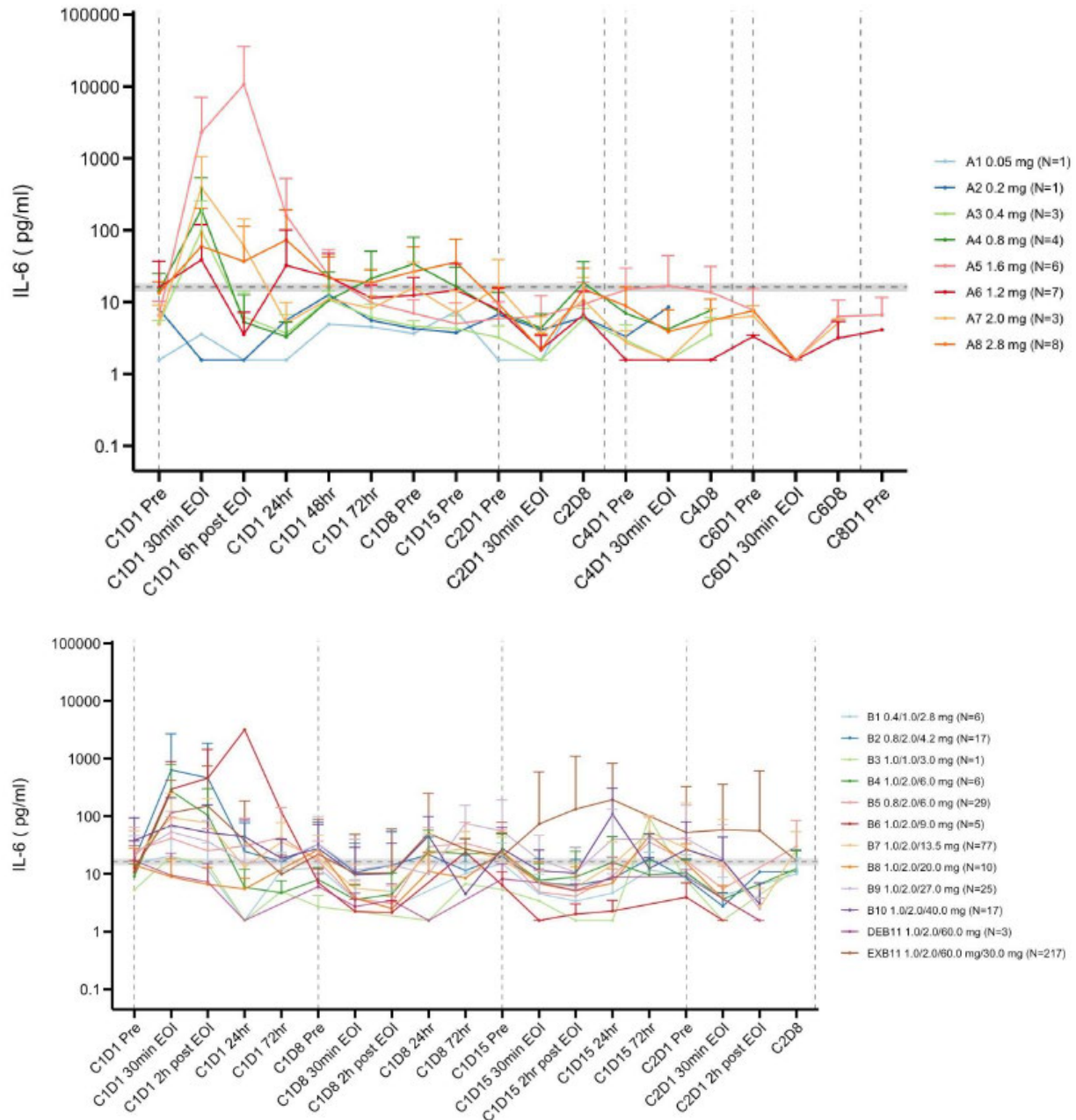
Figure 52: Overlay of Exposure-Response Relationships Between Mosunetuzumab RO_{max} and Plasma IFN- γ (Log₂- IFN- γ CFBL) Modulations Following Cycle 1 Step-up Dose Administrations on Day 1 (1st Dose), Day 8 (2nd Dose), and Day 15 (3rd Dose) in R/R NHL Patients (GO29781; Group B; Colored by Dose)



RO_{max} (%) = model-predicted maximum CD20 receptor occupancy for each Dose number and corresponding time interval; Blue solid line and blue circles represent the LOESS regression and the Log₂ maximal fold change IFN- γ at corresponding RO_{max} level for NHL patients at the 1st dose; Purple solid line and purple circles represent the LOESS regression and the Log₂ maximal fold change IFN- γ at corresponding RO_{max} level for NHL patients at the 2nd dose; Red solid line and red circles represent the LOESS regression and the Log₂ maximal fold change IFN- γ at corresponding RO_{max} level for NHL patients at the 3rd dose; Note that the x-range of each curve represents the available data range as a result of 1) the underlying R and/or G level and 2) the dose range tested (i.e., Day 1 dose from 0.4 to 1 mg; Day 8 dose from 1 to 2 mg; Day 15 dose from 2.8 to 60 mg).

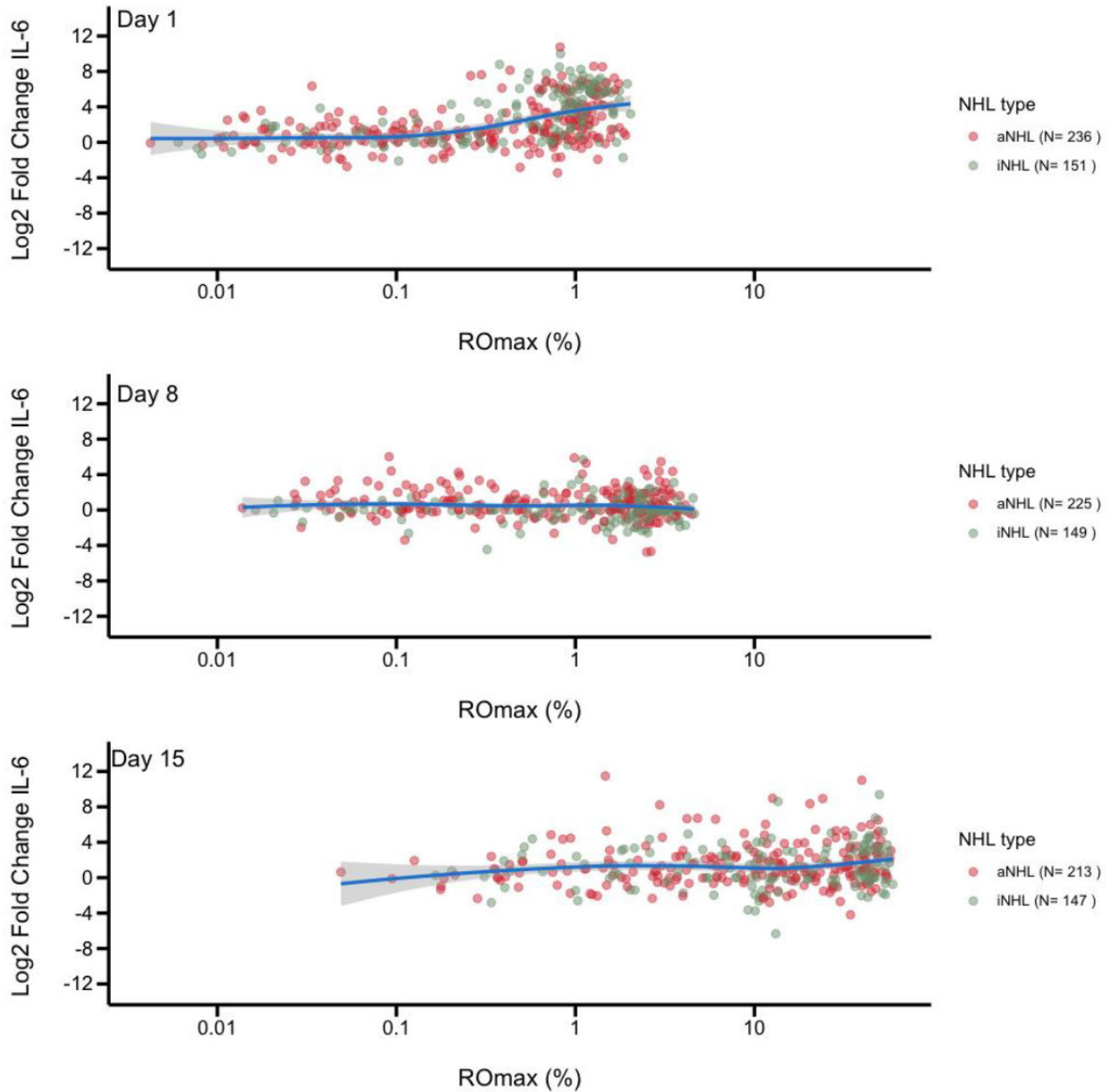
Source: Applicant's Exposure Response Analysis Report (ER-1112127), Figure 5.

