CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761344Orig1s000

MULTI-DISCIPLINE REVIEW

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

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: FDA review was conducted in conjunction with other regulatory authorities under Project Orbis. FDA collaborated with Brazilian Health Regulatory Agency (ANVISA), Health Canada (HC), Israel's Ministry of Health (IMoH), and United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA). While the conclusions and recommendations expressed herein reflect FDA's completed review of the application, the applications may still be under review at the other regulatory agencies.

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	BLA
Application Number(s)	BLA 761344
Priority or Standard	Priority
Submit Date(s)	October 12, 2023
Received Date(s)	October 12, 2023
PDUFA Goal Date	June 12, 2024
Division/Office	Division of Oncology 2/ Office of Oncologic Diseases
Review Completion Date	May 16, 2024
Established Name	Tarlatamab
(Proposed) Trade Name	IMDELLTRA
Pharmacologic Class	Delta-like Ligand 3-directed CD3 T-cell Engager
Code name	AMG 757
Applicant	Amgen, Inc. (Amgen)
Formulation(s)	Intravenous
Dosing Regimen	An initial dose of 1 mg on Day 1 followed by 10 mg on Days 8, 15, and every 2 weeks thereafter

Applicant Proposed Indication(s)/Population(s)	IMDELLTRA is indicated for the treatment of adult patients with advanced small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	IMDELLTRA is indicated for the treatment of adult patients with extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy

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Reviewers of Multi-Disciplinary Review and Evaluation

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Safety Analyst (if applicable)	Hua Zhou
Statistical Reviewer	Mengdie Yuan
Statistical Team Leader	Anup Amatya
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Cross-Disciplinary Team Leader	Amy Barone
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Division Director (OCP)	Nam Atiqur Rahman
Division Director (OB)	Shenghui Tang
Supervisory Associate Director (OOD)	Erin Larkins
Office Director (or designated signatory authority)	Paul Kluetz

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OSE/DEPI	Kate Gelperin (TL: Steven Bird)
OSE/DMEPA	Janine Stewart (TL: Ashleigh Lowery) Colleen Little (TL: Farinaz Beniesfahany) David Kaland, Graca Dores (TL: Afrouz Nayernama) Latonia Ford (TL: Janet Higgins)
OSE/DRISK	Ingrid Chapman (TL: Naomi Boston)
Other	Laurie Buonaccorsi (TL: Barbara Fuller)

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

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OBP DP Reviewer	Odile Engel
OBP Labeling Reviewer	Jennifer Kim
Immunogenicity Reviewer	Yanyan Cao
Immunogenicity TL	Ian McWilliams
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OPMA Facilities Reviewer	Michael Shanks
OPMA DS/DP Micro Reviewer	Maria Reyes Candauchacon

OPRO=Office of Program and Regulatory Compliance
RBPM= Regulatory Business Process Manage
OBP= Office of Biotechnology Products
DS= Drug Substance
DP= Drug Product
OPMA= Office of Pharmaceutical Manufacturing Assessment

Project Orbis #112 Partners

Health Canada (HC; Canada) Review team	
Director	(b) (6)
Clinical Manager (Clinical Evaluation Division – Oncology & Radiopharmaceuticals)	
Lead Clinical Reviewer	
Clinical Pharmacology Reviewer	
Non-clinical reviewer	
Biostatistics Reviewer	
Regulatory Affairs Supervisor	
Senior Regulatory Affairs Officer	
Risk Management Reviewer	
Quality Manager	
Leader Quality Reviewer	

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Brazil (ANVISA) Review team	(b) (6)
Clinical Assessor	
Quality Assessor	
Regulatory Project Manager	

United Kingdom (MHRA) Review team	
Clinical Assessor	
Non-Clinical Assessor	
Quality Assessor	

Ministry of Health (MOH) Review team	
Clinical Assessor	
Quality Assessor	
Risk Management Reviewer	
Project Orbis coordinators	

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Glossary

ADA	antidrug antibodies
ADME	absorption, distribution, metabolism, excretion
AIC	akaike information criterion
ALT	alanine aminotransferase
AMQ	Amgen MedDRA query
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{last}	area under the curve from time of dosing to the last measurable concentration
BIC	bayesian information criterion
BICR	blinded independent central review
BiTE	bispecific T-cell engager
BLA	Biologics License Application
BOR	best overall response
BSC	best supportive care
BTSR	best tumor size response
C_0	calculated drug concentration at time 0 after IV bolus dose
C1q	complement component 1q
CD3	cluster of differentiation 3
CFR	Code of Federal Regulations
CKD	chronic kidney disease
CL	clearance
C_{max}	maximum observed concentation
COA	Clinical Outcome Assessment
CR	complete response
CSF	cerebral spinal fluid
CRP	C-reactive protein
CRS	cytokine release syndrome
CSR	clinical study report
CTCAE	common terminology criteria for adverse events
DCO	data cutoff
DCR	disease control rate
DLL3	delta-like ligand 3
DoR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
eCRF	electronic case report form

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eCTD	electronic common technical document
EMR	electronic medical record
EOI	events of interest
ER	exposure response
ES-SCLC	extensive-stage small cell lung cancer
Fc	fragment crystallizable
FcγR	Fc-gamma receptors
FcRn	neonatal Fc receptor complex
FDA	Food and Drug Administration
FIH	first-in-human
GCP	good clinical practice
G-CSF	granulocyte-colony stimulating factor
GD	gestation days
GT	grouped term
GLP	good laboratory practice
ICANS	immune effector cell-associated neurotoxicity syndrome
ICH	International Council for Harmonisation
IFN	interferon
IFN-γ	interferon gamma
IL	interleukin
INN	International Nonproprietary Name
IPD	important protocol deviation
IQR	inter-quartile range
ISS	Integrated Summary of Safety
ITT	intent to treat
IV	intravenous
K_D	equilibrium dissociation constant
MCP-1	monocyte chemoattractant protein-1
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
NDA	new drug application
NE	not estimable
NEPC	neuroendocrine prostate cancer
NME	new molecular entity
OCE	Oncology Center of Excellence
OCP	Office of Clinical Pharmacology
OFV	objective function value
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells

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PD-1	programmed cell death 1
PD-L1	programmed death ligand 1
PDX	patient-derived xenograft
PFS	progression-free survival
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PPK	population pharmacokinetics
PRO	patient reported outcome
Q2W	every 2 weeks
Q3W	every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
REMS	Risk Evaluation and Mitigation Strategies
RP2D	Recommended Phase 2 Dose
SAP	statistical analysis plan
SCE	Summary of Clinical Efficacy
SCLC	small cell lung cancer
SCS	Summary of Clinical Safety
SOI	start of infusion
SPR	surface plasmon resonance
TCR	T-cell receptor
TEAE	treatment-emergent adverse event
TK	toxicokinetics
TNF	tumor necrosis factor
TRAE	treatment-related adverse event
ULN	upper limit of normal
US	United States

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1 Executive Summary

1.1. Product Introduction

Tarlatamab-dlle (herein referred to as tarlatamab) is a bispecific T-cell engager that binds to delta-like ligand 3 (DLL3) expressed on the surface of cells, including tumor cells, and CD3 expressed on the surface of T-cells. Tarlatamab causes T-cell activation, release of inflammatory cytokines and lysis of DLL3-expressing cells. Tarlatamab is a new molecular entity and is not currently approved in the United States or elsewhere.

In this biologics licensing application (BLA), Amgen's proposed indication for tarlatamab is "for the treatment of adult patients with advanced small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy."

The recommended dosing regimen for the proposed indication is an initial dose of tarlatamab of 1 mg on Day 1 followed by 10 mg on Days 8 and 15 and every 2 weeks thereafter.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The FDA review teams recommend accelerated approval of tarlatamab for the following indication: *Tarlatamab is indicated for the treatment of adult patients with extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy*.

The recommendation for accelerated approval, according to 21 CFR 314.510 Subpart H, is based on the results from Parts 1 and 2 of Study 20200491 (DeLLphi-301), an ongoing, multicenter, open-label, multi-cohort trial evaluating the efficacy and safety of tarlatamab as a single agent in adult patients with relapsed/refractory SCLC with disease progression after receiving previous treatment with platinum-based chemotherapy and at least one other line of prior therapy. The assessment of safety was also supported by results from Part 3 of Study 20200491 and from Study 20160323, an ongoing first-in-human (FIH), open-label, ascending, multiple dose study of tarlatamab in adult patients with advanced SCLC who have progressed or recurred after at least one platinum-based regimen.

The primary efficacy population consists of 99 patients enrolled in Parts 1 and 2 of Study 20200491 who received tarlatamab at the dosage proposed for marketing (initial dose of 1 mg of on Cycle 1 Day 1 followed by 10 mg on Days 8, 15, and every 2 weeks thereafter). Of the 99 patients, 73 patients (74%) had received prior anti-PD-(L)1 therapy; of these 73 patients, 58 (59%) received anti-PD-(L)1 therapy in combination with platinum-based chemotherapy in the

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first line setting. The confirmed blinded independent central review (BICR)-assessed overall response rate (ORR), as per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), was 40% (95% CI: 31%, 51%). The median duration of response (DoR) was 9.7 months (range 2.7 to 20.7+ months); 68% of responders had an observed DoR ≥6 months and 40% of responders had an observed DoR ≥12 months.

FDA considers response rate, supported by DoR, an appropriate early clinical endpoint for SCLC because it is a direct measure of the intervention; in the absence of therapy, tumors do not typically regress on their own. The observed ORR and DoR were clinically meaningful, and responses were observed across subgroups of patients with platinum-sensitive and platinum-refractory disease and across subgroups with various tumor DLL3 expression cut-offs.

Cytotoxic chemotherapies administered after disease has progressed on platinum-based chemotherapy are expected to have differential tumor response based on a patient's "sensitivity" to platinum-based chemotherapy, with very low response rates reported for patients with platinum resistant SCLC. Given this, efficacy has typically been assessed separately in subgroups of patients with platinum-sensitive or platinum-resistant SCLC; however, given the known mechanism of action of tarlatamab as a targeted agent that causes activation of the immune system, which differs from cytotoxic chemotherapy, platinum sensitivity is not expected to be a predictive factor for response to tarlatamab. With this caveat, it was still considered appropriate to evaluate ORR in these subgroups.

Among the 99 patients who received tarlatamab at the proposed dosage in Study 20200491, 69 patients had available data regarding platinum sensitivity status. In this subgroup of patients, ORR was 31% (95% CI: 18%, 47%) in 42 patients with platinum-sensitive SCLC (defined as ≥90 days after end of first line platinum therapy to date of progression) and 52% (95%: CI 32%, 71%) in 27 patients with platinum-resistant SCLC (defined as < 90 days after end of first line platinum therapy to date of progression). Although the ORR point estimates differ between these subgroups, the 95% confidence intervals overlap, and FDA considers that a true difference in efficacy based on platinum sensitivity status is unlikely with tarlatamab.

For this application, the proposed indication, SCLC with disease progression on or after platinum-based chemotherapy, differs from the population enrolled in Study 20200491, patients with SCLC with disease progression after receiving previous treatment with platinum-based chemotherapy and at least one other line of prior therapy. Overall, the ORR and DoR data from the primary efficacy population in Study 20200491, which enrolled a more heavily treated patient population (3rd line or greater), is greater than the ORR and DoR observed with topotecan, the only available therapy with traditional approval from the FDA for patients with SCLC previously treated with first-line chemotherapy (ORR of 24% in platinum-sensitive disease and 2-7% in platinum-resistant disease). Review of prior therapies in the primary efficacy population from Study 20200491 showed that 52% of patients received a topoisomerase I

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inhibitor as second-line therapy. Of the remaining patients, the grand majority (89%) received other second line therapies considered treatment options per U.S. standard of care. The ORR in the subgroups of patients who received prior topoisomerase I inhibitor and who did not receive prior topoisomerase I inhibitor (including and not including patients who received standard of care therapies) were generally consistent across subgroups and consistent with the ORR observed in the overall study population. Furthermore, it is not expected that treatment with additional therapies following platinum-based chemotherapy would increase the likelihood of response to tarlatamab relative to treatment with tarlatamab used as second-line therapy following platinum-based chemotherapy. In light of the observed results and particularly considering the ORR observed with tarlatamab in patients with platinum-resistant SCLC, which far exceeds ORR reported with standard of care therapies, the available data for tarlatamab supports the proposed indication for treatment of SCLC with disease progression on or after platinum-based chemotherapy.

Overall, the ORR and durable responses observed with tarlatamab in Study 20200491 are consistent with a meaningful advantage over available therapies for the proposed indication and provide substantial evidence of effectiveness and support a recommendation of accelerated approval for tarlatamab for the following indication: *treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy*.

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1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Lung cancer is the leading cause of cancer-related mortality in the US and worldwide (Siegel, 2023). Approximately 15% of lung cancers diagnosed are small cell lung cancer (American Cancer Society, 2024). The majority of patients with SCLC have extensive-stage SCLC (ES-SCLC) at presentation. Current first-line treatment for ES-SCLC generally consists of etoposide in combination with platinum chemotherapy and a programmed death ligand 1 (PD-L1) immune checkpoint inhibitor (atezolizumab or durvalumab). Although the response rate to initial treatment is high with ORR of 60-70%, nearly all patients relapse after initial therapy and the median overall survival from front-line ES-SCLC trials is approximately 12 to 13 months (Liu 2021, Paz-Ares 2022). The 5-year survival for ES-SCLC is less than 2% (Basumallik 2023). Depending on the interval between completion of chemotherapy and detection of relapse, treatment options include retreatment with a platinum-based regimen or use of single agent chemotherapy.

Topotecan is the only therapy with traditional approval in the US for patients with SCLC whose disease has progressed after first-line chemotherapy; the approved indication is for platinum-sensitive SCLC, with topotecan demonstrating an overall response rate (ORR) of 24% (95% CI: 16%, 32%) with a median duration of response (DoR) of 3.3 months. There is no therapy with traditional approval for patients with platinum-resistant SCLC. Lurbinectedin has received accelerated approval for the treatment of adult patients with metastatic SCLC whose disease has progressed on or after platinum-based chemotherapy based on an ORR as assessed by independent review committee of 30% (95% CI: 22%, 40%) with a median DoR of 5.1 months (95% CI: 4.9, 6.4). The ORR was 43% (95% CI 31%, 57%) in the platinum-sensitive subgroup and 13% (95% CI 5%, 27%) in the platinum-resistant subgroup. In addition to topotecan and lurbinectedin, other therapeutic options that are not FDA approved include taxanes, irinotecan, doxorubicin, gemcitabine, and temozolomide.

Tarlatamab is a bispecific delta-like ligand 3 (DLL3)-directed CD3 T-cell engager. Tarlatamab causes T-cell activation, production of inflammatory cytokines and release of cytotoxic proteins which results in redirected lysis of DLL3-expressing cells. Currently, tarlatamab is not approved in the US for any indication.