Figure 53: Plasma cytokine IL-6 Concentration vs. Time Profiles



Source: Response to FDA request for information, SN#0039, Figure 8.1 and Figure 8.2

Figure 54: Exposure-Response Relationships Between Mosunetuzumab ROmax and Plasma IL-6 (Log2-IL-6,CFBLmax) Modulations Following Cycle 1 Step-up Dose Administrations on Day 1 (1st Dose), Day 8 (2nd Dose), and Day 15 (3rd Dose) in R/R NHL Patients (GO29781; Group B; Colored by Histology, N=387)

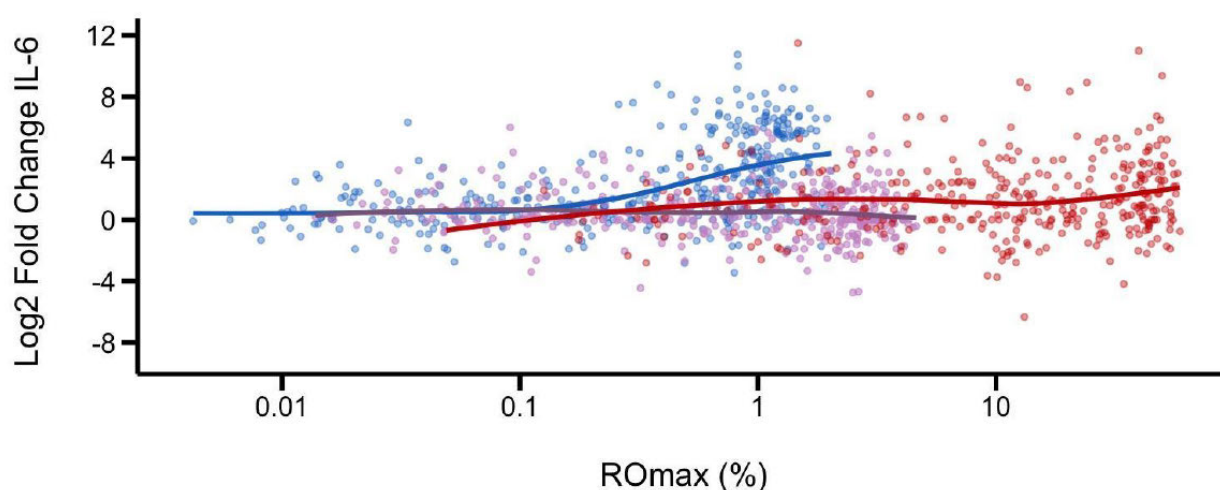


aNHL = aggressive Non-Hodgkin Lymphoma histologies (e.g., Diffuse Large B-Cell Lymphoma [DLBCL], transformed follicular lymphoma [trFL], Mantle Cell Lymphoma [MCL], Richter's Transformation, transformed Marginal Zone Lymphoma [trMZL]); iNHL = indolent Non-Hodgkin Lymphoma histologies (e.g., Follicular Lymphoma, Marginal Zone Lymphoma [MZL], Small Lymphocytic Lymphoma [SLL]); RO_{max} (%) = model-predicted maximum CD20 receptor occupancy (RO%) for the dose interval; Solid blue lines represent the LOESS regression; Gray shaded area represent 90% confidence interval; Red circles represent the Log2 maximal fold change IL-6 at

corresponding RO_{max} level for aNHL patients; Green circles represent the Log2 maximal fold change IL-6 at corresponding RO_{max} level for iNHL patients; Note that the x-range of each curve represents the available data range as a result of 1) the underlying R and/or G level and 2) the dose range tested (i.e., Day 1 dose from 0.4 to 1 mg; Day 8 dose from 1 to 2 mg; Day 15 dose from 2.8 to 60 mg).

Source: Response to FDA request for information, SN#0027, Figure 1

Figure 55: Overlay of Exposure-Response Relationships Between Mosunetuzumab RO_{max} and Plasma IL-6 (Log2- IL-6 CFBL) Modulations Following Cycle 1 Step-up Dose Administrations on Day 1 (1st Dose), Day 8 (2nd Dose), and Day 15 (3rd Dose) in R/R NHL Patients (GO29781; Group B; Colored by Dose, N=387)



RO_{max} (%) = model-predicted maximum CD20 receptor occupancy for each Dose number and corresponding time interval; Blue solid line and blue circles represent the LOESS regression and the Log2 maximal fold change IL-6 at corresponding RO_{max} level for NHL patients at the 1st dose; Purple solid line and purple circles represent the LOESS regression and the Log2 maximal fold change IL-6 at corresponding RO_{max} level for NHL patients at the 2nd dose; Red solid line and red circles represent the LOESS regression and the Log2 maximal fold change IL-6 at corresponding RO_{max} level for NHL patients at the 3rd dose; Note that the x-range of each curve represents the available data range as a result of 1) the underlying R and/or G level and 2) the dose range tested (i.e., Day 1 dose from 0.4 to 1 mg; Day 8 dose from 1 to 2 mg; Day 15 dose from 2.8 to 60 mg).

Source: Response to FDA request for information, SN#0027, Figure 2

The FDA's Assessment:

The Applicant's additional E-R analyses for pharmacodynamic biomarkers are acceptable and supportive.

20.4.6. Population PK Analysis for Tocilizumab and sIL-6R

20.4.6.1. Executive Summary

The FDA's Assessment:

In support of the use of tocilizumab (TCZ) for the management of CRS induced by anti- CD20 T cell engaging (TCE) bispecifics antibodies (i.e., mosunetuzumab and glofitamab), the Applicant submitted updated PopPK report with study GO29781 (Mosunetuzumab) and NP30179 (Glofitamab). The PopPK analyses were updated from the previous PK model of tocilizumab by using data from multiple studies in adult patients with RA and pediatric patients with sJIA and pcJIA.

The PK of tocilizumab was described by a two-compartment model with parallel linear and Michaelis-Menten elimination, and the first-order subcutaneous absorption. The PK of total sIL-6R was characterized by equations of quasisteady-state (QSS) approximation of the target-mediated drug disposition (TMDD) model. The final PopPK models for tocilizumab and sIL-6R were validated and the updated PopPK model is generally in line with the previous model.

The covariate analysis showed CRS had significant effects on tocilizumab PK parameters and sIL6R parameters. Different TCZ dosing regimen scenarios were simulated and the following TCZ dosing recommendations were shown to maintain TCZ concentrations below the "safety threshold" during the full treatment duration of mosunetuzumab or glofitamab treatment: Two consecutive TCZ doses at least 8 hours apart, maximum two doses per CRS event; maximum three TCZ doses within each time period of 6 weeks of mosunetuzumab or glofitamab.

The Applicant's PopPK analyses for tocilizumab and sIL-6R were verified by the reviewer, with no significant discordance identified. (b) (4)

(b) (4) Refer to section 8.2.4.1 for details.

20.4.6.2. PPK Assessment Summary for Tocilizumab and sIL-6R

The FDA's Assessment:

A total of 289 TCZ PK observations and 254 sIL-6R observations from 67 patients were available for the PK-sIL6R analysis. Of those, a total of 266 TCZ PK observations and 218 sIL-6R observations from 61 patients were used for model development (model development population) and the remaining ones were used for external evaluation of the model. The summary of the available data is presented in Table 67. Summary statistics of the continuous and categorical covariates that were evaluated in the PopPK analysis are shown in Table 68 and Table 69, respectively.

Table 67: Summary of Available Data: Number of Subjects (Observations), by Study

260

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

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.

BLA Multi-disciplinary Review and Evaluation {BLA 761263, Lunsumio (Mosunetuzumab)}

Study	Model Development Data Set			All Data		
	All	Tocilizumab	sIL6R	All	Tocilizumab	sIL6R
GO29781	16(98)	16(52)	14(46)	16(98)	16(52)	14(46)
NP30179	45(386)	45(214)	41(172)	46(408)	46(224)	42(184)
GO40515	-	-	-	3(18)	2(4)	3(14)
GO40516	-	-	-	1(10)	1(5)	1(5)
GO40554	-	-	-	1(9)	1(4)	1(5)
Total	61 (484)	61 (266)	55 (218)	67 (543)	66 (289)	61 (254)

Source file: 178_sampleSummary.csv, 178msf_sampleSummary.csv (CRS_DiagnosticPlots.R)

Source: Applicant's Population PK Report (poppk-1114219), Table 3.

Table 68: Summary of Continuous Covariates in PPK Analysis

Covariate	Units	Mean (SD)			Median [Range]		
		GO29781	NP30179	Total	GO29781	NP30179	Total
N		16	45	61	16	45	61
AGE	years	63.8 (10.1)	62.7 (13.8)	63 (12.8)	62 [54-87]	66 [30-85]	64 [30-87]
WT	kg	84.4 (15.6)	72.6 (12.9)	75.7 (14.5)	81.4 [66.2-128]	71.4 [53-114]	73.8 [53-128]
BSA	m ²	2 (0.23)	1.84 (0.181)	1.88 (0.205)	2.03 [1.58-2.44]	1.81 [1.47-2.3]	1.83 [1.47-2.44]
BMI	kg/m ²	27.8 (5.13)	24.9 (4.33)	25.6 (4.65)	26.3 [22.4-39.2]	24.7 [18.2-38.8]	24.9 [18.2-39.2]
CRCLN	mL/min /1.73m ²	90.1 (30.5)	79.6 (24.4)	82.4 (26.3)	84.3 [44.5-147]	77.1 [33.4-155]	78.6 [33.4-155]
ALB	g/L	32.4 (6.31)	33.3 (6.25)	33.1 (6.22)	34 [17-39]	34 [20-46]	34 [17-46]
PROT	g/L	54.3 (7.78)	58.5 (6.49)	57.4 (7.04)	55 [36-67]	58 [45-73]	57 [36-73]
SIL6R	ng/mL	43.2 (26.5)	35.7 (20.1)	37.2 (21)	33.2 [24.4-82]	33.4 [20.3-103]	33.4 [20.3-103]
FERRITIN	pmol/L	2350 (3390)	1280 (1220)	1590 (2120)	1520 [103-14100]	846 [89.9-5560]	924 [89.9-14100]
CRP	mg/L	114 (102)	94.6 (96.2)	99.8 (97.2)	99.4 [3.4-332]	50 [4-446]	60.8 [3.4-446]
SCRT	µmol/L	80.3 (26.4)	82.6 (24.3)	82 (24.7)	73.8 [46.9-126]	75.2 [45-158]	75.2 [45-158]
HDL	mmol/L	1.5 (0)	1.24 (0.42)	1.31 (0.378)	1.5 [1.5-1.5]	1.32 [0.465-2.5]	1.5 [0.465-2.5]
log(IL6) ^a	log (ng/L)	5.64 (0.615)	6.48 (1.84)	6.29 (1.67)	5.66 [4.95-6.6]	7.06 [2.39-9.83]	6.26 [2.39-9.83]
IL6	ng/L	332 (235)	2410 (4710)	1940 (4210)	287 [141-736]	1160 [10.9-18600]	545 [10.9-18600]

SD=standard deviation

Source file: ContCovMean.csv, ContCovMedian.csv (CRS_ReportPlots.R)

Source: Applicant's Population PK Report (poppk-1114219), Table 4.

Table 69: Summary of Categorical Covariates: Number (Percent) of Subjects in PPK Analysis

Covariate	Level	Total (N=61)	Study GO29781 (N=16)	Study NP30179 (N=45)
Group	1 = Glofitamab	39 (63.9%)	-	39 (86.7%)
	2 = Glofitamab + Obinutuzumab	6 (9.8%)	-	6 (13.3%)
	3 = Mosunetuzumab	16 (26.2%)	16 (100%)	-
SEX	0 = female	17 (27.9%)	3 (18.8%)	14 (31.1%)
	1 = male	44 (72.1%)	13 (81.2%)	31 (68.9%)
RACE	1=White	53 (86.9%)	15 (93.8%)	38 (84.4%)
	2=Black	1 (1.6%)	1 (6.2%)	-
	3=Asian	1 (1.6%)	-	1 (2.2%)
	Unknown	6 (9.8%)	-	6 (13.3%)
Ethnicity	1= Hispanic or Latino	1 (1.6%)	-	1 (2.2%)
	2 = Not Hispanic or Latino	54 (88.5%)	16 (100%)	38 (84.4%)
	Missing	6 (9.8%)	-	6 (13.3%)
Grade of the first CRS	Missing	1 (1.6%)	1 (6.2%)	-
	1	8 (13.1%)	3 (18.8%)	5 (11.1%)
	2	39 (63.9%)	8 (50%)	31 (68.9%)
	3	9 (14.8%)	3 (18.8%)	6 (13.3%)
	4	4 (6.6%)	1 (6.2%)	3 (6.7%)
Maximum Grade of CRS	Missing	1 (1.6%)	1 (6.2%)	-
	1	7 (11.5%)	2 (12.5%)	5 (11.1%)
	2	39 (63.9%)	8 (50%)	31 (68.9%)
	3	10 (16.4%)	4 (25%)	6 (13.3%)
	4	4 (6.6%)	1 (6.2%)	3 (6.7%)

Source file: CatCov.csv (CRS_ReportPlots.R)

Source: Applicant's Population PK Report (poppk-1114219), Table 5.

The serum concentration-time course of tocilizumab following single and multiple IV administrations in adult patients with CRS was accurately described by a two compartment pharmacokinetic model with parallel linear and Michaelis-Menten elimination. The final PK model parameter estimates and the corresponding 95% confidence intervals (CIs) for TCZ and sIL-6R are presented in Table 70. The goodness-of-fit plots for the final PK model are presented in Figure 56. The prediction corrected visual predictive check (pcVPC) based on all data (Figure 57) illustrated the prediction percentiles and corresponding 95% CI of simulated concentrations overlaid on the observed TCZ and sIL-6R concentrations and the corresponding 5th and 95th percentiles. CRS had significant effects on tocilizumab PK parameters and sIL6R parameters. Specifically, linear clearance in patients with CRS grade 2 or higher was on average 60% (95% CI: 25-103%) higher than in patients with RA. Elimination rate of bound sIL-6R, was 109% (95% CI: 80-142%) higher in patients with CRS than in patients with RA. Degradation rate of free (unbound) sIL-6R was 76% (95% CI: 64-89%) higher in patients with CRS than in patients with RA. The CRS effect on VC was relatively minor (15% increase, 95% CI:

3-28%). Inter-compartment clearance Q was 3.59 times higher in patients with CRS than in patients with RA (95% CI: from 3.11 to 4.14 times higher).