The evaluation of the efficacy of tarlatamab is based on results from Parts 1 and 2 of Study 20200491 (DeLLphi-301 trial), an ongoing, multicenter, open-label, multi-cohort trial evaluating the efficacy and safety of tarlatamab as a single agent in adult patients with

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relapsed/refractory SCLC with disease progression after receiving previous treatment with platinum-based chemotherapy and at least one other line of prior therapy. The assessment of safety was also supported by results from Part 3 of Study 20200491 and from Study 20160323, an ongoing first-in-human (FIH), open-label, ascending, multiple dose study of tarlatamab in adult patients with advanced SCLC who have progressed or recurred after at least one platinum-based regimen.

The primary efficacy population consists of 99 patients enrolled in Parts 1 and 2 of Study 20200491 who received tarlatamab at the dosage proposed for marketing (initial dose of 1 mg of on Cycle 1 Day 1 followed by 10 mg on Days 8, 15, and every 2 weeks thereafter). Of the 99 patients, 73 patients (74%) had received prior anti-PD-(L)1 therapy. Of these 73 patients, 58 (59%) received anti-PD-(L)1 therapy in combination with platinum-based chemotherapy in the first line setting. The confirmed blinded independent central review (BICR)-assessed ORR, as per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), was 40% (95% CI: 31%, 51%). The median duration of response (DoR) was 9.7 months (range 2.7 to 20.7+ months); 68% of responders had an observed DoR ≥6 months and 40% of responders had an observed DoR ≥12 months. The observed ORR and DoR were clinically meaningful, and responses were observed across subgroups of patients with platinum-sensitive and platinum-refractory disease and across subgroups with various DLL3 expression cut-offs.

Cytotoxic chemotherapies administered after SCLC has progressed on platinum-based chemotherapy are expected to have differential tumor response based on a patient's "sensitivity" to platinum-based chemotherapy, with very low response rates reported for patients with platinum-resistant SCLC. Given this, efficacy has typically been assessed separately in subgroups of patients with platinum-sensitive or platinum-resistant SCLC; however., given the known mechanism of action of tarlatamab as a targeted agent that causes activation of the immune system, which differs from cytotoxic chemotherapy, platinum sensitivity is not expected to be a predictive factor for response to tarlatamab. With this caveat, it was still considered appropriate to evaluate ORR in these subgroups.

Among the 99 patients who received tarlatamab at the proposed dosage in Study 20200491, 69 patients had available data regarding platinum sensitivity status. In this subgroup of patients, ORR was 31% (95% CI: 18%, 47%) in 42 patients with platinum-sensitive SCLC (defined as ≥90 days after end of first line platinum therapy to date of progression) and 52% (95%: CI 32%, 71%) in 27 patients with platinum-resistant SCLC (defined as < 90 days after end of first line platinum therapy to date of progression). Although the ORR point estimates differ between these subgroups, the 95% confidence intervals overlap, and FDA considers that a true difference in efficacy based on platinum sensitivity status is unlikely with tarlatamab.

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For this application, the proposed indication, SCLC with disease progression on or after platinum-based chemotherapy, differs from the population enrolled in Study 20200491, patients with SCLC with disease progression after receiving previous treatment with platinum-based chemotherapy and at least one other line of prior therapy. Overall, the ORR and DoR data from Study 20200491, which enrolled a more heavily treated patient population (3rd line or greater), is greater than the ORR and DoR observed with topotecan, the only available therapy with traditional approval from the FDA for patients with SCLC previously treated with first-line chemotherapy (ORR of 24% in platinum-sensitive disease and 2-7% in platinum-resistant disease). Review of prior therapies in of the primary efficacy population from Study 20200491 showed that 52% of patients received a topoisomerase I inhibitor as second line therapy. Of the remaining patients, the grand majority (89%) received second line therapies considered treatment options per U.S. standard of care. The ORR in the subgroups of patients who received prior topoisomerase I inhibitor and who did not receive prior topoisomerase I inhibitor (including and not including patients who received standard of care therapies), were generally consistent with the response rate observed for the overall study population. Furthermore, it is not expected that treatment with additional therapies following platinum-based chemotherapy would increase the likelihood of response to tarlatamab relative to treatment with tarlatamab used as second-line therapy following platinum-based chemotherapy. In light of the observed results and particularly considering the ORR observed with tarlatamab in patients with platinum-resistant SCLC, which far exceeds ORR reported with standard of care therapies, the available data for tarlatamab supports the proposed indication for treatment of SCLC with disease progression on or after platinum-based chemotherapy.

Of note, the primary efficacy population included no Black/African American patients and one Hispanic/Latino patient, which is an underrepresentation of the incidence of SCLC in these racial and ethnic minority groups. Given this, a postmarketing commitment (PMC) will be issued to provide further analyses from ongoing or planned clinical trials to further characterize the safety, efficacy and pharmacokinetics of tarlatamab in these patient populations.

The safety assessment for tarlatamab is primarily supported by a pooled safety population which included 187 patients from Study 20200491 and Study 20160323 with ES-SCLC who were treated with tarlatamab at the dosage proposed for marketing. The most common adverse reactions (≥20%) were cytokine release syndrome, fatigue, pyrexia, dysgeusia, decreased appetite, musculoskeletal pain, constipation, anemia, and nausea.

The key safety concerns for tarlatamab are cytokine release syndrome (CRS) and neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS), both of which will be included in a Boxed Warning in the USPI. Other safety concerns include hepatotoxicity, infections, cytopenias, and hypersensitivity. These safety concerns are addressed in the Warnings and Precautions and Dosage and

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Administration sections of the tarlatamab U.S. Prescribing Information (USPI), and additional mitigation strategies for CRS and neurologic toxicity, including ICANS, are discussed below. The observed safety profile is considered acceptable when assessed in the context of a life-threatening disease.

In the pooled safety population (n = 187), CRS occurred in 55% of patients treated with tarlatamab, including 34% Grade 1, 19% Grade 2, 1.1% Grade 3 and 0.5% Grade 4. Recurrent CRS occurred in 24% of tarlatamab-treated patients (18% Grade 1 and 6% Grade 2). Most events (43%) of CRS occurred after the first dose with 29% of patients experiencing any grade CRS after the second dose and 9% of patients experiencing CRS following the third dose or later. Following the Day 1, Day 8, Day 15 infusions, 16%, 4.3%, and 2.1% of patients experienced ≥ Grade 2 CRS, respectively. The median time to onset of all grade CRS from most recent dose of tarlatamab was 13.5 hours (range: 1 to 268 hours). The median time to onset of ≥ Grade 2 CRS from most recent dose of tarlatamab was 14.6 hours (range: 2 to 566 hours).

Neurologic toxicity including ICANS occurred in 47% of patients in the pooled safety population, including 10% Grade 3; no Grade 4 events were reported. The most frequent neurologic toxicities were headache (14%), peripheral neuropathy (7%), dizziness (7%), insomnia (6%), muscular weakness (3.7%), delirium (2.1%), syncope (1.6%) and neurotoxicity (1.1%). ICANS occurred in 9% of patients and recurrent ICANS occurred in 1.6% of patients. Most patients experienced ICANS following cycle 2 day 1 (24%). Following Day 1, Day 8, and Day 15 infusions, 0.5%, 0.5% and 3.7% of patients experienced ≥ Grade 2 ICANS, respectively. The median time to onset of ICANS from the first dose of tarlatamab was 29.5 days (range: 1 to 154 days). The median time to resolution of ICANS was 33 days (range: 1 to 93 days).

Per the protocol for Study 20200491, patients were hospitalized for 48 hours post tarlatamab infusion for Cycle 1 Day 1 and Cycle 1 Day 8 doses, except for patients in Part 3 of Study 20200491, who were hospitalized for 24 hours post tarlatamab infusion for Cycle 1 Day 1 and Cycle 1 Day 8 doses. Based on review of all currently available safety data, it was determined that monitoring of patients for 22 to 24 hours on Cycle 1 Day 1 and Cycle 1 Day 8 in an appropriate healthcare setting is acceptable to ensure safe use, and this recommendation is incorporated in labeling.

Based on our review, we have determined that the safety risks of tarlatamab can be adequately conveyed through labeling. The USPI will include Boxed Warnings to communicate the risks of CRS and neurologic toxicity, including ICANS. In addition, enhanced pharmacovigilance and a Dear Healthcare Provider letter are non-REMS adjuncts recommended to help convey these risks. A post-marketing requirement (PMR) will also be issued to conduct an integrated safety analysis of data from patients with extensive stage small cell lung cancer to further characterize the long-term incidence, severity, and outcome of the known serious risks of cytokine release syndrome, immune effector cell-associated

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neurotoxicity syndrome and neurologic toxicity. This postmarketing requirement is intended to provide additional safety information that is needed to support the safety of the product.

Overall, the ORR and durable responses observed with tarlatamab in Study 20200491 are consistent with a meaningful advantage over available therapies for the proposed indication. Tarlatamab has an acceptable safety profile when assessed in the context of this life-threatening disease and current available therapy. Based on these results, tarlatamab has a favorable risk-benefit profile in the context of a life-threatening disease with an unmet medical need, and the submitted evidence meets the statutory evidentiary standard for accelerated approval. The review team's regulatory recommendation is to grant tarlatamab accelerated approval for the following indication: *Treatment of adult patients with extensive-stage small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy.*

Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial, conducted as a PMR. The Applicant proposes to verify the clinical benefit of tarlatamab in the treatment of patients with SCLC who have disease progression on or after prior platinum-containing therapy, based on the results of an ongoing randomized, controlled trial, DeLLphi-304 (Study 20210004), comparing tarlatamab to investigator's choice standard of care therapy with a primary endpoint of overall survival (OS). The status, including current enrollment and appropriateness of the proposed completion date, of the post-marketing trial, Dellphi-304, was assessed during the review of this application and the trial was considered to be well underway.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Lung cancer is the leading cause of cancer-related mortality in the US and worldwide. Approximately 15% of lung cancers diagnosed are small cell lung cancer (SCLC). The majority of patients with SCLC have ES-SCLC at presentation. • Current first-line treatment for ES-SCLC is etoposide in combination with platinum chemotherapy and PD-L1 inhibitor therapy (atezolizumab or durvalumab) which is associated with a median overall survival of approximately 9-13 months.	ES-SCLC is a serious and life-threatening condition with poor survival.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Depending on the interval between completion of chemotherapy and detection of progression or recurrence, treatment options include retreatment with a platinum-based regimen (for patients with recurrence >6 months from last dose of platinum) or use of single-agent chemotherapy	
Current Treatment Options	• In the second-line setting, topotecan is the only available therapy with traditional FDA approval for patients with SCLC platinum-sensitive disease who have progressed at least 60 days after initiation of first-line chemotherapy; the approved indication is for platinum-sensitive SCLC with topotecan demonstrating an ORR of 24% (95% CI: 16%, 32%) with a median duration of response of 3.3 months • Based on data from single arm studies using the more standard cut-off of ≥90 days for platinum-sensitive vs. platinum-resistant, reported response rates ranged from 11-31% for patients with platinum-sensitive disease and 2-7% in patients with platinum-resistant disease • In addition, lurbinectedin has received accelerated approval for the treatment of adult patients with metastatic SCLC whose disease has progressed on or after platinum-based chemotherapy. In this setting, lurbinectedin demonstrated ORR as assessed by independent review committee of 30% (95% CI: 22%, 40%) with a median DoR of 5.1 months (95% CI: 4.9, 6.4) and 35% of patients having a DoR of ≥6 months. The ORR was	There is an unmet medical need for patients with ES-SCLC with progression after prior platinum-containing therapy, particularly in patients with platinum-resistant disease.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	43% (95% CI 31%, 57%) in the platinum-sensitive subgroup and 13% (95% CI 5%, 27%) in the platinum-resistant subgroup. • In addition to topotecan and lurbinectedin, other therapeutic options that are not FDA approved include taxanes, irinotecan, doxorubicin, gemcitabine, and temozolomide. • There is no therapy with traditional FDA approval for patients with platinum-resistant SCLC who have no response to or disease progression after first-line chemotherapy or for patients with SCLC after progression on two prior lines of therapy.	
Benefit	• The evaluation of efficacy of tarlatamab was based on results from Study 20200491 (DeLLphi-301), an ongoing, multicenter, open-label, multi-cohort trial evaluating the efficacy and safety of tarlatamab as a single agent in adult patients with relapsed/refractory SCLC with disease progression after receiving previous treatment with platinum-based chemotherapy and at least one other line of prior therapy. • The primary efficacy population consists of 99 patients enrolled in Parts 1 and 2 of Study 20200491 who received tarlatamab at the dosage proposed for marketing. Of the 99 patients, 73 patients (74%) had received prior anti-PD-(L)1 therapy. Of these 73 patients, 58 (59%) received anti-PD-(L)1 therapy in combination with platinum-based	In Study 20200491, tarlatamab administered to patients with relapsed/refractory SCLC who progressed on or after platinum-based chemotherapy and at least one other prior therapy demonstrated an ORR and DOR that was clinically meaningful and was also seen across most subgroups of patients including different DLL3 cutoffs. Review of subgroup data by prior therapy support the justification for tarlatamab use in an earlier line (after platinum-based chemotherapy) than what was studied. It is not expected that treatment with additional therapies following platinum-based chemotherapy would increase the likelihood of response to tarlatamab relative to treatment with tarlatamab used as second-line therapy

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	chemotherapy in the first line setting. The confirmed blinded independent central review (BICR) overall response rate (ORR), as per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) was 40% (95% CI: 31%, 51%). The median duration of response (DoR) was 9.7 months (range 2.7 to 20.7+ months); 68% of responders had an observed DoR ≥6 months and 40% of responders had an observed DoR ≥12 months. Review of investigator-assessed ORR and DoR did not show large differences compared to the BICR assessed efficacy data. • The observed ORR and DoR were clinically meaningful and responses were observed across subgroups of patients with platinum-sensitive and platinum-refractory disease and across subgroups with various DLL3 expression cut-offs. Among the 99 patients who received tarlatamab at the proposed dosage in Study 20200491, 69 patients had available data regarding platinum sensitivity. In this subgroup of patients, ORR was 31% (95% CI: 18%, 47%) in 42 patients with platinum-sensitive SCLC and 52% (95% CI: 32%, 71%) in 27 patients with platinum-resistant SCLC. • The proposed indication, SCLC with disease progression on or after platinum-based chemotherapy, differs from the population enrolled in Study 20200491, patients with SCLC with disease progression after receiving previous treatment with platinum-based chemotherapy and at least one other line of prior therapy. Overall, the ORR and DoR	following platinum-based chemotherapy. In light of the observed results and particularly considering the ORR observed with tarlatamab in patients with platinum-resistant SCLC, which far exceeds ORR reported with standard of care therapies, the available data for tarlatamab supports the proposed indication for treatment of SCLC with disease progression on or after platinum-based chemotherapy. FDA considers response rate supported by DoR an evaluable endpoint for SCLC because it is a direct measure of the intervention; in the absence of therapy, tumors do not typically regress on their own. With a favorable risk-benefit profile in the context of a life-threatening disease with an unmet medical need, the submitted evidence meets the statutory evidentiary standard for accelerated approval. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial, conducted as a PMR. The Applicant proposes to verify the clinical benefit of tarlatamab in the treatment of patients with SCLC who have disease progression on or after prior platinum-containing therapy, based on the results of an ongoing, randomized controlled trial, DeLLphi-304 (Study 20210004), comparing tarlatamab to investigator's choice standard of care