Table 70: Parameter Estimates of the Tocilizumab Population PK-sIL6R Model 178

Parameter	Estimate	%RSE	95%CI	Variability	Shrinkage	
CL (L/day)	exp(θ_1)	0.211	1.03	0.207 ; 0.215		
V _c (L)	exp(θ_2)	3.36	1.09	3.29 ; 3.44		
V _p (L)	exp(θ_3)	3.29	1.53	3.19 ; 3.39		
Q (L/day)	exp(θ_4)	0.392	1.36	0.381 ; 0.402		
V _M (mg/L/day)	exp(θ_5)	2.31	0.972	2.26 ; 2.35		
K _M (mcg/mL)	exp(θ_6)	0.414	1.96	0.398 ; 0.43		
k _a (1/day)	exp(θ_7)	0.209	2.61	0.199 ; 0.22		
F _{SC}	exp(θ_8)	0.710	2.35	0.678 ; 0.744		
CL _{WT} , Q _{WT}	θ_9	0.502	3.07	0.472 ; 0.532		
V _{C,WT} , V _{P,WT}	θ_{10}	0.750	1.79	0.723 ; 0.776		
CL _{HDL}	θ_{11}	-0.252	9.17	-0.298 ; -0.207		
V _{ALB}	θ_{12}	-0.526	9.85	-0.627 ; -0.424		
V _{PROT}	θ_{13}	0.562	13.8	0.41 ; 0.714		
V _{M,CRCLN}	θ_{14}	0.357	5.41	0.319 ; 0.395		
k _{a,AGE}	θ_{15}	-0.354	7.78	-0.408 ; -0.3		
k _{a, NA25220}	exp(θ_{16})	0.807	3.54	0.753 ; 0.865		
F _{SC,SJT3}	θ_{17}	0.692	2.78	0.654 ; 0.73		
σ_{SDL}	θ_{18}	0.999	2.98	0.94 ; 1.06		
σ_{SDH}	θ_{19}	0.117	2.06	0.112 ; 0.122		
σ_{SD50}	θ_{20}	2.19	5.37	1.96 ; 2.42		
CL _{maturation}	θ_{21}	0.262	40.4	0.0542 ; 0.469		
t _{1/2,matnr} (years)	θ_{22}	2.44	52.5	-0.0684 ; 4.95		
F _{SC, Age50} (years)	θ_{23}	12.0	29.6	5.05 ; 19.0		
sBASE	exp(θ_{24})	47.6	9.6	39.4 ; 57.4		
k _{int}	exp(θ_{25})	0.0731	0.507	0.0724 ; 0.0738		
k _{deg}	exp(θ_{26})	1.34	0.432	1.33 ; 1.35		
K _{SS}	exp(θ_{27})	0.241	1.5	0.234 ; 0.248		
k _{int,sBASE}	θ_{28}	0.193	7.75	0.164 ; 0.222		
k _{deg,sBASE}	θ_{29}	-0.528	2.29	-0.551 ; -0.504		
k _{deg,WT}	θ_{30}	-0.0781	9.87	-0.0932 ; -0.063		
ω^2_{CL}	$\Omega(1,1)$	0.0673	4.58	0.0612 ; 0.0733	CV=25.9%	18.8%
ω^2_{VC}	$\Omega(2,2)$	0.0398	5.93	0.0351 ; 0.0444	CV=19.9%	23.4%
R $\omega^2_{VC\omega_{VP}}$	$\Omega(2,3)$	0.0345	9.36	0.0282 ; 0.0409	R=0.434	
ω^2_{VP}	$\Omega(3,3)$	0.159	4.53	0.145 ; 0.173	CV=39.9%	21.0%
ω^2_Q	$\Omega(4,4)$	0.01	Fixed		CV=10.0%	73.5%
ω^2_{VM}	$\Omega(5,5)$	0.01	Fixed		CV=10.0%	51.5%
ω^2_{KM}	$\Omega(6,6)$	0.01	Fixed		CV=10.0%	82.8%
ω^2_{ka}	$\Omega(7,7)$	0.205	6.77	0.178 ; 0.233	CV=45.3%	23.1%
ω^2_{FSC}	$\Omega(8,8)$	0.00879	19	0.00552 ; 0.0121	CV=9.4%	52.3%
ω^2_{sBASE}	$\Omega(9,9)$	0.381	15.2	0.268 ; 0.494	CV=61.7%	
$\omega^2_{k_{int}}$	$\Omega(10,10)$	0.0186	6.36	0.0163 ; 0.0209	CV=13.6%	26.6%
$\omega^2_{k_{deg}}$	$\Omega(11,11)$	0.013	5.59	0.0116 ; 0.0144	CV=11.4%	26.3%
ω^2_{KSS}	$\Omega(12,12)$	0.0994	8.62	0.0826 ; 0.116	CV=31.5%	40.9%
$\omega^2_{EPS,TCZ}$	$\Omega(13,13)$	0.128	3.88	0.118 ; 0.137	CV=35.7%	3.6%
$\omega^2_{EPS,sIL6R}$	$\Omega(14,14)$	0.354	3.12	0.332 ; 0.375	CV=59.5%	-4.1%
σ^2_{TCZ}	$\Sigma(1,1)$	1	Fixed		CV=100%	4.4%
σ^2_{sIL6R}	$\Sigma(2,2)$	0.015	3.41	0.014 ; 0.016	CV=12.2%	1.4%

PE: Parameter Estimate; SE: Standard Error; RSE: Relative Standard Error, RSE=100·abs(SE/PE); 95% CI: 95% confidence interval; SD: Standard Deviation; CV: coefficient of variation, CV = 100*SD %.

Source file: 142saemFSC4ParEst.csv of [1]

$CL=CL_{RA} \cdot CL_{CRS,males,grade>1}$; $V_C=V_{C,RA} \cdot V_{C,CRS,males} \cdot V_{C,GO29781}$; $V_P=V_{P,RA} \cdot V_{P,CRS,males} \cdot V_{P,GO29781}$;
 $k_{int}=k_{int,RA} \cdot k_{int,CRS}$; $k_{deg}=k_{deg,RA} \cdot k_{deg,CRS}$, where CL_{RA} , $V_{C,RA}$, $V_{P,RA}$, $k_{int,RA}$, and $k_{deg,RA}$ are parameter estimates for patients with RA described by Table 2.

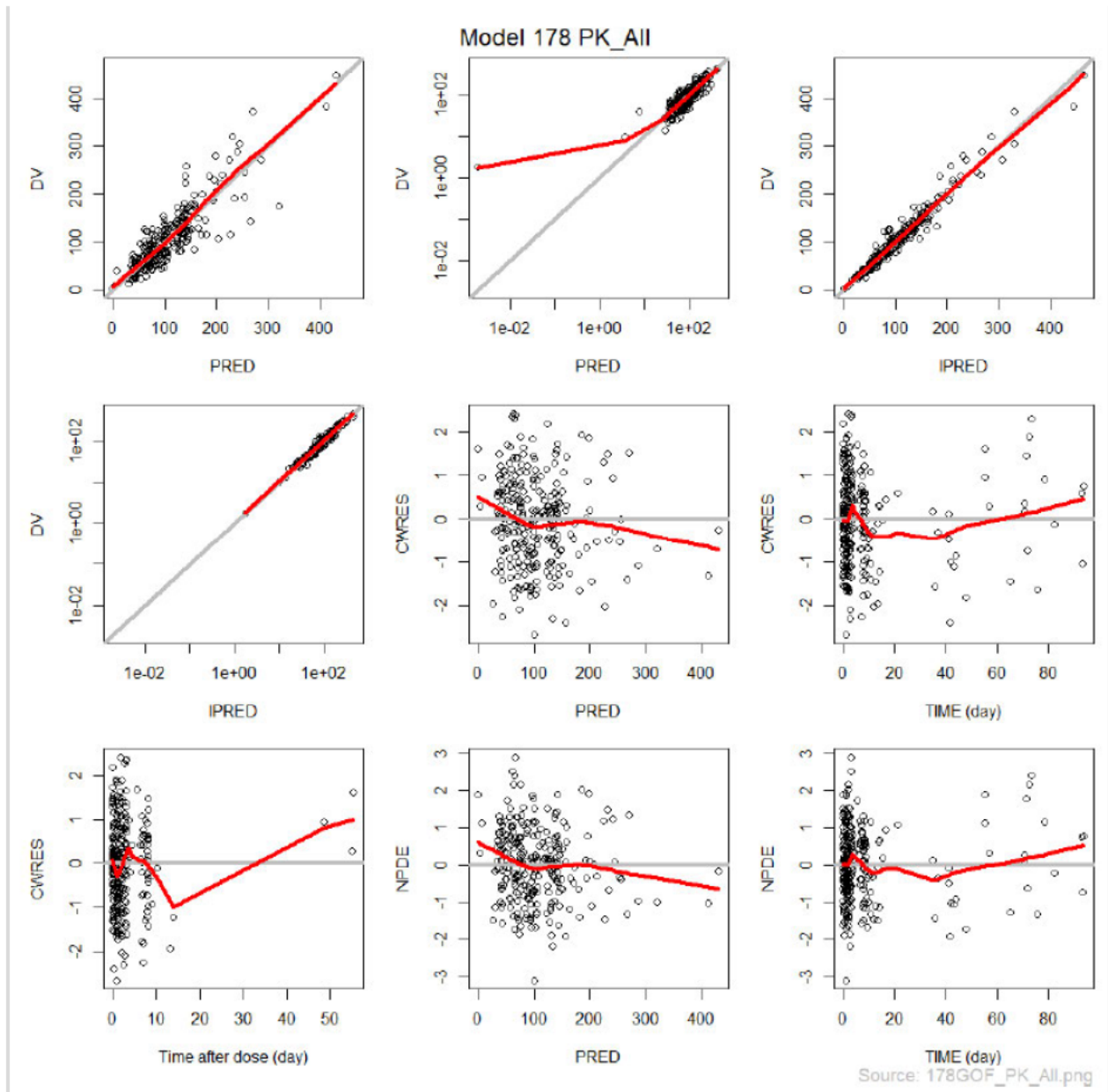
Parameter	Estimate	%RSE	95%CI	Variability	Shrinkage	
V_{ALB}	θ_{12}	0	Fixed			
V_{PROT}	θ_{13}	0	Fixed			
sBASE	$\exp(\theta_{24})$	29.4	11.2	23.6 ; 36.7		
$CL_{CRS,grade>1}$	$\exp(\theta_{31})$	1.60	12.4	1.25 ; 2.03		
$V_{C,CRS}=V_{P,CRS}$	$\exp(\theta_{32})$	1.15	5.49	1.03 ; 1.28		
Q_{CRS}	$\exp(\theta_{33})$	3.59	7.34	3.11 ; 4.14		
$k_{int,CRS}$	$\exp(\theta_{34})$	2.09	7.51	1.8 ; 2.42		
$K_{deg,CRS}$	$\exp(\theta_{35})$	1.76	3.74	1.64 ; 1.89		
ω^2_{CL}	$\Omega(1,1)$	0.291	49.0	0.0114 ; 0.57	CV=53.9%	18.30%
$\omega^2_{VC,VP}$	$\Omega(2,2)$	0.0681	23.6	0.0367 ; 0.0996	CV=26.1%	5.70%
ω^2_{sBASE}	$\Omega(9,9)$	0.381	Fixed		CV=61.7%	-9.8%
ω^2_{kdeg}	$\Omega(11,11)$	0.0130	Fixed		CV=11.4%	20.6%
$\omega^2_{EPS,TCZ}$	$\Omega(13,13)$	0.128	Fixed		CV=35.7%	45.0%
$\omega^2_{EPS,sIL6R}$	$\Omega(14,14)$	0.354	Fixed		CV=59.5%	27.2%
σ^2_{TCZ}	$\Sigma(1,1)$	1	Fixed		-	17.8%
σ^2_{sIL6R}	$\Sigma(2,2)$	0.015	Fixed		CV=12.2%	6.7%