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	data from Study 20200491 which enrolled a more heavily treated patient population (3rd line or greater), is greater than the ORR and DoR observed with topotecan, the only available therapy with traditional approval from the FDA for patients with SCLC previously treated with first-line chemotherapy (ORR of 24% in platinum sensitive disease and 2-7% in platinum resistant disease [Topotecan USPI]). Review of prior therapies showed that a grand majority of patients received second line therapy considered treatment options per U.S. standard of care. The ORR in the subgroups of patients who received prior topoisomerase I inhibitors and who did not receive prior topoisomerase I inhibitors (including and not including patients who received standard of care therapies) were generally consistent across subgroups and with the response rate observed for the overall study population. • The primary efficacy population included no Black/African American patients and one Hispanic/Latino patient, which is an underrepresentation of the incidence of SCLC in these racial and ethnic minority groups.	therapy with a primary endpoint of overall survival (OS). The primary efficacy population did not consist of an adequate proportion of racial and ethnic minorities that would be representative of the incidence of SCLC in these populations. Given this, a postmarketing commitment (PMC) will be issued to provide further analyses from ongoing or planned clinical trials to further characterize the safety, efficacy and pharmacokinetics of tarlatamab in these patient populations
Risk and Risk Management	• The pooled safety population included 187 patients from Study 20200491 and Study 20160323 with extensive stage SCLC who were treated with tarlatamab at a step dose of 1 mg on Cycle Day 1 followed by the proposed dose of 10 mg on Cycle 1 Day 8, Cycle 1 Day 15 and every 2 weeks thereafter.	The observed safety profile is considered acceptable when assessed in the context of a life-threatening disease. The safety risks of tarlatamab can be adequately conveyed through labeling (including a Boxed Warnings to communicate the risks of CRS and neurologic toxicity, including ICANS). In addition, enhanced

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The key safety concerns for tarlatamab are cytokine release syndrome (CRS) which occurred in 55% of patients and neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS) which occurred in 47% of patients. Other safety concerns include hepatotoxicity, infections, cytopenias, and hypersensitivity.	pharmacovigilance and a Dear Healthcare Provider letter are non-REMS adjuncts recommended to help convey these risks. A post-marketing requirement (PMR) will also be issued to submit the final study report and datasets from a multicenter randomized clinical trial intended to verify and describe the clinical benefit of tarlatamab in patients with ES-SCLC who have had disease progression on or after platinum-based chemotherapy. An additional PMR to characterize the long-term incidence, severity, and outcome of the known serious risks of CRS, ICANS and neurologic toxicity will also be issued.

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1.4. Patient Experience Data

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

| | | |

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Globally, lung cancer is the second most commonly diagnosed cancer and leading cause of cancer death, representing approximately 1 in 10 (11.4%) cancers diagnosed and 1 in 5 (18.0%) cancer deaths (Sung et al, 2021). Small cell lung cancer (SCLC) accounts for approximately 15% of overall lung cancer cases with approximately 330 000 new cases worldwide each year based on an estimated 2.2 million cases of lung cancer in 2020 (National Cancer Institute [NCI], 2023; National Organization for Rare Disorders, 2021; Rudin et al, 2021; Sung et al, 2021). There are approximately 270 000 new deaths worldwide due to SCLC based on approximately 1.8 million lung cancer deaths in 2020 (Sung et al, 2021).

Small cell lung cancer is a high-grade neuroendocrine tumor marked by an exceptionally high proliferative rate, strong predilection for early metastasis, and poor prognosis (Rudin et al, 2021). While 30% of patients present with disease that can be encompassed by one radiotherapy field (limited stage), the majority of cases have disease diagnosed as extensive stage. Although 20% to 30% of patients with limited-stage SCLC can be cured with radio-chemotherapy, treatment is rarely curative in extensive stage, and SCLC is associated with poor long-term survival (5-year survival is $<10\%$) (American Cancer Society, 2022).

(b) (4)

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Overall, the results from the [redacted] (b) (4) published literature show that patients with SCLC have poor treatment outcomes with existing therapies in second line or later, and their prognosis in the overall population and in the subset treated with first-line anti-PD-L1 therapy is poor. Therefore, there remains a significant unmet medical need in patients with advanced SCLC for novel therapies that can support longer survival and reduce disease-associated symptoms with an acceptable safety profile. Tarlatamab is being developed with the goal of addressing this unmet need.

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

2.2. Analysis of Current Treatment Options

The Applicant's Position:

Current first-line treatment of SCLC generally consists of etoposide in combination with either cisplatin or carboplatin with the addition of radiation for limited-stage SCLC and the addition of a PD-L1 immune checkpoint inhibitor (atezolizumab or durvalumab) for extensive-stage SCLC (National Comprehensive Cancer Network [NCCN] SCLC Guidelines, 2023; Guidelines for Diagnosis and Treatment of Lung Cancer in Japan, 2022; Rudin et al, 2021; Ganti et al, 2021). Although this first-line regimen in extensive-stage SCLC has a relatively high response rate of 60% to 70%, resistance and relapse almost always occur, usually within the first year after treatment for nearly all patients with extensive-stage SCLC (Rudin et al, 2021; Yoon et al, 2019; Chan and Coward, 2013), and median OS is approximately 12 to 13 months (Tariq et al, 2021; Paz-Ares et al, 2019; Horn et al, 2018).

Treatment options for patients with relapsed SCLC are limited, and with currently available therapy, prognosis remains poor. In addition to consideration of platinum rechallenge or clinical trial participation, other recommended regimens in the relapsed or refractory setting include topotecan (Eckardt et al, 2007; O'Brien et al, 2006; von Pawel et al, 1999), lurbinectedin (Trigo et al, 2020), other chemotherapy agents (eg, cyclophosphamide/doxorubicin/vincristine, docetaxel, etoposide, gemcitabine, temozolomide), or immunotherapy agents (eg, nivolumab, pembrolizumab).

National Comprehensive Cancer Network guidelines include several therapies as other recommended regimens for patients who progress subsequent to initial systemic therapy; however, only topotecan is Food and Drug Administration (FDA) approved for use in patients with SCLC platinum-sensitive disease who progress at least 60 days after initiation of first-line chemotherapy (NCCN, 2023) (Table 1). Of note, topotecan was approved based on a study comparing topotecan to cyclophosphamide, doxorubicin, and vincristine combination

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chemotherapy, which did not show statistically significant improvements in response rate, duration of response (DOR), time to progression, or OS (topotecan US Prescribing Information, 2019; von Pawel et al, 1999). In the study, topotecan demonstrated an objective response rate (ORR) (95% CI) of 24.3% (16.2%, 32.4%) and median (95% CI) DOR of 3.3 (3.0, 4.1) months (Table 1); cyclophosphamide, doxorubicin, and vincristine combination chemotherapy demonstrated an ORR (95% CI) of 18.3% (10.8%, 25.7%) and median (95% CI) DOR of 3.5 (3.0, 5.3) months.

National Comprehensive Cancer Network guidelines (2023) also include lurbinectedin as a recommended regimen in patients who progress subsequent to initial systemic therapy with platinum-based chemotherapy (NCCN, 2023). Lurbinectedin received accelerated approval in August 2020 based on an ORR (95% CI) as assessed by investigator of 35% (26%, 45%) and median (95% CI) DOR of 5.3 (4.1, 6.4) months (Zepzelca US Prescribing Information, 2023). It is important to note that all subjects enrolled in this study had progressed on or after platinum-based chemotherapy, with only 8% of subjects also having prior immunotherapy.

Recent novel therapeutic strategies such as immunotherapy with programmed cell death 1 (PD-1) checkpoint inhibitors have not improved outcomes compared with topotecan in the second-line or later setting (Das et al, 2021; Giffin et al, 2021; Trigo et al, 2020), and the need for durable responses remains high. Additionally, the benefits of immunotherapy in first-line treatment of extensive-stage SCLC are relatively modest (approximately 2 to 3 month increase in median OS) (Paz-Ares et al, 2019; Horn et al, 2018) compared with that observed in non-small cell lung cancer in first-line treatment. Small cell lung cancer is considered an immune-cold lung cancer subtype due to the limited infiltration of immune cells, reduced PD-L1 expression, and lack of antigen presentation (Caliman et al, 2023; Sutherland et al, 2022). Although SCLC has a high tumor mutational burden related to the carcinogenic activity of tobacco exposure, this does not appear to translate to a similar favorable response to PD-L1 and PD-1 inhibitors as in non-small cell lung cancer (Sutherland et al, 2022) and other alternative immunotherapeutic approaches may be of interest.

A meta-analysis of 27 studies, enrolling a total of 2792 patients, suggests heterogeneity in the prevalence of PD-L1 expression across studies. No statistical association has been confirmed, although positive PD-L1 expression seems to be a favorable prognostic factor for SCLC (Acheampong et al, 2020). The sensitivity of immunotherapy may be associated with the disease itself, according to the molecular classification biology of SCLC (Caliman et al, 2023). Further studies are necessary to determine which patient groups would benefit the most from immunotherapy treatment.

Currently there are no approved therapies for patients failing 2 or more prior lines of therapy (NCCN SCLC Guidelines, 2023; Giffin et al, 2021). Patients receiving best supportive care in third line had an extremely poor survival outcome with a median OS of 0.9 months, whereas patients receiving systemic therapy in third line had a median OS of 4.4 months (Coutinho et al, 2019).

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

Product (s) Name	Relevant Indication	Year of Approval And Type of Approval	Dosing/ Admin-istration	Efficacy Information	Important Safety and Tolerability Issues	Other comments
FDA Approved Treatments						
Lurbinectin (Zepzelca)	Treatment of adult patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy	2020 Accelerated Approval	3.2 mg/m^2 IV over 1 hour every 21 days	Primary Endpoint - ORR: 35% (95% CI: 26, 45) Secondary Endpoints – mDOR: 5.3 months (95% CI: 4.1, 6.4) m mPFS: 3.5 months (95% CI: 2.63, 4.34) mOS: 9.3 mo (95% CI: 6.3, 11.8)	Myelosuppression, hepatotoxicity, extravasation resulting in tissue necrosis, rhabdomyolysis, and embryo-fetal toxicity	The FDA review teams recommended accelerated approval of lurbinectedin for the treatment of adult patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy. This was supported by results from PM1183-B-005-15 (Study B-005), an ongoing, multicenter, open-label, non-randomized, multi-cohort trial evaluating the safety and efficacy of lurbinectedin as a single-agent in adult patients with advanced solid tumors. The efficacy is primarily based on results from a cohort of 105 patients with metastatic SCLC who had disease progression on or after first-line treatment with platinum-based chemotherapy. All patients had received prior platinum-based therapy and 8% had received prior immunotherapy.
Topotecan (Hycamtin) oral capsules	Treatment of patients with relapsed SCLC	1996 (Ovarian Cancer) 2007 (Oral Dosage Form)	2.3 mg/m^2 /day QD for 5 consec- utive days repeated every 21 days	mOS: 6.0 months; HR: 0.64 (95% CI: 0.45, 0.90)	Diarrhea, interstitial lung disease and embryo-fetal toxicity	Randomized, open-label study comparing oral topotecan with BSC to BSC alone in patients with relapsed SCLC who were prior responders to first-line chemotherapy

Footnotes on last page of table.

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

Product (s) Name	Relevant Indication	Year of Approval And Type of Approval	Dosing/ Administra-tion	Efficacy Information	Important Safety and Tolerability Issues	Other comments
Topotecan (Hycamtin)	Treatment of patients with platinum-sensitive disease who progressed at least 60 days after initiation of first-line chemotherapy	1998 Full Approval	1.5 mg/m^2 IV infusion over 30 min daily on days 1 to 5 of each 21-day cycle until disease progression.	ORR: 24% mDOR: 3.3 mo mOS: 5.8 months Hazard ratio (95% CI): 1.04 (0.78, 1.39) The results of the trial did not show statistically significant improvements in response rate, response duration, time to progression, or OS	Interstitial lung disease, extravasation and tissue injury, and embryo-fetal toxicity. Box Warning: HYCAMTIN can cause severe myelosuppression. Administer first cycle only to patients with baseline neutrophil counts greater than or equal to 1,500/mm^3 and platelet counts greater than or equal to 100,000/mm^3. Monitor blood cell counts on all patients receiving topotecan.	Randomized, open-label study comparing topotecan and CAV in patients with limited or extensive-stage SCLC who progressed at least 60 days after completion of first-line chemotherapy Three open-label, single-arm studies in patients with recurrent or progressive SCLC after treatment with first-line chemotherapy. Study populations included patients with platinum-sensitive SCLC (responders who subsequently progressed ≥ 90 days after completion of first-line therapy) and platinum refractory SCLC (no response to first-line chemotherapy or response followed by progression within 90 days of completing first-line therapy).

BSC = best supportive care; IV = intravenous; mDOR = median duration of response; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; QD = once daily; SCLC = small cell lung cancer

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The FDA's Assessment:
FDA generally agrees with the Applicant's presentation of current treatment options. Cytotoxic chemotherapies are expected to have differential tumor response based on a patient's "sensitivity" to platinum-based chemotherapy and given this, efficacy is usually assessed separately in subgroups of platinum-sensitive or platinum-resistant with the former group being generally defined as patients who have had disease progression ≥ 90 days after completion of first-line platinum-based chemotherapy and the latter group being defined as patients who have progression < 90 days after completion of first-line platinum-based chemotherapy. Based on data from single arm studies with topotecan using the more standard cut-off of ≥90 days for platinum-sensitive vs. platinum-resistant, reported response rates ranged from 11-31% for patients with platinum-sensitive disease and 2-7% in patients with platinum-resistant disease. For lurbinectedin, accelerated approval was granted based on an ORR of 35%; ORR was 43% (95% CI: 31%, 57%) in the platinum-sensitive subgroup and 13% (95% CI: 5%, 27%) in the platinum-resistant subgroup.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:
Tarlatamab (International Nonproprietary Name [INN]; AMG 757) is not currently registered (or approved) in the US or in any other part of the world.

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

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

A summary of key interactions with the FDA regarding tarlatamab for the proposed indication, the subject of this marketing application, is provided in Table 2.

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Table 2. Applicant – Summary of Key Presubmission Regulatory Activities for Tarlatamab

Date	Regulatory Interaction/Milestone
18 July 2017	New IND (134859) submitted for Study 20160323, the first-in-human study of tarlatamab in subjects with small cell lung cancer
17 August 2017	Study May Proceed received for Protocol 20160323
27 December 2018	Orphan Drug Designation was granted to tarlatamab for the treatment of SCLC
14 September 2020	Type B (End of Phase 1) meeting to discuss the clinical development program for tarlatamab in SCLC
02 September 2021	Type C meeting to discuss the proposed phase 2 Study 20200491 and phase 3 Study 20210004 to support the future BLA of tarlatamab for treatment of patients with SCLC
18 October 2021	Submitted the phase 2 registrational Study 20200491 in subjects with SCLC
05 December 2022	Type B (pre-phase 3) meeting to discuss proposed Study 20210004 to support regular approval of tarlatamab for a second-line SCLC indication and will serve as the confirmatory study to support full approval for the proposed indication
22 December 2022	New phase 3 confirmatory Study 20210004 (IND 134859) submitted, titled "A Randomized, Open-label, Phase 3 Study of Tarlatamab compared With Standard of Care in Subjects With Relapsed Small Cell Lung Cancer After Platinum-based First-line Chemotherapy"
06 February 2023	Type C Structure and Format WRO meeting to discuss the proposed structure, format, and content of the planned BLA for tarlatamab for the treatment of adult patients with advanced SCLC and to seek feedback on the proposed principal concepts of the integrated summaries and feedback on the mock submission of electronic data
21 July 2023	Type B CMC WRO meeting to discuss the quality aspects of the planned BLA
15 August 2023	Teleconference to discuss the preliminary Breakthrough Therapy Designation Request
08 September 2023	Type B pre-BLA meeting to discuss the clinical and nonclinical aspects of the tarlatamab program in advance of the planned BLA
12 October 2023	Final submission under Real-Time Oncology Review to BLA 761344 completed

BLA = Biologics License Application; CMC = Chemistry, Manufacturing, and Controls; IND = Investigational New Drug; PD-1 = programmed cell death 1; RP2D = recommended phase 2 dose; SCLC = small cell lung cancer; WRO = written request only

The FDA's Assessment:

FDA agrees with the Applicant's characterizations of key regulatory milestones that occurred during the planning and conduct of Study 20200491 and the tarlatamab advanced SCLC development program with the following clarifications:

- At the EOP1 meeting in September 2020, FDA informed the Applicant that for development in second line SCLC, a significant proportion of patients should have received anti-PD-(L)1 therapies.

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- On October 5, 2022, the Applicant submitted a rationale for recommended Phase 2 dose document for FDA review. On November 9, 2022, FDA agreed with the Applicant's rationale/proposal that the tarlatamab 10 mg dose appeared acceptable as the dose to be continued for further evaluation in patients with relapsed/refractory SCLC.

- On October 18, 2023, FDA granted breakthrough therapy designation for tarlatamab for the treatment of adult patients with extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-base chemotherapy.

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

4.1. Office of Scientific Investigations (OSI)

An OSI audit was conducted for this BLA. The review division (DO2) and OSI selected three investigator sites, and the imaging contract research organization (CRO) (b) (4) for clinical inspection. The three investigators selected were Dr. Byoung Chul Cho (Site ID #25054), Dr. Myung-Ju Ahn (Site ID #66264) and Dr. Enrique Felip Font (Site ID #29404).

The inspection of Dr. Ahn revealed protocol violations, including enrollment of two patients who did not meet eligibility criteria and underreporting of adverse events (AEs). Specifically, Patient (b) (6) had a new diagnosis of adenocarcinoma and should not have been enrolled in the study, as the patient did not fulfill inclusion criterion to have "histologically or cytologically confirmed relapse/refractory SCLC." This patient received the tarlatamab 100 mg dose. Patient (b) (6) had abdominal aneurysm with thrombosis and should have been excluded from study based on the exclusion criteria. Based on the available information, this protocol deviation did not appear to have impact on this patient's safety.

Inspection of Dr. Ahn's site also revealed underreporting of AEs in 14 out of 19 patients enrolled at the site. A total of 61 AEs including three Grade 3 AEs and two Grade 5 AEs (death due to underlying disease) were not reported to the BLA in the Applicant's data listings. The root cause of the violations was due to lack of human resources at the site as well as failure in the Applicant's monitoring activities. On January 31, 2024, OSI, in conjunction with the review Division, requested that the Applicant provide a root-cause and impact analysis for the eligibility and AE discrepancies at Dr. Ahn's site, and to perform a source record review of subject's eligibility and adverse events for all subjects enrolled at all 5 sites in South Korea. Based on the Applicant's source record review of the Korean sites, an additional 42 unreported AEs at 3 of the 4 remaining sites and involving 12 patients were identified.

Root cause analysis showed the following factors that caused inadequate AE reporting by the site: 1) lack of Good Documentation Practices for adverse events tracking – study coordinators entered adverse events information on an undisclosed source document, 2) Lack of electronic medical record (EMR) access by study coordinators - study coordinators could not enter adverse events into EMR, 3) Undisclosed source documents to the clinical research associate (CRA) - source document was not disclosed to the CRA when inquiring about potential adverse events under-reporting and 4) Under-resourcing of study coordinators at site during high enrollment periods. Site 66264 remains on hold in the Applicant's clinical trials until the Applicant is satisfied that the robustness of the site's processes will prevent recurrence of GCP inspection findings identified.

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The following preventative measures have been implemented by the Applicant regarding AE reporting:

- Review the root cause of each missing AE at each of the impacted sites to identify and correct the unique causes at each site.
- Document the availability of the site AE reporting procedure and ensure site's training logs are completed and up to date with respect to the current versions of the procedure.
- Plan to update the Monitoring Plan to incorporate regular verification of the site AE reporting procedures and associated site staff training by April 30, 2024.
- Re-training of AE reporting for all sites on study.
- Implementation of additional edit checks in Electronic Data Capture (EDC) for AE reporting verification
- Plan to add the study specific risk of AE reporting and associated mitigations and actions into the risk management system by April 30, 2024.

Inspections of Drs. Cho and Font's sites also revealed unreported AEs that are unlikely to significantly affect overall reliability of safety or efficacy data for these sites. The large number of underreported AEs by the Korean sites, not captured during the Applicant's monitoring activities, is a major concern and put into question the integrity of the safety data submitted to support the approval of tarlatamab for the proposed indication.

The Applicant has acknowledged the deficiencies and decided to further expand their review to conduct 100% source data verification (SDV)/source data review (SDR) for all sites involved in 20200491. Based on SDR of imaging records, 25 previously unsubmitted scans were identified in 17 patients. Of the 25 scans, 23 were unscheduled scans and were previously not submitted as these scans were completed as part of standard of care or for patient AE assessment. Of the remaining 2 scans, one was a scheduled brain MRI that was not submitted for central review due to a technical imaging upload error and the other was a baseline abdominal MRI that was not submitted as the site erroneously indicated that only baseline CT was available.

These unsubmitted scans were submitted to BICR for review and from this the Applicant updated the ORR by BICR from 40% to 41% for the tarlatamab 10 mg group and from 32% to 33% in the tarlatamab 100 mg group. The median DoR did not change in the 10 mg group and changed from 8.1 to 7.6 months in the 100 mg group. However, upon further review by FDA, none of the newly identified scans that were submitted factored into the update of response for these patients and the update of ORR was from re-adjudication of previous target lesion assessments. Given this, FDA did not agree to update the ORR the DoR summary statistics would be based on the previous ORR by BICR of 40%.

The following preventative measures have been implemented by the Applicant regarding collection of imaging data for BICR:

- Re-training of protocol specific criteria for image submission requirement, specifically unscheduled scans are collected
- Plan to update the Monitoring Plan to incorporate confirmation of image submission expectation training in case of site staff changes by April 30, 2024.
- Re-training of the Medical Data Reviewer on image verification expectation.
- Re-training of Data Management staff on image review and reconciliation completed on March 15, 2024.
- Plan to add the study specific risk of images missing in BICR and associated mitigations and actions into the risk management system by April 30, 2024.

From the 100% SDR/SDV of AEs, a total of 393 previously unreported AEs were identified in 111 patients. Of these, 371 events in 107 patients were treatment-emergent AEs. Of these newly identified AEs, 3 were SAEs and 28 were grade 3 AEs. No new grade 4 or fatal AEs were identified.

Inspection of the imaging CRO, (b) (4), revealed no significant discrepancies or regulatory violations. Based on this inspection, the data generated by (b) (4) appear acceptable in support of the proposed indication.

Overall, the large number of underreported AEs by the Korean sites, not captured during the Applicant's monitoring activities, was a major concern and put into question the integrity of the safety data submitted to support the approval of tarlatamab for the proposed indication. However, based on the revised 90-day safety update and FDA's analysis, most of the unreported AE's were ≤ Grade 2 with Grade 1 events of CRS and ICANS in 2 patients each respectively; these updated data were used to support this review and to inform the USPI. Refer to Section 8.2.4 for safety analysis of unreported AEs. The 100% SDR/SDV of safety and imaging from all sites along with the proposed mitigations from the Applicant appear acceptable to support this BLA.

4.2. Product Quality

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The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761344 for IMDELLTRA (tarlatamab-dlle) manufactured by Amgen Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of IMDELLTRA (tarlatamab-dlle) is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert. The CMC post-marketing commitment (PMC) listed below should be included in the action letter.

- To develop a Monocyte Activation Test (MAT) for reliable endotoxin detection of the IVSS. The method feasibility study results will be submitted to the Agency by January 2025. If the method feasibility study is successful, method validation with three batches of IVSS product will be submitted by January 2026. If the MAT method proves infeasible, Amgen commits to develop an alternative endotoxin detection method which is not subject to low endotoxin recovery for the IVSS and to provide a timeline for those studies.

In studies evaluating leachables from the drug product container closure system after storage at 2°C to 8°C for 12 to 24 months, (b) (4) was identified as a potential leachable impurity in the 1 mg and 10 mg vials. Based on measured leachable (b) (4) levels and the recommended dose of tarlatamab, the maximum delivered dose of (b) (4) impurity is (b) (4) in the 10 mg vial. There were no pharmacology/toxicology concerns given that the (b) (4) level is within the range of approved products with the same route of administration. All other impurities identified in leachable studies with the drug substance or drug product are not a safety concern as potential organic leachable impurities were identified at levels that result in a maximum delivered dose below the safety concern threshold (SCT) of (b) (4) and potential elemental impurities were below permitted daily exposures (PDEs) established in ICH Q3D.

Please refer to Quality Executive Summary submitted in DARRTS (April 29, 2024) for full review.

4.3. Clinical Microbiology

No approvability issues were identified from a sterility assurance or microbiology product quality perspective. Please refer to Quality Executive Summary submitted in DARRTS (April 29, 2024) for full review.

4.4. Devices and Companion Diagnostic Issues

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The proposed indication for tarlabamab is not limited to a biomarker-selected population. There was no device or companion diagnostic test reviewed as part of this application.

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Reference ID: 5382024

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Tarlatamab (AMG 757) is a bispecific T cell engager that binds to delta-like ligand 3 (DLL3) and CD3. DLL3 is a Notch ligand that is expressed during fetal development but has limited expression on the cell surface in healthy adult tissues. DLL3 has also been reported to be expressed on the cell surface of some cancers, including small cell lung cancer (SCLC). CD3 is expressed on T cells, and upon simultaneously binding to the surface of DLL3-expressing target cells and CD3 on T cells, tarlatamab promotes T cell activation and T cell-dependent lysis of DLL3-expressing cells, including SCLC cells. The Applicant proposes to use tarlatamab at 1 mg on Day 1, then 10 mg on Days 8, 15, and every 2 weeks thereafter. The proposed indication is for the treatment of adult patients with SCLC with disease progression on or after platinum-based chemotherapy.

As assessed by surface plasmon resonance (SPR), tarlatamab bound human and monkey CD3 with K_Ds of 14.9 nM and 12 nM, respectively. Tarlatamab bound CHO cells expressing human or monkey DLL3 with K_Ds of 0.64 nM and 0.5 nM, respectively. Tarlatamab also bound human and monkey T cells at a concentration of 50 ng/mL but did not bind T cells from mice, rats, rabbits, dogs, or minipigs. The cynomolgus monkey was selected for toxicology testing given that tarlatamab similarly bound human and monkey CD3 and DLL3 but did not bind CD3 from other species. However, the monkey may not be pharmacologically relevant considering DLL3 is expressed intracellularly in normal cells and tissues. It is unknown if other conditions or disease states can lead to expression of DLL3 on the surface of some cells.

The ability of tarlatamab to activate T cells and mediate T cell cytotoxicity was evaluated in in vitro assays. In co-cultures with human peripheral blood mononuclear cells (PBMCs) and DLL3-expressing human small cell lung cancer cell lines, tarlatamab resulted in upregulation of T cell activation markers and cytokine release, as well as cytotoxicity of DLL3-postive target cells. Tarlatamab mediated T cell lysis of several human SCLC cell lines with EC_{50}s of 32 pM to 161 pM. Additionally, the ability of tarlatamab to mediate cytotoxicity of DLL3-postive target cells positively correlated with levels of DLL3 expressed on the surface of target cells. Tarlatamab also demonstrated ability to activate CD4 and CD8 T cells in co-cultures with DLL3-expressing human cancer cell lines as assessed by increased expression of T cell activation markers, such as CD25 and CD69, and cytotoxicity markers, perforin and granzyme B, as well as release of cytokines, including the proinflammatory cytokines IL-2, IL-6, TNF-α, and IFNγ. Tarlatamab did not mediate cytokine release from human PBMCs when co-cultured with target cells lacking expression of DLL3.

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In the presence of dexamethasone, a glucocorticoid used clinically to antagonize severe inflammatory reactions, the ability of tarlatamab to mediate T cell activation and cytotoxicity of DLL3-expressing human SCLC cell lines was reduced approximately 3-fold. Tarlatamab-mediated release of IFNγ, TNF-α, IL-10, and IL-6 were also reduced in co-cultures of human PBMCs and SCLC cell lines compared to cultures that were not treated with dexamethasone.

Consistent with its mutated Fc region, tarlatamab demonstrated low affinity binding to FcγRI and no binding to FcγRII, FcγRIII, or C1q, thus tarlatamab is not expected to mediate Fc-effector functions; the mutations in the Fc region did not affect the ability of tarlatamab to bind the neonatal Fc receptor (FcRn). In an in vitro assay, tarlatamab resulted in low level upregulation of activation markers CD25 and CD69 on human T cells when PBMCs were cultured alone or in the presence of HCT-116 cells lacking expression of DLL3, suggesting the potential for tarlatamab to mediate T cell activation independently of DLL3 engagement via binding of the ScFc region of tarlatamab to FcγRI on target cells and simultaneous binding to CD3 on T cells; however, upregulation of CD25 and CD69 were abolished in the presence of physiological levels of human IgG. This finding suggests that competitive binding from human IgG can block tarlatamab binding to FcγRs, thereby inhibiting target-independent T cell activation. Notably, antigen-independent upregulation of T cell activation markers did not correlate with cytokine release from unstimulated PBMCs in an in vitro assay described above, further indicating that potential interactions with FcγRI are weak and are unlikely to lead to T cell activation or Fc-mediated effector functions.