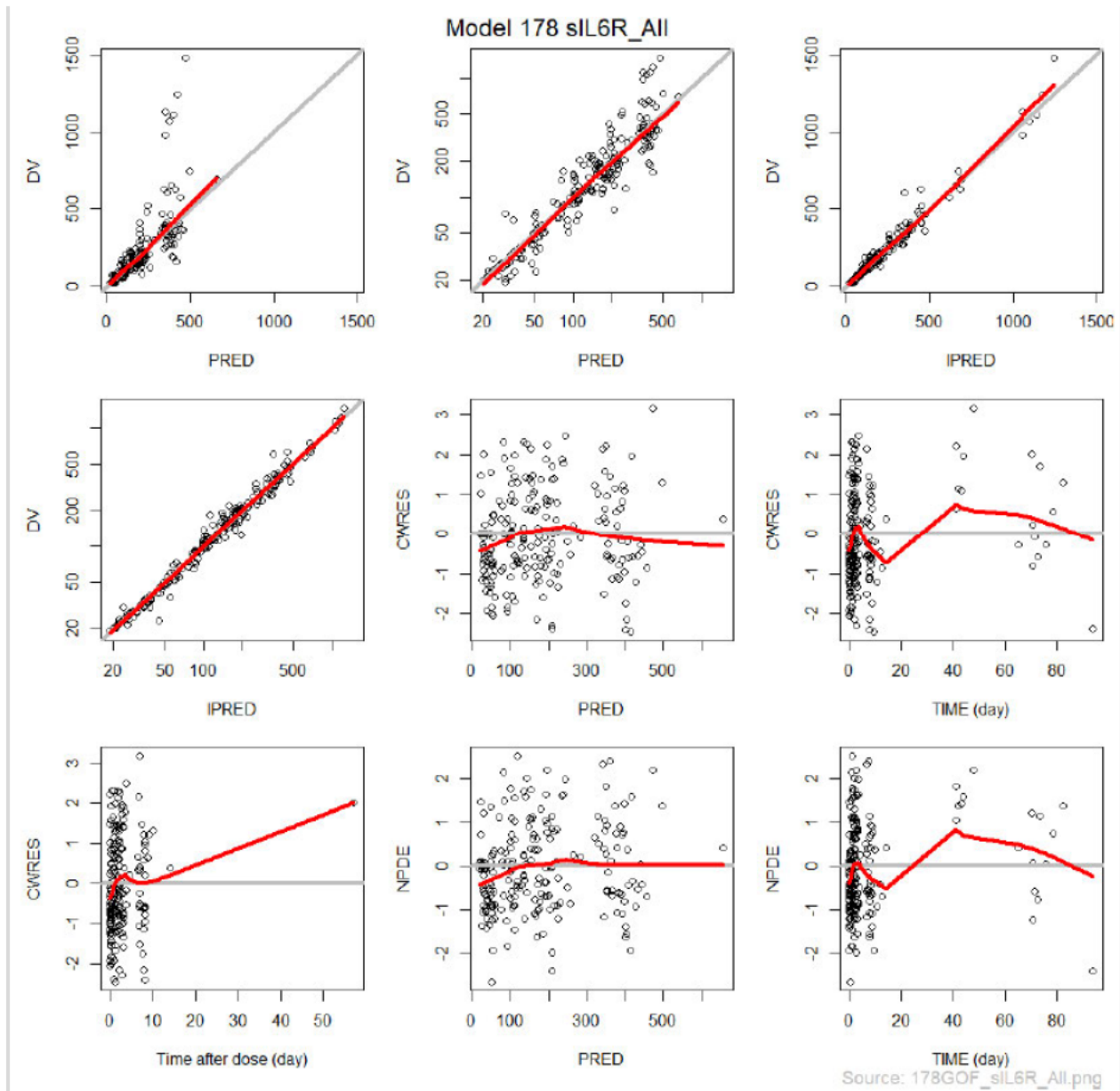
PE: Parameter Estimate; SE: Standard Error; RSE: Relative Standard Error, $RSE=100 \cdot \text{abs}(SE/PE)$; 95% CI: 95% confidence interval; SD: Standard Deviation; CV: coefficient of variation, $CV = 100 \cdot SD \%$.

Source file: 178ParEst.esv (CRS_DiagnosticPlots.R)

Source: Applicant's Population PK Report (poppk-1114219), Table 2 and Table 8.

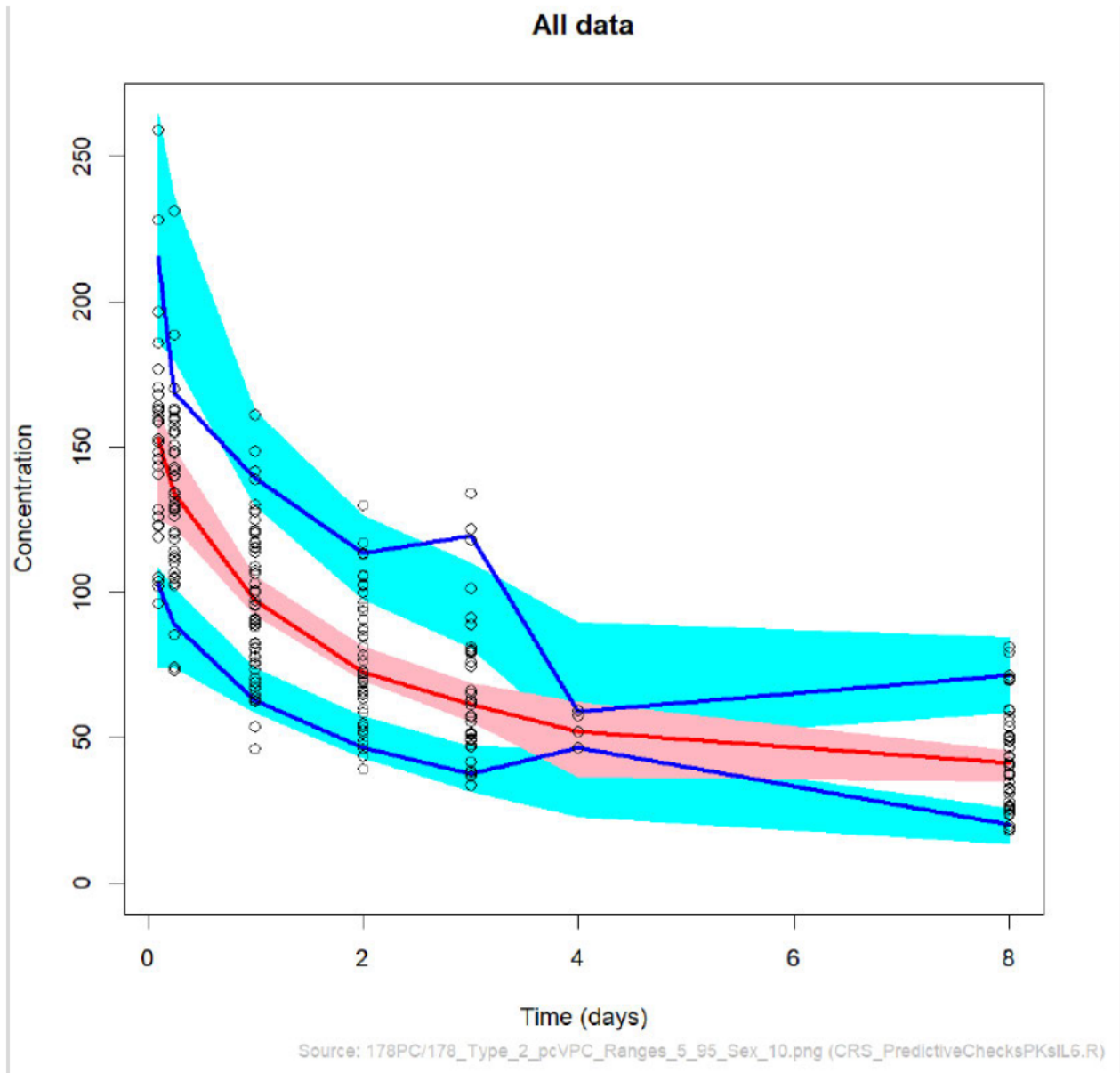
Figure 56: Goodness of Fit for Final Model: Tocilizumab and sIL-6R