Tarlatamab inhibited tumor growth in multiple mouse tumor models. Because tarlatamab does not bind mouse CD3, the in vivo anti-tumor activity of tarlatamab was evaluated using immunodeficient mice administered human PBMCs or T cells by IV infusion prior to treatment with tarlatamab. In orthotopic models of SCLC, tarlatamab inhibited tumor growth when administered at doses ≥0.1 mg/kg once weekly via intraperitoneal injection. Anti-tumor activity in SCLC models was associated with expanded CD4 and CD8 T cell populations in tumors from mice administered tarlatamab compared to tumors from mice treated with an isotype control bispecific antibody. Overall, based on primary pharmacology data the established pharmacologic class (EPC) of tartalamab is bispecific delta-like ligand (DLL3)-directed CD3 T-cell engager.

The Applicant evaluated the safety of tarlatamab administered intravenously, the intended route of administration, using cynomolgus monkeys in GLP-compliant 1- and 3-month repeat-dose toxicology studies, as well as a non-GLP 10-day study. No mortalities occurred in these studies at doses up to 4500 µg/kg, the maximal feasible dose that could be administered to monkeys. Findings in these studies included decreases in lymphocytes at doses ≥1000 µg/kg in all repeat-dose toxicology studies in monkeys; this finding improved after a drug-free period. Changes in lymphocytes also correlated with decreases in total CD3, CD4, and CD8 T cell

populations in monkeys administered ≥100 µg/kg or 4500 µg/kg in the 10-day and 1-month studies, respectively; these changes also demonstrated reversibility. In a 1-month toxicology study in mice administered muS757, a tarlatamab surrogate that binds mouse DLL3 and CD3, decreased lymphocytes were also noted at ≥500 mg/kg muS757 and correlated with decreased lymphoid cellularity in the lymph nodes. Additionally, decreased neutrophils were noted in monkeys at 4500 µg/kg in the 1-month study and in mice administered ≥500 µg/kg muS757. Other hematological changes, including decreased red blood cells, hemoglobin, and hematocrit were noted at doses ≥100 µg/kg in the 10-day study in monkeys. The changes in red blood cell parameters were not noted in the GLP studies of up to 3-months duration; however, anemia was observed in humans. Consistent with nonclinical findings, decreases in lymphocytes and neutropenia have occurred clinically and the IMDELLTRA (tarlatamab) label includes a warning for neutropenia.

Signs of an inflammatory response were noted in the 10-day study, including increases in C-reactive protein (CRP), MCP-1, and IFNγ at doses ≥100 µg/kg. Transient increases in heart rate occurred in the 1-month monkey study at ≥500 µg/kg following the first dose, but this finding was not noted at any time point in the 3-month study in monkeys. At doses ≥50 µg/kg, minimal to mild mononuclear cell infiltrates were noted in the pituitary gland of monkeys; however, a tissue-cross reactivity study using tissues from humans and monkeys demonstrated only cytoplasmic DLL3 expression in pituitary and brain tissues, indicating DLL3 in these tissues is not expected to be accessible to tarlatamab. Additionally, minimal to mild mononuclear and/or mixed cell infiltrates were observed in multiple tissues in all toxicology studies in monkeys.

The Applicant did not conduct genetic toxicology studies as they generally are not appropriate for antibody-based therapies. In addition, the Applicant did not conduct dedicated studies to assess fertility. In general, these studies are not needed to support a marketing application for a drug intended to treat patients with advanced cancer. There were no adverse or notable effects on male or female reproductive organs in the repeat-dose toxicology studies conducted in sexually mature cynomolgus monkeys.

Based on mechanism of action of tarlatamab, the expression of DLL3 during fetal development, and data from a literature-based risk assessment, the pharmacology/toxicology team recommends a warning for embryo-fetal toxicity in the label for IMDELLTRA. Tarlatamab causes T cell-dependent depletion of DLL3-expressing cells, and T cell activation may result in cytokine release and associated inflammatory effects that may adversely affect the ability to maintain a pregnancy. Two administrations of a tarlatamab surrogate, mus757, that binds mouse CD3 and DLL3, to pregnant mice on gestational days (GD) 6 and GD 13 did not result in maternal toxicity or embryo-fetal development toxicity at doses ≤4500 µg/kg. muS757 was detected in fetal serum at concentrations up to 30-times higher than maternal serum concentrations, indicating the potential for tarlatamab to cross the placenta. Additionally, studies using genetically engineered mice demonstrate that DLL3 loss-of-function mutations or deletion of DLL3

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disrupted somitogenesis during embryogenesis leading to disorganization of the axial skeleton and disruption of vertebral formation, suggesting that fetal exposure to tarlatamab may increase the risk of abnormal skeletal development (Chapman et al., 2011, Dunwoodie et al., 2002, Kusumi et al. 1998). In these studies, DLL3 was only detected intracellularly during embryogenesis, which may explain the lack of findings in the embryo-fetal development study in mice using muS757 given that tarlatamab is expected to target DLL3 expressed on the cell surface.

Human immunoglobulin G (IgG) is known to cross the placenta via FcRn; tarlatamab can bind FcRn, therefore, tarlatamab has the potential to be transmitted from the mother to the developing fetus. Consistent with the recommendation for non-genotoxic drugs that are teratogenic or embryo-fetal lethal as described in the FDA Guidance for Industry Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations, and considering the half-life of 11.2 days for tarlatamab, FDA recommends advising females of reproductive potential to use effective contraception during treatment with IMDELLTRA and for 2 months after the last dose. The Applicant did not evaluate the presence of tarlatamab in milk; however, maternal IgG is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed child to IMDELLTRA are unknown. Because of the potential serious adverse effects of IMDELLTRA on a breastfed child, the review team recommends advising patients not to breastfeed during treatment with IMDELLTRA and for 2 months after the last dose.

Recommendation:
There are no outstanding issues from a pharmacology/toxicology perspective that would prevent the approval of IMDELLTRA.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:
Not applicable

The FDA's Assessment:
The FDA agrees.

5.3. Pharmacology

Primary pharmacology

Tarlatamab (also designated as AMG 757) is a bispecific T-cell engager (BiTE®) molecule that

targets the tumor-associated antigen delta-like ligand 3 (DLL3). Tarlatamab consists of 2 single-chain variable fragment binding domains, specific for DLL3 and the T-cell receptor (TCR)-associated protein cluster of differentiation 3 (CD3), fused to a silenced fragment crystallizable (Fc) immunoglobulin domain to extend serum half-life. Tarlatamab is designed to simultaneously bind to DLL3 that is expressed on the surface of cancer cells and CD3 expressed on the surface of T cells.

The mechanism of action of tarlatamab is T cell-dependent lysis of tumor cells. The pharmacological effect of tarlatamab is mediated by specific redirection of T cells to kill DLL3-expressing tumor cells. The primary pharmacology of tarlatamab was assessed in SCLC cell lines in vitro and in SCLC xenograft models in vivo.

Tarlatamab binding to human and cynomolgus monkey DLL3 was assessed by flow cytometry, and binding to human and cynomolgus monkey CD3 was measured by surface plasmon resonance (SPR) analysis (Table 3; Study Number: 122717/ electronic common technical document [eCTD] Location: Module 4.2.1.1).

The binding of tarlatamab to Fc-gamma receptors (FcγR), the neonatal Fc receptor complex (FcRn/B2M) and complement component 1q (C1q) was assessed by SPR analysis (Table 3; Study Number: 157053/ eCTD Location: Module 4.2.1.1).

While the single-chain Fc region of tarlatamab showed low affinity binding to FcγRI/CD64, it did not interact with FcγRIIa/CD32a and FcγRIIIa/CD16a. The interaction with FcγRI/CD64 was characterized by very fast association and dissociation rates, and the equilibrium dissociation constant (K_D) value was about 7000-fold lower than that of a control monoclonal antibody, rituximab (Study 157053). Tarlatamab did not bind to human C1q (Study 157053). Thus, tarlatamab is not expected to mediate effector functions such as antibody-dependent cell mediated cytotoxicity and complement-dependent cytotoxicity. Furthermore, tarlatamab showed a pH-dependent interaction with human FcRn/B2M heterodimer receptors with a K_D value of 444 nM, which was comparable to rituximab (345 nM) (Study 157053).

Table 3. Applicant – Binding Affinities of Tarlatamab for Human and Cynomolgus Monkey DLL3 and CD3ε

Antigen	K_D	Human
DLL3	[nM]	0.64 (mean, N=2)
CD3ε	[nM]	14.9 (mean, N=2)
CD64 (FcgRI)	[nM]	297
CD32 (FcgRII)	[nM]	n.b.
CD16 (FcgRIII)	[nM]	n.b.

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Antigen	K_D	Human
FcRn/B2M	[nM]	444
C1q	[nM]	n.b.

CD3ε = cluster of differentiation 3, epsilon subunit ; DLL3 = delta-like ligand 3 ; K_D = equilibrium dissociation constant ; n.b. = no binding
Source: Module 2.6.2 Pharmacology Written Summary (or Module 4.2.1.1 or Study 122717 or Study 157053)

Tarlatamab engaged T cells from human or cynomolgus monkey to effectively lyse SCLC cells in vitro (Table 4; Study Number: 122717/ eCTD Location: Module 4.2.1.1). The cross-reactivity of tarlatamab to cynomolgus monkey shown by similar binding affinity and cytotoxic activity supported selection of cynomolgus monkey for nonclinical toxicology studies.

Table 4. Applicant – EC_{50} Values of Tarlatamab-mediated Redirected Lysis by Human T Cells

EC_{50} Cytotoxicity [pM]	Human PBMC			
Target Cells	Mean	±	SD	N
COR-L279	57	±	34	12
DMS 79	33	±	27	10
H-2171	161	±	127	9
NCI-H82	37	±	31	6
NCI-H889	447	±	314	5
SHP-77	32	±	24	16

EC_{50} = concentration required for half-maximal effect; PBMC = peripheral blood mononuclear cells; SD = standard deviation; N = number of experiments
Source: Module 2.6.2 Pharmacology Written Summary (or Module 4.2.1.1 Study 122717)

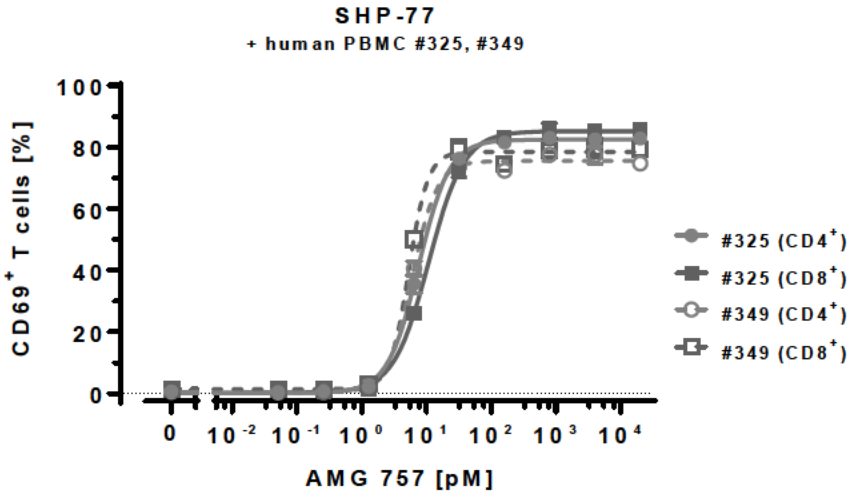
Bispecific binding of tarlatamab to DLL3 on tumor cells and the TCR/CD3 complex on T cells induces similar effects as antigen-specific recognition of peptide-major histocompatibility complex by the TCR of T cells. Thus, tarlatamab initiates activity of cytotoxic T lymphocytes through the upregulation of key molecules of T-cell activation and transient cytokine production by T cells (Study 122717).

In co-cultures of DLL3-expressing SHP-77 and human T cells, tarlatamab-induced dose-dependent upregulation of T-cell activation markers, including CD69 (Figure 1; Study Number: 122717/ eCTD Location: Module 4.2.1.1).

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Figure 1. Applicant – Tarlatamab-induced Activation of Human T Cells



CD4 = surface antigen on T helper cells; CD8 = surface antigen on cytotoxic T cells and natural killer cells; CD69 = early T cell activation antigen; PBMC = peripheral blood mononuclear cells; SHP-77 = human pulmonary small cell carcinoma cell line

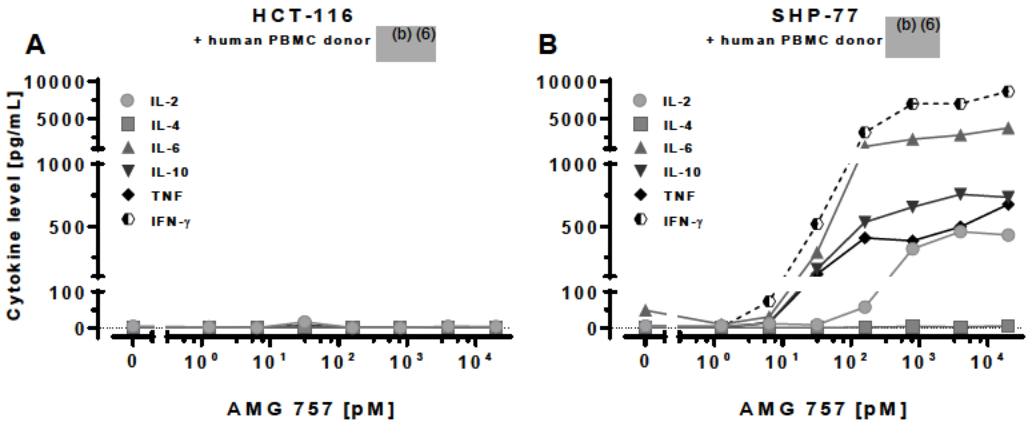
SHP-77 cells were co-cultivated with human PBMC at an E:T cell ratio of 5:1 with increasing concentrations of tarlatamab for 48 hours. Surface expression of CD69 on $CD4^+$ and $CD8^+$ T cells was determined by flow cytometry using antigen-specific fluorochrome-conjugated monoclonal antibodies. Each data point represents the mean of duplicate measurements. Error bars represent the standard deviation.
Source: Module 2.6.2 Pharmacology Written Summary (or Module 4.2.1.1 Study 122717)

Activated cytotoxic T cells secrete inflammatory cytokines following TCR engagement. The ability of tarlatamab to promote cytokine release was investigated in co-cultures of human peripheral blood mononuclear cells (PBMC) with DLL3-expressing target cells (Study Number: 122717/ eCTD Location: Module 4.2.1.1). Human T cell-induced target cell killing was accompanied by the dose-dependent release of interferon gamma (IFN-γ), interleukin (IL)-6, IL-10, tumor necrosis factor (TNF) as well as IL-2 in the presence of DLL3-positive SHP-77 cells (Figure 2B). Cytokine release was highly specific for the co-cultures that contained DLL3-expressing cells, as no cytokines were detected in co-cultures of human effector cells with DLL3-negative HCT-116 cells after exposure to tarlatamab (Figure 2A; Study 122717).

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Figure 2. Applicant – Tarlatamab-induced Release of Human Cytokines



(b) (4) CBA = cytometric bead array; DLL3 = delta-like ligand 3; E:T = effector-to-target; HCT-116 = human colon carcinoma cell line; PBMC = peripheral blood mononuclear cells; SHP-77 = human pulmonary small cell carcinoma cell line; Th1/Th2 = T helper cells 1/2

Human PBMC of 1 healthy donor were co-cultured with either target-negative HCT-116 (A) or DLL3-expressing SHP-77 (B) at an E:T cell ratio of 5:1 and increasing concentrations of tarlatamab for 48 hours. Cytokine concentrations in the cell culture supernatants were measured with the human (b) (4) CBA Th1/Th2 kit.

Source: Module 2.6.2 Pharmacology Written Summary (or Module 4.2.1.1 Study 122717)

Tarlatamab bound to cynomolgus monkey DLL3 and CD3 with similar binding affinity as to human DLL3 and CD3, and induced T-cell activation, transient cytokine production and T cell-mediated lysis of target cells in co-cultures of cynomolgus monkey effector cells and target cells that expressed cynomolgus monkey DLL3 comparable to that in the human system (Study Number: 122717/ eCTD Location: Module 4.2.1.1). Furthermore, the cynomolgus monkey was considered a relevant animal model based on similarity of DLL3 expression in cynomolgus monkey tissues as compared with human.

Following the proposal of the FDA, a murine surrogate molecule of tarlatamab, designated muS757, was developed to evaluate potential effects of a DLL3-targeting BiTE molecule on embryofetal development in mice. The comparability assessment of muS757 demonstrated similar binding affinity, bioactivity (Study Numbers 122717 (tarlatamab) and 154479 (muS757) / eCTD Location: Module 4.2.1.1), pharmacokinetic properties (Study Number 154480 / eCTD Location: Module 4.2.2.2), and tolerability profile to tarlatamab (Study Number 153960 / eCTD Location: Module 4.2.2.3), indicating that it is a suitable surrogate molecule for embryofetal toxicology assessment. The FDA, (b) (4) greed that, based on these data, muS757 is a valid surrogate for tarlatamab for embryofetal development toxicity assessment.

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In vivo, tarlatamab activity was evaluated in xenograft models of SCLC. The SHP-77 and NCI-H82 cell lines that had been characterized in the in vitro studies were used in orthotopic xenograft models. The SHP-77 cells primarily formed tumors in the lung to mimic primary SCLC tumors, and the NCI-H82 cells formed tumor metastases predominantly in liver, characteristic of typical SCLC metastasis. In addition, 2 patient-derived xenograft (PDX) tumor models that were used, LXFS 1129 and LXFS 538, were representative of the DLL3 expression levels and tumor heterogeneity observed in human SCLC tumors (Giffin et al, 2021).

The tarlatamab mechanism of action requires the simultaneous binding to DLL3 on tumor cells and CD3 on T cells. As tarlatamab does not cross-react to mouse CD3, the xenograft models used in the nonclinical pharmacology studies were conducted in immunocompromised mice (non-obese diabetic/severe combined immunodeficiency, interleukin 2 receptor gamma [NSG]) that were injected with activated, expanded human T cells before treatment with tarlatamab. Together, the xenograft models enabled direct testing of the clinical molecule tarlatamab and facilitated evaluation of pharmacodynamic activity in tumors (T-cell infiltration and/or expansion, T-cell activation, and tumor cell apoptosis) and antitumor activity.

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The FDA's Assessment:

The FDA generally agrees with the Applicant's position. In addition to these findings, the FDA notes the following results:

At a concentration of 50 ng/mL, tarlatamab bound human and cynomolgus T cells, but did not bind T cells from mice, rats, rabbits, dogs, or minipigs (Study# R20140017). Binding to human and monkey CD3 and DLL3 was further characterized in in vitro assays. Tarlatamab bound CHO cells expressing human or monkey DLL3 with K_D values of 0.64 nM and 0.5 nM, respectively; tarlatamab did not bind untransfected CHO cells (Study# 122717). As assessed by SPR, tarlatamab bound human CD3 with a K_D of 14.9 nM and monkey CD3 with a K_D of 12 nM. Additionally, tarlatamab demonstrated similar binding to human and monkey FcRn in a qualitative SPR assay (Study# 122717). Given that tarlatamab demonstrated the ability to bind monkey CD3 and DLL3 similarly to human CD3 and DLL3, the monkey was selected for toxicity testing of tarlatamab.

Tarlatamab mediated lysis of multiple human small cell lung cancer cell lines endogenously expressing DLL3 on the cell surface by human and monkey PBMCs but did not mediate lysis of HCT-116 human colon cancer cells that do not express DLL3 (Study # 122717). Cytotoxicity was also dependent on the expression level of DLL3 on target cells as demonstrated by findings of lower EC_{50} values in assays with target cells expressing high levels of DLL3 (SHP-77, EC_{50}=32 pM) compared to assays using target cells with intermediate (COR-L279, EC_{50} = 57 pm) or low levels of DLL3 (H-2171, EC_{50}=161 pM).

Tarlatamab-mediated T cell lysis of $DLL3^+$ target cells was time-dependent with cytotoxicity initially observed after 16 hours of culture and maximum cytotoxicity observed after 48 hours of culture. Though maximum cytotoxicity increased over time, EC_{50} values remained consistent across the incubation period with EC_{50} values of 23.2 pM to 41.4 pM for co-cultures with DMS 79 cells and EC_{50} values of 5.5 to 7.7 pM for co-cultures with SHP-77 cells (Study # 122717).

The effect of donor variability on in vitro T cell mediated lysis was assessed by co-culturing human PBMCs (n=12) with $DLL3^+$ SHP-77 target cells at an effector-to target cell ratio (E:T) of 5:1 for 48 hours, then evaluating target cell viability by flow cytometry. PBMCs from all donors mediated cytotoxicity of SHP-77 cells with an average EC_{50} of 26.4 pM and maximum cytotoxicity of 74% to 86% (Study # 122717).

The ability of tarlatamab to mediate lysis of $DLL3^+$ target cell by CD4 or CD8 T cells was evaluated in an in vitro assay (Study# R20140017). CD4 and CD8 T cells were enriched from human PBMCs and co-cultured with SHP-77 cells at an E:T of 5:1 for up to 72 hours, then cytotoxicity was assessed by flow cytometry. Though maximal cytotoxicity was similar after 24 to 72 hours of co-culture in assays using CD4 or CD8 T cells, EC_{50} values for CD4-mediated lysis

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(EC_{50}=29.7 pM to 47.8 pM) were slightly higher than EC_{50} values for CD8-mediated lysis (EC_{50}=3.8 to 16.1 pm). These results indicate that both CD4 and CD8 T cells contribute to tarlatamab-mediated lysis of $DLL3^+$ target cells by T cells. Similar findings were also observed in cultures using CD4 and CD8 T cells from monkey PBMCs (Study # 122717).

In the presence of DLL3-expressing SHP-77 cells, treatment with tarlatamab resulted in increased expression of CD71, PD-1, and PD-L1, in addition to CD69 expression on CD4 and CD8 T cells (Study # 122717). These findings further indicate the ability of tarlatamab to activate CD4 and CD8 T cells.

In a separate assay, treatment with tarlatamab resulted in upregulation of activation markers CD25 and CD69 on human T cells when PBMCs were cultured alone or in the presence of HCT-116 cells lacking expression of DLL3, suggesting tarlatamab may mediate T cell activation independently of DLL3 engagement; however, upregulation of CD25 and CD69 were abolished when physiological levels of human IgG were added to the assay conditions (Study # 122717). These findings suggest that low affinity binding of the ScFc region of tarlatamab to FcγRI on target cells and simultaneous binding to CD3 on T cells can induce T cell activation but competitive binding from human IgG can block tarlatamab binding to FcγRs, thereby inhibiting target-independent T cell activation. These findings were further confirmed in an assay using an anti-CD64 blocking antibody (Study # 122717).

Dose dependent cytokine release was also observed in co-cultures with H-2171, NCI-H889, and SHP-77 human SCLC cell lines (Study # 122717). Higher maximal cytokine release was noted in co-cultures with SHP-77 cells endogenously expressing high levels of DLL3 compared to H-2171 cells expressing comparatively lower levels of DLL3, further suggesting that tarlatamab activity is dependent upon expression levels of DLL3 on target cells (Study # 122717). Cytokine release was also time-dependent with maximal release of IL-2, IL-4, IL-10, TNF-α, and IFNγ occurring after approximately 16 hours of culture, then decreasing by 24 hours; however, IFNγ levels remained elevated through 72 hours of culture. Comparatively, IL-6 release peaked after 48 hours of cultures.

In addition to increased expression of activation markers in co-cultures with $DLL3^+$ target cells, tarlatamab resulted in increased expression of granzyme B and perforin, markers of cytotoxic activity on T cells (Study # 122717). Human PBMCs were co-cultured with either SHP-77 or DMS 79 human SCLC cells at an E:T of 2:1 in the presence of tarlatamab for up to 72 hours, then expression of perforin and granzyme B were assessed by flow cytometry. Up to 50% of CD8 T cells were positive for perforin in the presence of tarlatamab, though only a minor percentage of CD4 T cells expressed perforin after co-culture with DLL3-expressing target cells in the presence of tarlatamab. Tarlatamab also resulted in increased expression of granzyme B in CD4 and CD8 T cells in a concentration-dependent manner with similar maximal increases in both T cell populations (Study # 122717).

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Dexamethasone may be used clinically to antagonize severe inflammatory responses. To evaluate the effect of dexamethasone on the activity of tarlatamab, human PBMCs were co-cultured with DMS 79 or SHP-77 human small cell lung cancer cell lines in the presence of tarlatamab and dexamethasone, then T cell activation and target cell cytotoxicity were assessed by flow cytometry and supernatants were collected to evaluate cytokine release. Results were compared to co-cultures treated with tarlatamab but not dexamethasone. Though tarlatamab resulted in concentration-dependent increased expression of the T cell activation markers CD69 and CD25 in cultures treated with and without dexamethasone, maximal responses were lower and EC_{50} values were approximately 3.3- and 3.7-times higher for co-cultures with DMS 79 and SHP-77 cells, respectively. Treatment with dexamethasone also resulted in lower release of IFNγ, TNF-α, IL-10, and IL-6. These findings suggest dexamethasone may reduce tarlatamab-mediated T cell activation in the presence of $DLL3^+$ target cells (Study# 122718).

As described by the Applicant above, tarlatamab inhibited growth of multiple DLL3-expressing tumors in mice when administered intraperitoneally at doses ≥0.1 mg/kg. Anti-tumor activity of tarlatamab was associated with expansion of tumor-infiltrating CD4 and CD8 T cells in mice bearing SHP-77 or NCI-H82 SCLC tumors compared to mice treated with an isotype control (Study#s R201330093 and R20190094).

Secondary Pharmacology

The Applicant's Position:

The DLL3 expression profile was analyzed in normal human and cynomolgus monkey tissues:

- DLL3 transcript variants exist that do not contain the sequences recognized by tarlatamab (Study Numbers: 124207; 124208/ eCTD Location: Module 4.2.1.2).
- The quantification of canonical DLL3 transcripts that contain the tarlatamab binding region indicates extremely low levels of expression in a small subset of normal tissues (Study Numbers: 122642; 123658; 124208; / eCTD Location: Module 4.2.1.2).
- The DLL3 protein expression is extremely low in this limited subset of tissues (Study Numbers: 123377 and 123293/ eCTD Location: Module 4.2.1.2).
- The expression pattern appears to be restricted to the cytoplasm although membranous expression below the limit of detection might be possible (Study Number: 123377/ eCTD Location: Module 4.2.1.2).

Therefore, it is anticipated that tarlatamab administration is not associated with secondary pharmacodynamics leading to normal tissue damage since DLL3 in the cytoplasm would not be accessible to tarlatamab.

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To evaluate the potential for off-target activation of platelets, tarlatamab was tested in a flow cytometry assay for platelet activation at concentrations of 125, 41.7, 13.9, 4.6, 1.5, and 0.5 µg/mL in both human and cynomolgus monkey whole blood. No activation of platelets was observed in either human or cynomolgus monkey whole blood (Study Number 122111 / eCTD Location: Module 4.2.1.2).

The FDA's Assessment:
The FDA generally agrees with the Applicant's position. Additional findings include:

Non-canonical DLL3 mRNA transcript variants were identified in normal human and monkey tissues, but these transcripts do not contain sequences coding for tarlatamab binding regions of DLL3 (Study# 123658, 124207). DLL3 mRNA transcripts for canonical, full length DLL3 were identified at low levels in in the optic nerve of monkeys and the brains of humans and monkeys (Study#s 124208, 123658, 122642).

As assessed by immunohistochemistry, cytoplasmic DLL3 staining was noted in the pituitary, pancreatic islets, and in neurons in several regions of the brain (cerebrum, cerebellum, hypothalamus, hippocampus), though staining was noted as generally weak to occasionally mild in intensity (Study# 123377). These findings suggest that though DLL3 may be expressed in some tissues, DLL3 is retained intracellularly and would not be expected to be accessible for tarlatamab.

Safety Pharmacology

Consistent with the International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use Guideline: Nonclinical Evaluation for Anticancer Pharmaceuticals S9 (ICH, 2010) no stand-alone safety pharmacology studies were conducted for tarlatamab. Electrocardiographic assessments, respiratory rate, body temperature measurements, and neurologic examinations were included on the toxicology studies in the cynomolgus monkey (Section 5.5.1 / Study Numbers 121423; 121424; 122516 / eCTD location: Module 4.2.3.2).

The FDA's Assessment:
The FDA agrees.

5.4. ADME/PK

The Applicant's Position:

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The pharmacokinetics (PK) of tarlatamab was characterized after single intravenous (IV) bolus injections (Study 121985 / eCTD Location: Module 4.2.2.2), short IV infusions (Study 121424 / eCTD Location: Module 4.2.3.2), IVs slow bolus administration (Study 122516 / eCTD Location: Module 4.2.3.2), and subcutaneous administration in cynomolgus monkeys (Study 157064 / eCTD Location: Module 4.2.3.6). After a single IV bolus injection, serum concentrations of tarlatamab declined in a biphasic manner with a mean terminal half-life of 234 hours (Study 121985 / eCTD Location: Module 4.2.2.2).