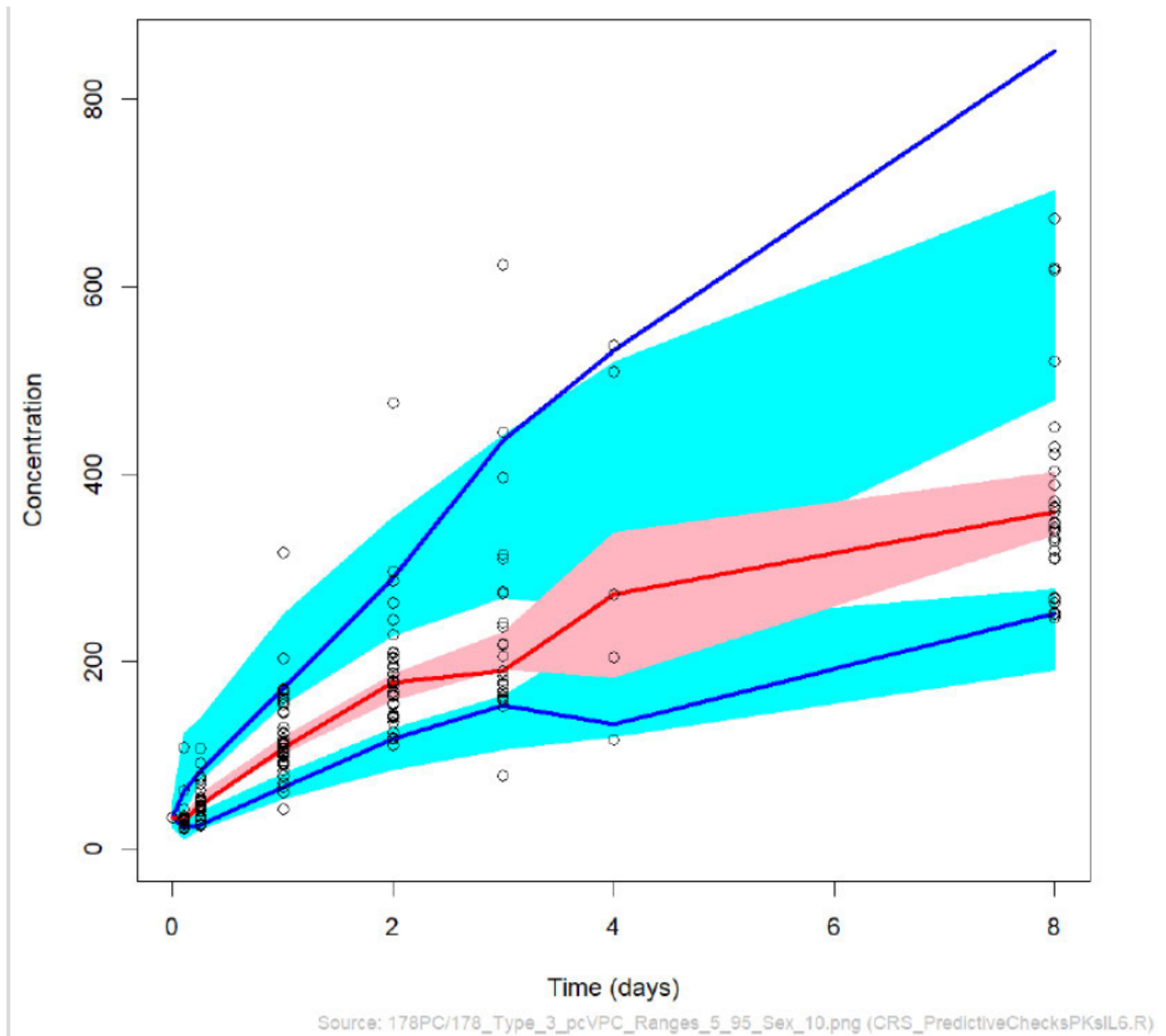




Source: Applicant's Population PK Report (popk-1114219), Figure 37 and Figure 38.

Figure 57: Prediction-Corrected Visual Predictive Check for Final Model: Tocilizumab (upper) and siL-6R (lower)

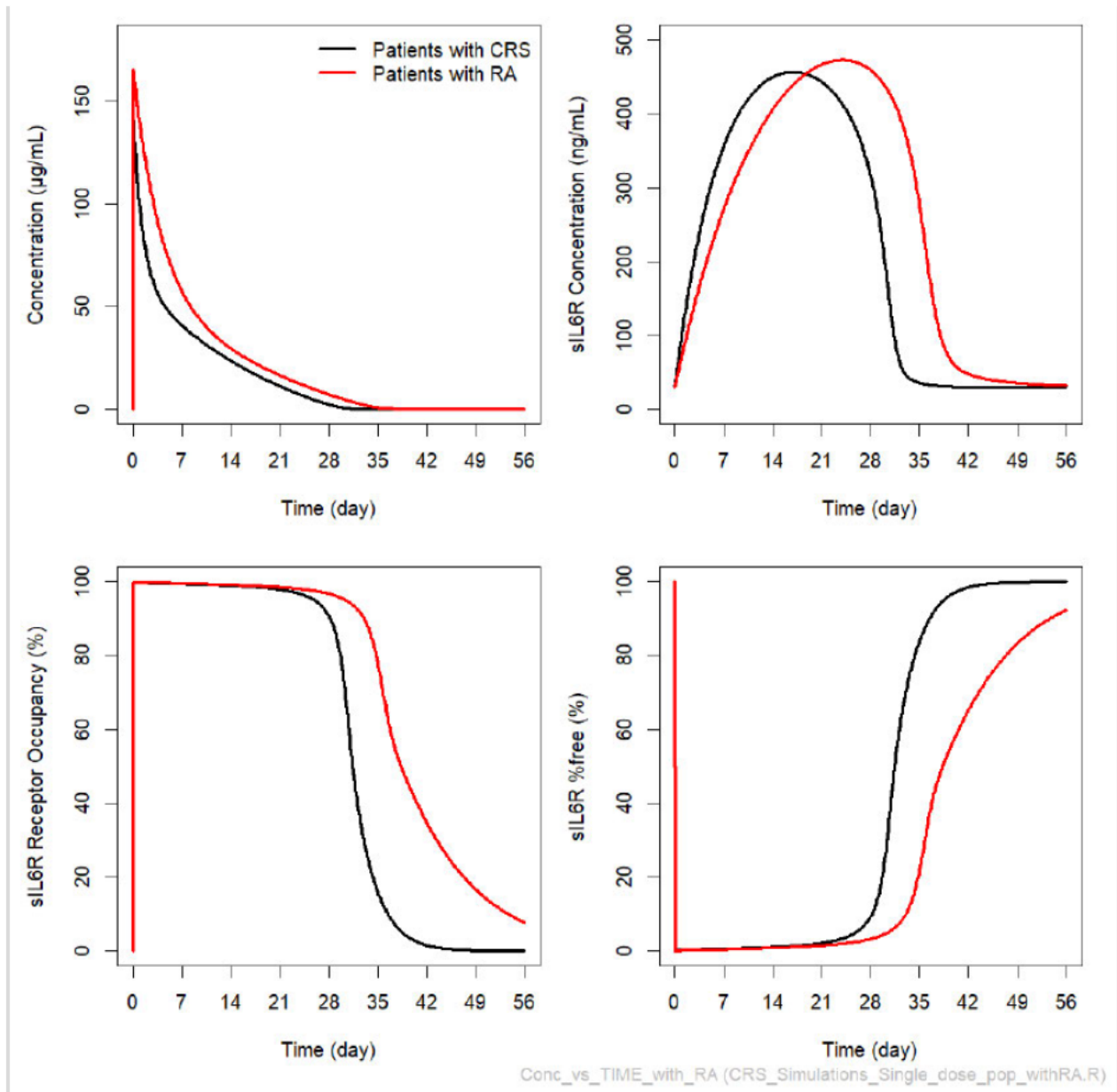




Source: Applicant's Population PK Report (poppk-1114219), Figure 78 and Figure 83.

Population predictions of final Model for the single 8 mg/kg dose are shown in Figure 58, and the patients with CRS had slightly lower exposure (C_{max} and AUC) than patients with RA, for patients with CRS, more than 90% sIL6R receptor occupancy was maintained for a median of 30.1 days (range 13.8 - 55.1 days) following a single 8 mg/kg dose.

Figure 58: Population Predictions of Final Model for a Typical Patient following Administration of Single 8 mg/kg IV Dose, by Disease



Source: Applicant's Population PK Report (poppk-1114219), Figure 112.

Various dosing scenarios described in Table 71 were investigated to formulate clinical rules for tocilizumab administration in patients with CRS. The distributions of maximum concentrations predicted by the model for these scenarios are presented in Figure 59. Model-based simulations indicated that up to two consecutive TCZ doses at least 8 hours apart per CRS event and maximum three TCZ doses within each time period of 6 weeks of mosunetuzumab or glofitamab allow to maintain the TCZ concentrations below the "safety threshold" used by FDA to determine the TCZ dose recommendation to manage CRS during CAR-T therapy.

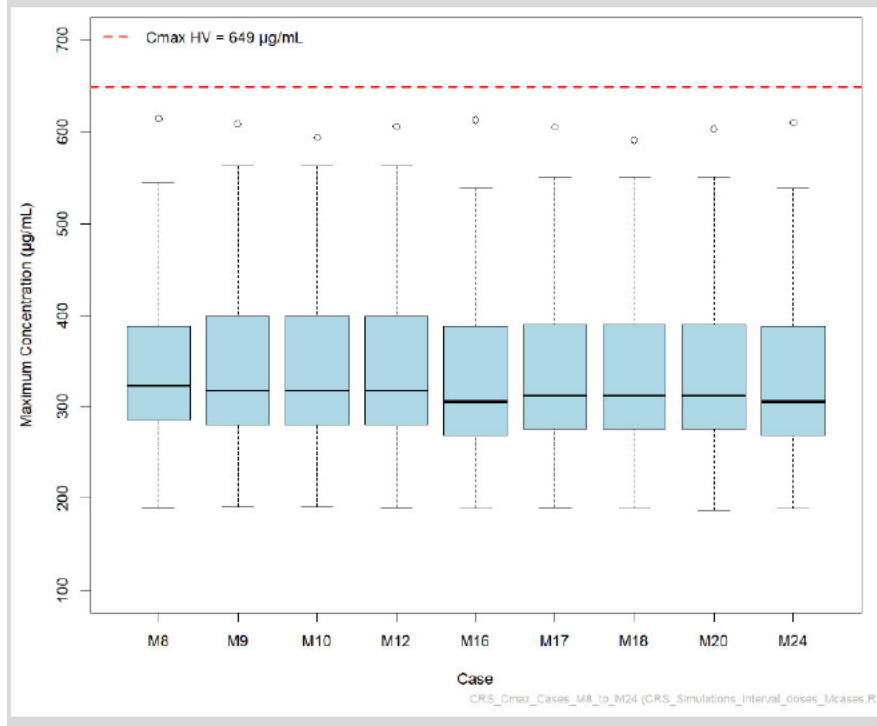
Table 71: Simulation Scenarios for Tocilizumab Administration: Number of Tocilizumab Doses Administered 8 Hours apart to Mitigate CRS

C1 - C8: treatment cycle.

Scenario	C1			C2	C3	C4	C5	C6	C7	C8
	Day 0	Day 7	Day 14	Day 21	Day 42	Day 63	Day 84	Day 105	Day 126	Day 147
M8	0	0	1	2	1	2	1	2	1	2
M9	0	0	2	1	2	1	2	1	2	1
M10	0	0	2	1	2	1	2	1	1	2
M12	0	0	2	1	2	1	1	2	1	2
M16	0	0	2	1	1	2	1	2	1	2
M17	0	1	1	1	2	1	2	1	2	1
M18	0	1	1	1	2	1	2	1	1	2
M20	0	1	1	1	2	1	1	2	1	2
M24	0	1	1	1	1	2	1	2	1	2

Source: Applicant’s Population PK Report (poppk-1114219), Table 9.

Figure 59: Individual Predictions of Maximum Concentrations for Patients from the Analysis Dataset following Simulation Scenarios



All Patients Threshold (649 µg/mL) used by FDA for assessing a safe TCZ dose regimen for CAR-T cell therapy. It is the highest TCZ concentration measured in Study BP19461 for which Roche/GNE has safety data.

Source: Applicant's Population PK Report (poppk-1114219), Figure 117.

In general, the Applicant's PopPK analyses for tocilizumab and sIL-6R are considered acceptable.

20.4.7. Physiologically Based Pharmacokinetic Analyses Review

Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's physiologically based pharmacokinetic (PBPK) analyses to assess the drug-drug interaction (DDI) potential of mosunetuzumab with CYP3A sensitive substrates midazolam and simvastatin and duration of the potential effects.

(b) (4)

The Division of Pharmacometrics has reviewed the PBPK analyses report (report 1110241), the response to FDA's information requests submitted on August 22nd (seq 0039, 20220822-response), and the modeling supporting files to conclude that

- The Applicant's PBPK analyses are inadequate (b) (4)
- Based on the reviewer's evaluation of available clinical data in the literature, the magnitude of effect of mosunetuzumab administration on CYP3A activity is expected to be (b) (4) to that observed in rheumatoid arthritis (RA) patients, 1.5 to 2.4-fold increase in the exposure of sensitive CYP3A substrates. CYP3A activity is estimated to take approximately (b) (4) after Cycle 2 mosunetuzumab administration to return to the (b) (4)% of its baseline.

Background

Mosunetuzumab (BTCT4465A, RO7030816) is a full-length, humanized immunoglobulin G 1 (IgG1), CD3/CD20 bispecific antibody in development for the treatment of adult patients with relapsed or refractory follicular lymphoma (R/R FL) who have received at least two prior systemic therapies. Mosunetuzumab is proposed to be administered for 8 cycles for patients who achieve a complete response, and for 17 cycles for patients who achieve partial response or have stable disease in response to the treatment. Mosunetuzumab is given every 3 weeks for the treatment duration, in which the antibody is administered via IV infusion at 1-, 2- and 60-mg on Day 1, 8 and 15 of Cycle 1 (C1D1, C1D8, C1D15), respectively, at 60-mg on Day 1 of Cycle 2 (C2D1), and at 30-mg on Day 1 of Cycle 3 and subsequent cycles.

Mosunetuzumab acts by recruitment of effector T-cells via CD3 to engage with target CD20-expressing B cells, leading to T-cell activation and T-cell mediated B cell cytolysis in a target- and dose-dependent manner (20220822-response). Cytokines including interleukin 6 (IL-6) are known to modulate CYP activities in humans. Mosunetuzumab treatment induced transient elevation of cytokines such as IL-6. This review focused on whether the Applicant's PBPK modeling is adequate to predict the magnitude and duration of drug interaction effects of mosunetuzumab on CYP3A activity via IL-6 elevation.

Methods

All simulations were performed using the PK/PD Profiles mode in the Simcyp® Simulator (Version 17, Certara, Sheffield, UK). Schemes of the PBPK simulation strategy are shown in Figure 60, which summarizes the model development and verification of the IL-6 PBPK model, and model applications in assessing the effect of IL-6 elevation on midazolam pharmacokinetics.

(b) (4)

Is PBPK Prediction Adequate to Address the Concern of Potential Effect of Mosunetuzumab on CYP substrates?

No, PBPK analyses are considered inadequate to evaluate drug interaction potential of mosunetuzumab and duration of its effect on CYP3A substrates because exposure-response relationships between cytokines and CYP3A activity in human have not been established. The reviewer's assessment of the PBPK analyses is detailed below.

1. Uncertainty about in-vitro-in-vivo extrapolation of IL-6 suppression data

Currently, an exposure-response relationship between plasma IL-6 levels and change in CYP3A activity in humans has not been established. (b) (4)

(b) (4)

(b) (4)

2. *The ability of PBPK modeling to predict the time course of the effect of IL-6 on CYP3A activity has not been established*

In response to FDA's information request (seq 0039, 20220822-response), the Applicant simulated the duration of drug interaction with the CYP3A substrate midazolam caused by IL-6 elevation following mosunetuzumab treatment (1/2/60 mg at C1D1, C1D8, C1D15, and 60 mg at C2D1) (Figure 62), and concluded

(b) (4)

(b) (4)

(b) (4). The FDA did not agree with this proposal. To date, the time course of the effects of cytokine release caused by antibody treatment on CYP enzyme activity in non-RA patients has not been studied. Therefore, the ability of PBPK modeling to predict the time course of the effect of IL-6 on CYP3A activity cannot be assessed.

(b) (4)

(b) (4)

(b) (4). The Applicant's PBPK modeling may not capture the time course of recovery from the suppression effect triggered by mosunetuzumab administration.

(b) (4)

Source: Reviewer's analysis

3. Potential underprediction of CYP3A suppression

The in vitro CYP3A suppression parameters ($E_{\min}/EC_{50}$, Table 73), used to simulate interactions between tocilizumab and simvastatin and between sarilumab and midazolam in RA patients, were applied to simulate the interaction with midazolam following mosunetuzumab administration in Cycle 1.