The toxicokinetics (TK) of tarlatamab was characterized in cynomolgus monkeys after weekly IV doses of 50, 500, and 4500 mg/kg for up to 3 months. The studies have been described in detail in Section 2.2 of Module 2.6.6, Toxicology Written Summary. Briefly, tarlatamab exposure increased with dose and with repeated dosing. No difference (within 2-fold) in exposure, as assessed by the area under the curve from the time of dosing to the last measurable concentration (AUC_{last}) and calculated drug concentration at time 0 after IV bolus dose (C_0) was observed between male and female animals.

The TK of muS757 was characterized in BALB/c mice after weekly IV doses of 50, 500, and 4500 mg/kg for up to 28 days. The study has been described in detail in Section 2.2 of Module 2.6.6, Toxicology Written Summary. Briefly, muS757 exposure was dose-proportional and increased over time, particularly at the ≥ 500 mg/kg dose levels. There was no sex-based difference in exposure in AUC_{last} and maximum observed concentration (C_{max}) on days 1 and 22.

muS757 exposure increased approximately in proportion to dose in both females and fetuses. At the single sampling time point included (GD 13, 120 hr) fetal serum concentrations were 22.6- to 29.5-fold higher than female serum concentrations (Reference Table 8 and Table 9).

The FDA's Assessment:

The FDA generally agreed with the Applicant's summaries of the nonclinical ADME/PK data; however, see the FDA's additional noteworthy results and comments below.

Type of Study	Major Findings
Absorption	
Collection of Samples for Pharmacokinetic Analysis of PL-45242, PL-45244 and PL-45246 in Naïve Male Cynomolgus Monkeys Following a Single Bolus Intravenous Dose (Study# 121985)	• Male monkeys (n=2) were administered a single IV dose of 12 µg/kg tarlatamab PK Parameters in Monkeys: C_{max} (µg/mL): 0.239 AUC_{last} (µg·hr/mL): 16.7 $T_{1/2}$ (hr): 234 CL (mL/h/kg): 0.487 V_{ss}: 146 Hr = hours CL = clearance V_{ss} = volume of distribution at steady state

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.

Reference ID: 5382024

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>A Repeat-Dose muS757 Pharmcokinetic and Immunogenicity Study in BALB/c Mice (Study# 154480)</td><td>
• Female BALB/c mice (n=3/group) were untreated or administered 0.5 mg/kg of muS757, a murine tarlatamab surrogate, on Days 1, 8, 15, and 22 via IV bolus injection.
PK Parameters for repeat dosing of muS757 in Mice:
<table>
<tr><th></th><th>Day 1</th><th>Day 22</th></tr>
<tr><td>C_{max} (µg/mL)</td><td>8.08</td><td>11.50</td></tr>
<tr><td>AUC_{last} (µg·hr/mL)</td><td>500</td><td>754</td></tr>
<tr><td>AUC_{168h} (µg·hr/mL)</td><td>358</td><td>754</td></tr>
<tr><td>AUC_{inf} (µg·hr/mL)</td><td>580</td><td>1310</td></tr>
<tr><td>$T_{1/2}$ (hr)</td><td>119</td><td>140</td></tr>
<tr><td>CL (mL/h/kg)</td><td>0.86</td><td>0.38</td></tr>
<tr><td>V_z</td><td>148</td><td>77</td></tr>
</table>
Hr = hours
CL = clearance
V_z = volume of distribution
</td></tr>
<tr><td>Distribution</td><td>Not conducted</td></tr>
<tr><td>Metabolism</td><td>Not conducted</td></tr>
<tr><td>Excretion</td><td>Not conducted</td></tr>
<tr><td>28-Day Intravenous Infusion Toxicology Study in Cynomolgus Monkeys with a 28-Day Recovery Period (Study# 121424)</td><td>
Monkey
T_{max}: 0.08-2.7 hours
Dose proportionality: C_0 and AUC_{last} increased greater than dose-proportionally from 50 µg/kg to 500 µg/kg in females on Days 1 and 22. C_0 and AUC_{last} increased less than dose-proportionally in from 500 µg/kg to 4500 µg/kg in males and females on Day 22.
Accumulation: AUC_{last} was up to 4.2-times higher in females at 50 µg/kg and 500 µg/kg on Day 22 compared to Day 1, suggesting slight accumulation.
Sex differences: Exposure (C_0 and AUC_{last}) was up to 3.7-times higher in males than females at 50 µg/kg on Day 1.
Anti-drug antibodies (ADA): ADAs were detected at all dose levels and resulted in decreased exposure in the 4500 µg/kg group on Day 22.
<table>
<tr><th rowspan="2">Day</th><th rowspan="2">Dose (ug/kg)</th><th colspan="2">C_0 (µg/mL)</th><th colspan="2">AUC_{last} (µg·hr/mL)</th><th colspan="2">T_{max} (hr)</th></tr>
<tr><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th></tr>
<tr><td rowspan="3">1</td><td>50</td><td>0.731</td><td>0.199</td><td>38.4</td><td>10.2</td><td>0.08</td><td>0.08</td></tr>
<tr><td>500</td><td>11.2</td><td>7.59</td><td>565</td><td>415</td><td>0.08</td><td>1.7</td></tr>
<tr><td>4500</td><td>88.3</td><td>102</td><td>4780</td><td>5120</td><td>0.08</td><td>0.08</td></tr>
<tr><td rowspan="3">22</td><td>50</td><td>1.15</td><td>0.448</td><td>80</td><td>43.3</td><td>0.08</td><td>2.7</td></tr>
<tr><td>500</td><td>12.2</td><td>12.7</td><td>633</td><td>1090</td><td>0.08</td><td>0.08</td></tr>
<tr><td>4500</td><td>43.5</td><td>81.1</td><td>754</td><td>3130</td><td>0.08</td><td>0.08</td></tr>
</table>
Hr = hours
</td></tr>
<tr><td>AMG-757: 3-Month Intravenous Toxicology Study in the Cynomolgus Monkey (Study# 122516)</td><td>
Monkey
T_{max}: approximately 0.083 hours
Dose proportionality: Exposure (C_0 and AUC_{last}) increased approximately dose-proportionally on Days 1 and 22. C_0 and AUC_{last} increased greater than dose proportionally in males from 50 µg/kg to 4500 µg/kg on Day 85.
</td></tr>
</table>

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Reference ID: 5382024

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td></td><td>Accumulation: C_0 and AUC_{last} increased 2.1- to 4.9-fold in females at 50 µg/kg and 4500 µg/kg and males at 4500 µg/kg on Day 85 compared to Day 1. No accumulation was noted in males at 50 µg/kg.
Sex differences: No sex differences
Anti-drug antibodies (ADA): ADAs were detected at 50 µg/kg (6/8 animals) and 4500 µg/kg (7/8 animals) on Day 85.
<table>
<tr><th rowspan="2">Day</th><th rowspan="2">Dose (ug/kg)</th><th colspan="2">C_0 (µg/mL)</th><th colspan="2">AUC_{last} (µg·hr/mL)</th></tr>
<tr><th>M</th><th>F</th><th>M</th><th>F</th></tr>
<tr><td rowspan="2">1</td><td>50</td><td>1.44</td><td>1.31</td><td>79.9</td><td>68.8</td></tr>
<tr><td>4500</td><td>128</td><td>123</td><td>6970</td><td>7040</td></tr>
<tr><td rowspan="2">22</td><td>50</td><td>2.12</td><td>1.98</td><td>225</td><td>165</td></tr>
<tr><td>4500</td><td>231</td><td>214</td><td>21600</td><td>19600</td></tr>
<tr><td rowspan="2">85</td><td>50</td><td>1.47</td><td>2.76</td><td>146</td><td>335</td></tr>
<tr><td>4500</td><td>362</td><td>268</td><td>43700</td><td>27400</td></tr>
</table>
Hr = hours</td></tr>
<tr><td>muS757: 1-Month Intravenous Toxicology Study in the BALB/c Mouse
(Study# 153960)</td><td>Mouse
T_{max}: 0.5 hours
Dose proportionality: Exposure (C_0 and AUC_{last}) increased approximately dose-proportioanlly on Days 1 and 22.
Accumulation: C_0 and AUC_{last} were up to 2.6-times higher in males and females at 4500 µg/kg on Day 22 compared to Day 1, suggesting slight accumulation.
Sex differences: No sex differences
<table>
<tr><th rowspan="2">Day</th><th rowspan="2">Dose (µg/kg)</th><th colspan="2">C_{max} (µg/mL)</th><th colspan="2">AUC_{last} (µg·hr/mL)</th><th colspan="2">T_{max} (hr)</th></tr>
<tr><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th></tr>
<tr><td rowspan="3">1</td><td>50</td><td>1.3</td><td>1.1</td><td>70.7</td><td>54.3</td><td>0.5</td><td>0.5</td></tr>
<tr><td>500</td><td>9.9</td><td>8.4</td><td>530</td><td>448</td><td>0.5</td><td>0.5</td></tr>
<tr><td>4500</td><td>83.8</td><td>90.9</td><td>6250</td><td>5860</td><td>0.5</td><td>0.5</td></tr>
<tr><td rowspan="3">22</td><td>50</td><td>1.5</td><td>1.4</td><td>103</td><td>80.4</td><td>0.5</td><td>0.5</td></tr>
<tr><td>500</td><td>13.7</td><td>14.0</td><td>1170</td><td>1060</td><td>0.5</td><td>0.5</td></tr>
<tr><td>4500</td><td>171.0</td><td>172.0</td><td>15100</td><td>15000</td><td>0.5</td><td>0.5</td></tr>
</table>
Hr = hours</td></tr>
</table>

5.5. Toxicology

5.5.1. General Toxicology

All pivotal nonclinical studies were conducted in good laboratory practice (GLP)-compliant testing facilities in the US, that are signatories of the Organization for Economic Cooperation and Development Mutual Acceptance of Data program in accordance with the Organization for Economic Cooperation and Development Test Guidelines and Principles of GLP.

While the target (DLL3) expression is low and mainly cytoplasmic in normal cells, DLL3 is

upregulated in neuroendocrine tumor cells and localizes to the tumor cell surface. This differential expression profile makes DLL3 a compelling, tumor-selective therapeutic target. Therefore, tarlatamab-associated changes observed in the toxicology studies were limited and are consistent with the expected mechanism of action given that DLL3 has a limited tissue distribution combined with low levels of intracellular expression.

The cynomolgus monkey was selected as species for nonclinical safety evaluation of tarlatamab based on target binding affinity and bioactivity data. The IV route of administration was chosen for in vivo nonclinical studies based on the intended clinical route of administration. Due to the physicochemical properties of tarlatamab, the maximal feasible dose that could be administered to cynomolgus monkey was limited to 4500 μg/kg.

The nonclinical safety assessment of tarlatamab was based on a 10-day exploratory as well as 28-day GLP and 3-month GLP repeat-dose IV toxicology studies with once weekly doses of up to 4500 μg/kg.

In the 10-day exploratory toxicology study with dosages of ≤ 1000 μg/kg, tarlatamab-related effects were limited to a body temperature increase in a single high-dose animal on day 10, decreases in lymphocyte populations, minimal increases in C-reactive protein (CRP), monocyte chemoattractant protein-1 (MCP-1) and IFNγ serum concentrations. Tarlatamab-related light microscopy findings were limited to minimal and mild mixed inflammatory cell infiltration in lung, liver, and pituitary gland with no indication of cellular damage in any tissue.

In the 28-day study with dosages of ≤ 4500 μg/kg, tarlatamab-related changes consistent with redirected cell lysis were limited to a minor decrease in lymphocyte populations (detected after the second dose only) at 4500 ≤μg/kg. The only other tarlatamab-related effects were a slightly increased heart rate (on day 2 but not at day 23) at ≥ 500 μg/kg as well as a minimal to mild mixed cell infiltrate comprised of lymphocytes and eosinophils in the pituitary at 50 μg/kg and 500 μg/kg which showed evidence of reversibility by the end of the 28-day recovery period. A dose-related increase in incidence of antidrug antibodies (ADAs) occurred, which potentially contributed to variability in exposure levels at the end of the study. One animal had vascular injury-associated changes in the heart and lung that were consistent with secondary effects likely mediated by ADA-related immune complexes.

In the 3-month study, tarlatamab-related clinical pathology changes were limited to a minimal decrease in lymphocytes at 4500 μg/kg, the maximum dose administered. In addition, tarlatamab-related changes were observed in the pituitary gland at ≥ 50 μg/kg, characterized as a minimal to mild mononuclear cell infiltrate composed primarily of lymphocytes with no evidence of tissue injury.

Local tolerance of IV administration of tarlatamab was evaluated in the 28-day and the 3-month toxicology studies in the cynomolgus monkey. In the 28-day as well as the 3-month study, no evidence of irritation or other local tarlatamab-related effects were observed at the IV administration sites.

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Tarlatamab-related changes are reversible and clinically monitorable, and the highest non-severely toxic dose was determined to be 4500 μg/kg based on the absence of any tarlatamab-related adverse findings.

Following the proposal of the FDA, a murine surrogate molecule of tarlatamab, designated muS757, was developed to evaluate potential effects of a DLL3-targeting BiTE molecule on embryofetal development in mice.

Tarlatamab: 28-Day Intravenous Infusion Toxicology Study in the Cynomolgus Monkey with a 28-Day Recovery Period / Study Number: 121424 / eCTD location**:** Module 4.2.3.2 Key Drug-related Adverse Findings No adverse effects on any toxicology or safety pharmacology parameters evaluated at up to the high dose of 4500 μg/kg weekly for 28 days as well as after the 28-day recovery period. GLP compliance: Yes

Methods	
Dose and frequency of dosing:	0, 50, 500, 4500 μg/kg weekly for 28 days; 0 and 500 μg/kg for 28 days and 28-day recovery phase
Route of administration:	IV infusion (4-min infusion)
Formulation/Vehicle:	(b) (4) glutamic acid, (b) (4) sucrose, (b) (4) polysorbate 80, pH 4.2)
Species/Strain:	Monkey/Cynomolgus monkey
Number/Sex/Group:	3/sex/group; 2/sex/group for recovery
Age:	2.5 to 4.6 years
Satellite groups:	None
Major Effects	- There were tarlatamab-related slight increases in heart rate at ≥ 500 μg/kg that were associated with decreased PR, RR, and QT intervals. Throughout the 24 hour collection period, the mean change in heart rate was less than 10% higher than the control group. - Changes were not evident in any animal regardless of ADA status on day 23. Given the low magnitude of the heart rate increase and the absence of an effect at the end of study despite continued dosing, this finding was not considered adverse.