(b) (4)

(b) (4)

4. Potential effects of other factors on CYP3A cannot be ruled out

In the PBPK report, the Applicant focused on predicting the effect of IL-6 on midazolam PK. The Applicant's rationale is that CYP3A was reported to be the enzyme most sensitive to cytokine-mediated suppression, and IL-6 was the most potent suppressor among the cytokines tested in vitro. In addition, the evidence for the impact of other cytokines on CYP activity is inconclusive and often confounded by the coexistence of significant level of IL-6 (Chen et al 2022).

(b) (4)

Conclusions

The proposed (b) (4) cannot be supported by the PBPK analyses, which are considered inadequate due to lack of the established exposure-response relationships between cytokines and CYP3A activity in human. The effect of mosunetuzumab administration on CYP3A activity is expected to be (b) (4) to that observed in RA patients, and CYP3A activity is estimated to take approximately (b) (4) (b) (4) after Cycle 2 mosunetuzumab administration to return to the (b) (4) % of its baseline.

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

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11. Chen et al. PBPK modelling to predict drug-biologic interactions with cytokine modulators: Are these relevant and is IL-6 enough? Drug Metab Dispos. 2022; doi: 10.1124/dmd.122.000926.
12. Aitken A and Morgan ET. Gene-specific effects of inflammatory cytokines on cytochrome P450 2C, 2B6 and 3A4 mRNA levels in human hepatocytes. Drug Metab Dispos. 2007 Sep;35(9):1687-93.

(b) (4)

20.5. FDA Grouped Preferred Terms

The FDA's Assessment:

The FDA used the following grouped preferred terms in the review of safety for this application.

Table 75: FDA Table of Grouped Preferred Terms

FDA Grouped PT	Included	Excluded
Abdominal pain	Abdominal discomfort, abdominal pain lower, abdominal pain upper	Abdominal distention
Chest pain	Chest discomfort, chest pain	
Colitis	Colitis, enterocolitis bacterial	
Cough	Cough, productive cough, upper airway cough syndrome	
Dyspnea	Dyspnea, dyspnea exertional	
Edema	Fluid overload, generalized edema, edema, peripheral edema, peripheral swelling, pulmonary edema, swelling face	Eye edema, localized edema, swelling
Fatigue	Asthenia, fatigue, lethargy	

Hemolytic anemia	Hemolysis, Hemolytic anemia	
Hemorrhage	Catheter site hemorrhage, epistaxis, hematuria	Hemorrhage intracranial
Lower respiratory tract infection	Bronchitis, eosinophilic bronchitis, lower respiratory tract infection	
Musculoskeletal pain	Back pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain	Arthralgia, arthritis, musculoskeletal chest pain
Nonmelanoma skin cancer	Basal cell carcinoma, Bowen's disease	
Peripheral neuropathy	Burning sensation, dysaesthesia, hyperaesthesia, hypoaesthesia, neuralgia, paraesthesia, peripheral neuropathy, peripheral motor neuropathy, peripheral sensory neuropathy	
Pneumonia	Pneumocystis jirovecii pneumonia, pneumonia, pneumonia mycoplasma, pneumonia staphylococcal	
Rash	Dermatitis, dermatitis acneiform, dermatitis contact, erythema, exfoliative rash, palmer erythema, palmar-plantar erythrodysesthesia, rash erythematous, rash macular, rash maculopapular, rash morbilliform, rash pustular, rash pruritic, rash pustular,	Dermatitis exfoliative
Renal insufficiency	Acute kidney injury, azotemia, blood creatinine increased, renal impairment	
Sepsis	Bacteremia, sepsis, septic shock, Staphylococcal bacteremia	
Thrombocytopenia	Platelet count decreased, thrombocytopenia	
Thrombosis	Deep vein thrombosis, device related thrombosis, mesenteric vein thrombosis, pulmonary	

	embolism, thrombosis	
Transaminase elevation	Alanine aminotransferase increase, aspartate aminotransferase increase, hepatic enzyme increased, hepatic function abnormal, hypertransaminasemia, transaminases increased	
Upper respiratory tract infection	Nasopharyngitis, pharyngitis, rhinovirus infection, sinusitis, upper respiratory tract infection	
Xerosis	Dry eye, dry mouth, dry skin	

Multi-Disciplinary Review Signature Page

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Miao Zhao, PhD	OCP/DCPI	Sections: 6, 19.4	Select one: ☐ Authored ☐ Approved
	Signature: Miao Zhao -S Date: 2022.12.01 10:31: 4 -0500 Digitally signed by Miao Zhao -S			
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: 2022.12.01 09:35:47 -0500			
Pharmacometrics Reviewer	Yuzhuo Pan, PhD	OCP/DPM	Sections: 6, 19.4	Select one: ☐ Authored ☐ Approved
	Signature: Yuzhuo Pan -S Date: 2022.12.01 09:46:25 -0500 Digitally signed by Yuzhuo Pan -S			
Pharmacometrics Team Leader	Jiang Liu, PhD	OCP/DPM	Sections: 6, 19.4	Select one: ☐ Authored ☐ Approved
	Signature: Jiang Liu -S Digitally signed by Jiang Liu -S Date: 2022.12.01 09:33:47 -0500			
PBPK Reviewer	Ying-Hong Wang, PhD	OCP/DPM	Sections: 6, 19.4	Select one: ☐ Authored ☐ Approved
	Signature: Ying-hong Wang -S Digitally signed by Ying-hong Wang -S Date: 2022.12.01 13:32:55 -0500			
PBPK Team Leader	Manuela Grimstein, PhD	OCP/DPM	Sections: 6, 19.4	Select one: ☐ Authored ☐ Approved
	Signature: Manuela D. Grimstein -S Digitally signed by Manuela D. Grimstein -S Date: 2022.12.01 11:22:57 -0500			
Statistical Reviewer	Xin Wang, PhD	OB/DBIX	Sections: 8	Select one: ☒ Authored ☐ Approved
	Signature: Xin Wang -S Date: 2022.12.01 17:14:08 -0500 Digitally signed by Xin Wang -S			
Statistical Team Leader	Lisa Rodriguez, MD	OB/DBIX	Sections: 8	Select one: ☐ Authored ☐ Approved
	Signature: Lisa R. Rodriguez -S Digitally signed by Lisa R. Rodriguez -S Date: 2022.12.01 17:27:53 -0500			

Safety Analyst	Shan Pradhan, MD	OOD	Sections: 2, 4, 7, 8, 9	Select one:
				Authored
				X Approved
Signature: ∞				
Non-Clinical Reviewer	Simon Williams, PhD	DHOT	Sections: 5	Select one:
				Authored
				X Approved
Signature: ~~Simon Williams -S~~ Digitally signed by Simon William Date: 2022.12.02 14:51:02 -05'00'				
Non-Clinical Team Leader	Brenda Gehrke, PhD	DHOT	Sections: 5	Select one:
				Authored
				X Approved
Signature: Brenda Gehrke -S Digitally signed by Brenda Gehrke -S Date: 2022.12.02 15:11:48 -05'00'				
Clinical Reviewer	Pamela Seam, MD	OOD/DHM2	Sections: All	Select one:
				Authored
				X Approved
Signature: ∞				
Associate Director for Labeling	Elizabeth Everhart, MSN, RN, ACNP	OOD	Sections: 11	Select one:
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				Approved
Signature: Elizabeth E. Everhart -S Digitally signed by Elizabeth E. Everhart -S Date: 2022.12.05 19:45:37 -05'00'				
Cross-Disciplinary Team Leader (CDTL)	Nicholas Richardson, DO, MPH	OOD/DHM2	Sections: All	Select one:
				Authored
				X Approved
Signature: ∞				
Division Director (DHOT)	Haleh Saber, PhD, MS	DHOT	Sections: All	Select one:
				Authored
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Signature: Haleh Saber -S Digitally signed by Haleh Saber -S Date: 2022.12.04 12:14:08 -05'00'				
Division Deputy Director (Statistics)	Lisa Rodriguez, PhD	OB/DBIX	Sections: All	Select one:
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Division Director (Statistics)	Mark Levenson, PhD	OB/DBIX	Sections: All	Select one:
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Division Director (OCP)	Brian Booth, PhD	OCP/DCPI	Sections: All	Select one: ☒ Authored ☐ X Approved
	Signature:  Brian P. Booth -S Digitally signed by Brian P. Booth -S Date: 2022.12.01 13:44:47 -0500			
Division Director (Clinical)	Nicole Gormley, PhD	OOD/DHM2	Sections: All	Select one: ☐ Authored ☒ X Approved
	Signature: 			
Office Director (Clinical)	Mark Theoret, MD	OOD/DHM2	Sections: All	Select one: ☐ Authored ☒ X Approved
	Signature: 			
DCPI = Division of Cancer Pharmacology I  ☒ DPM = Division of Pharmacometrics  ☐ OB = Office of Biostatistics  DBIX = Division of Biometrics IX  OOD = Office of Oncologic Diseases  DHM2 = Division of Hematologic Malignancies II 				

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