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	- At the end of the dosing phase, minimal to mild levels of tarlatamab-related mixed cell infiltrates were observed in the pituitary gland in 3 of 6 animals at both 50 and 500 mg/kg. The infiltrates were comprised predominantly of lymphocytes together with variable-to-abundant numbers of eosinophils and were restricted to the interface between the pars intermedia and pars nervosa, which is consistent with the expression pattern of DLL3 in the pituitary (Study 123377). There was no evidence of tissue injury associated with the infiltrate. - Despite higher exposure levels at 4500 µg/kg, the absence of this change correlated with the presence of ADAs in all animals at this dose level as well as 3 of 6 animals at 500 mg/kg. - After the recovery phase, the mixed cell infiltrate in the pituitary gland was partially reversed, with full reversibility expected with additional time.
Tabulated TK parameters	Table 6

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Reference ID: 5382024

Table 6. Applicant – Toxicokinetic Parameters for Tarlatamab After IV Administration for 28 days in the Cynomolgus Monkey (Sexes Combined)

Dose (mg/kg)			Day 1 T_{max} (hr)	Day 1 C_0 (mg/mL)	Day 1 AUC_{last} (hr·mg/mL)	Day 22 T_{max} (hr)	Day 22 C_0 (mg/mL)	Day 22 AUC_{last} (hr·mg/mL)
50	All Animals	N	6	6	6	6	6	6
		Mean	0.08	0.465	24.3	1.4	0.801	61.6
		SD	0	0.404	21.9	3.2	0.477	25.6
	ADA Negative Only[a]	N	5	5	5	5	5	5
		Mean	0.08	0.554	29.2	0.08	0.905	65.8
		SD	0	0.381	20.6	0	0.452	26.3
500	All Animals	N	10	10	10	10	10	10
		Mean	0.87	9.41	490	0.08	12.5	861
		SD	2.5	3.5	139	0	4.83	662
	ADA Negative Only[a]	N	10	10	10	4	4	4
		Mean	0.87	9.41	490	0.08	16.4	1430
		SD	2.5	3.5	139	0	1.54	115
4500	All Animals	N	6	6	6	6	6	6
		Mean	0.08	95.1	4950	0.08	62.3	1940
		SD	0	8.33	280	0	46.6	2570
	ADA Negative Only[a]	N	6	6	6	0	0	0
		Mean	0.08	95.1	4950	N/A	N/A	N/A
		SD	0	8.33	280			

ADA = antidrug antibody; AUC_{last} = area under the concentration-time curve from time zero to the time of the last quantifiable concentration (up to 168 hours); C_0 = calculated drug concentration at time zero after an IV bolus dose; n = number of animals; N/A = not applicable; SD = standard deviation; T_{max} = time to reach C_{max}.

[a] For day 1 data, ADA negative animals did not have detectable binding ADAs at the prestudy time point. For day 22 data, ADA negative animals did not have detectable binding ADAs at both day 22 and day 29 time points.

Tarlabamab concentrations were not quantifiable in plasma samples collected from the control group.

Tarlatamab concentrations were also measured in the cerebral spinal fluid (CSF) in all animals at the end of the study. On day 29, tarlatamab was detected in the CSF of 3 animals (2 ADA negative animals at 500 μg/kg and 1 ADA positive animal at 4500 μg/kg) with concentrations of 2.13 ng/mL and 4.28 ng/mL at 500 μg/kg and 3.15 ng/mL at 4500 μg/kg, which corresponds to approximately 0.05% of the exposure level detected in serum at the same time point.

Tarlatamab: 3-Month Intravenous Toxicology Study in the Cynomolgus Monkey / Study Number: 122516 /eCTD location**:** Module 4.2.3.2
Key Drug-related Adverse Findings
No adverse effects on any toxicology or safety pharmacology parameters evaluated at up to the high dose of 4500 μg/kg weekly for 3 months.

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Reference ID: 5382024

GLP compliance: Yes

Methods	
Dose and frequency of dosing:	0, 50, 4500 µg/kg weekly for 3 months
Route of administration:	IV (slow) bolus
Formulation/Vehicle:	(b) (4) Diluent (b) (4)-glutamic acid, (b) (4) sucrose, (b) (4) polysorbate 80, pH 4.2)
Species/Strain:	Monkey/Cynomolgus monkey
Number/Sex/Group:	4/sex/group
Age:	2.2 to 2.4 years
Satellite groups:	None
Major Effects	- Tarlatamab-related clinical pathology changes were limited to a minimal decrease in lymphocytes at 4500 µg/kg. By light microscopy, there were tarlatamab-related changes in the pituitary gland at ≥ 50 µg/kg, characterized as a minimal to mild mononuclear cell infiltrate composed primarily of lymphocytes, located at the interface between the pars intermedia and pars nervosa, with occasional infiltration into the pars intermedia, which is consistent with the expression pattern of DLL3 in the pituitary - Additional microscopic changes at ≥ 50 µg/kg included a minimal, mononuclear, and/or mixed inflammatory cell infiltrate in multiple tissues (heart, lung, brain, and gallbladder) composed primarily of small foci of lymphocytes with a perivascular orientation. Although the cell infiltrate is similar in composition, severity, and distribution to a spontaneous infiltrate commonly observed in this species, the increased incidence in multiple tissues of animals administered tarlatamab was attributed to the IV administration of a foreign biotherapeutic and/or the presence of ADAs
Tabulated TK parameters	Table 7

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Reference ID: 5382024

Table 7. Applicant – Toxicokinetic Parameters for Tarlatamab After IV Administration for 3 Months in the Cynomolgus Monkey (Sexes Combined)

Dose (mg/kg)		Day 1		Day 22		Day 85	
		C_0 (mg/mL)	AUC_{last} (hr·mg/mL)	C_0 (mg/mL)	AUC_{last} (hr·mg/mL)	C_0 (mg/mL)	AUC_{last} (hr·mg/mL)
50	N	8	8	8	8	6[a]	6[a]
	Mean	1.37	74.4	2.05	195	2.33	272
	SD	0.0966	7.13	0.296	57.1	2.03	268
4500	N	8	8	8	8	8	8
	Mean	126	7000	222	20600	315	35500
	SD	14.9	602	28.6	5010	90.1	13200

AUC_{last} = area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (up to 168 hours); C_0 = calculated drug concentration at time 0 after an IV bolus dose; IV = intravenous
[a] There were insufficient data points to ascertain mean C0 or AUClast on day 85 for 2 animals.

Table 8. Applicant – Tabulated Summary of the Non-pivotal Toxicology Studies

muS757: 1-Month Intravenous Toxicology Study in the BALB/c Mouse / Study Number: 153960 / eCTD location: Module 4.2.2.3**:** Key Drug-related Adverse Findings No adverse effects on any toxicology parameter evaluated at up to the high dose of 4500 µg/kg weekly for 1 month. GLP compliance: No	
<u>Methods</u>	
Dose and frequency of dosing:	0, 50, 4500 µg/kg weekly for 1 month
Route of administration:	IV bolus
Formulation/Vehicle:	(b) (4) Diluent ((b) (4) glutamic acid, (b) (4) sucrose, (b) (4) polysorbate 80, pH 4.2)
Species/Strain:	Mouse/BALB/c
Number/Sex/Group:	10/sex/group
Age:	7 weeks
Satellite groups:	Toxicokinetics: n=6/sex/group
Major Effects	- Clinical pathology changes related to muS757 at ≥ 500 µg/kg on day 29 limited to a minimal decrease in total white blood cells (males and

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	females) associated with a decrease in lymphocytes and neutrophils (males only). - A minimal decrease in triglycerides was observed in males only.
Tabulated TK parameters	Table 8
Tarlatamab: 10-Day Intravenous Toxicology Study in the Female Cynomolgus Monkey / Study Number: 12123 / eCTD location: Module 4.2.3.2 Key Drug-related Adverse Findings No adverse effects on any toxicology or safety pharmacology parameter evaluated at up to the high dose of 1000 µg/kg once weekly for 10 days. GLP compliance: No	
Methods	
Dose and frequency of dosing:	100, 1000 µg/kg weekly for 10 days
Route of administration:	IV bolus
Formulation/Vehicle:	(b) (4) Diluent ((b) (4) glutamic acid, (b) (4) sucrose, (b) (4) polysorbate 80, pH 4.2)
Species/Strain:	Monkey/Cynomolgus monkey
Number/Sex/Group:	2/females/group
Age:	2 to 5 years
Satellite groups:	None
Major Effects	- Body temperature was increased in a single high-dose animal on day 10. - Minimal transient increase of C-reactive protein (CRP) in the 2 low dose animals and one high dose animal 24 hours after the first dose. One high-dose animal had a minimal increase in serum CRP on day 11. - Slight test article-related increases in concentrations of IFNγ and MCP-1. No significant increases in IL-6 and TNFa levels.
Tabulated TK parameters	Table 9

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Reference ID: 5382024

Table 9. Applicant – Mean Serum muS757 Noncompartmental Toxicokinetic Parameters in BALB/c Mice Following Once Weekly Intravenous Bolus Injection of muS757 at 50, 500 or 4500 µg/kg

	Days					
	Day 1			Day 22		
Dose (µg/kg)	T_{max} (hr)	C_{max} (ng/mL)	AUC_{last} (hr*ng/mL)	T_{max} (hr)	C_{max} (ng/mL)	AUC_{last} (hr*ng/mL)
50	0.05	1150	62500	0.05	1440	91800
500	0.05	9280	493000	0.05	13900	1110000
4500	0.05	88100	6080000	0.05	171000	150000000

AUC_{last} = area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (up to 168 hours); T_{max} = time where the maximum concentration was observed

Table 10. Applicant – Tarlatamab Serum Toxicokinetics Following Repeat Weekly Intravenous Bolus Administration to Female Cynomolgus Monkeys for 10 days

Dose (µg/kg)	Subject	AUC_{all} (µg*day/mL)	AUC_{0-48} (µg*day/mL)	$AUC_{168-216}$ (µg*day/mL)	AR	$C_{max\ obs_dose1}$ (µg/mL)	$C_{max\ obs_dose2}$ (µg/mL)
100	1501	16.2	3.58	3.90	1.09	2.73	4.14
	1502	15.5	4.06	3.62	0.891	3.87	3.85
1000	2501	110	27.6	26.3	0.954	24.3	28.9
	2502	98.5	24.2	24.4	1.01	23.8	24.3

AUC_{all} = AUC from time 0 to 240 hr; AUC_{0-48}=AUC from time 0 to 48 hours; $AUC_{168-216}$=AUC from time 168 to 216 hours; AR= accumulation ratio of AUC from 0 to 48 hours following administration of dose 2 ($AUC_{168-216hr}$)/AUC from 0 to 48 hours following administration of dose 1 (AUC_{0-48hr}); $C_{max\ obs_dose1}$ = maximum observed serum concentration following the administration of the first dose of tarlatamab; $C_{max\ obs_dose2}$ = maximum observed serum concentration following the administration of the second dose of tarlatamab.

The FDA's Assessment:

The FDA generally agrees with the Applicant's summaries of the repeat-dose toxicology studies in monkeys. Though the monkey was chosen for toxicity testing based on the ability of tarlatamab to bind human and monkey CD3 and DLL3 similarly in in vitro assays, toxicity associated with tarlatamab may be underrepresented in the monkey given that immunohistochemistry data described above indicates that DLL3 is expressed intracellularly in normal tissues and cells.

In addition to decreases in lymphocytes that were noted in all toxicology studies in monkeys, increases in large unstained cells (up to 213%) and decreases in neutrophils (up to -52%) were noted at ≥50 µg/kg in the 1-month study and decreased eosinophils (up to -76%) were noted at

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4500 µg/kg in the 3-month study compared to controls. All hematologic changes noted in the 1-month study improved after a drug-free recovery period.

Though interpretation of findings from the 10-day study in monkeys is limited by the study design, including lack of a vehicle-treated control and limited number of animals (n=2 females/group), findings suggestive of a systemic inflammatory response were noted in monkeys administered 1000 µg/kg, including transient increases in CRP (300%) and neutrophils (468%) that occurred 4 to 24 hours after the first dose compared to baseline values, as well as histological signs of minimal to mild mixed cell infiltrates in the liver, lung, and pituitary gland.

Changes in lymphocyte populations in monkeys correlated with decreased CD3, CD4, and CD8 T cell populations following the first or second dose of tarlatamab at ≥100 µg/kg in the 10-day study and at 4500 µg/kg in the 1-month study; decreases in T cell populations improved by the end of the dosing phase in the 1-month monkey study. Decreases in B cells and NK cells also occurred at ≥100 µg/kg in the 10-day monkey study.

Similar findings of decreased leukocytes, lymphocytes, and neutrophils were also noted in mice administered ≥500 µg/kg of a mouse tarlatamab surrogate, muS757, and correlated with decreased lymphoid cellularity in the lymph nodes at 4500 µg/kg.

Though signs of anemia were not observed in the 1-month or 3-month studies in monkeys administered tarlatamab or the 1-month study in mice with a mouse surrogate of tarlatamab, hematologic changes noted in the 10-Day study in monkeys included decreases in red blood cells (up to -21%), hemoglobin (up to -20%), and hematocrit (up to -21%) and increased reticulocytes (up to 447%) in animals administered ≥100 µg/kg compared to pre-dose values. These changes occurred 4 hours after the first dose and persisted through the dosing phase.

A transient increase in AST (up to 450% compared to pre-dose values) occurred at 1000 µg/kg in the 10-day study following the first dose but improved by the end of the dosing phase. The relevance of this finding is unclear as there was no histologic correlate and liver changes were not noted at doses ≤4500 µg/kg in the 1-month or 3-month monkey studies.

Though transient increases in heart rate were observed at doses ≥500 µg/kg in the 1-month toxicology study, this finding was only noted in 2 male monkeys on Day 2 and increased heart rate or other ECG changes were not noted in the 3-month monkey study.

Additional findings noted in the 3-month monkey study at doses ≥50 µg/kg include abnormal feces color and decreased thyroid weight, though the relevance of these findings is unclear as no correlates were identified and they only occurred in females.

There were no notable findings in reproductive organs in the 10-day, 1-month, or 3-month

repeat-dose toxicology studies in monkeys.

5.5.2. Genetic Toxicology

The Applicant's Position:

No studies evaluating the genotoxic or mutagenic potential of tarlatamab have been conducted. Tarlatamab is a recombinant BiTE molecule made up entirely of naturally-occurring amino acids and contains no inorganic or synthetic organic linkers or other non-protein portions. Therefore, no genotoxicity studies have been conducted or are planned, consistent with ICH Harmonised Tripartite Guideline S6, "Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals" (ICH S6[R1], 2011).

The FDA's Assessment:
The FDA agrees.

5.5.3. Carcinogenicity

The Applicant's Position:

No carcinogenicity studies have been conducted nor are any planned in accordance with ICH S9 (ICH, 2010).

The FDA's Assessment:
The FDA agrees.

5.5.4. Reproductive and Developmental Toxicology

Following the proposal of the FDA, a murine surrogate molecule of tarlatamab, designated muS757, was developed to evaluate potential effects of a DLL3-targeting BiTE molecule on embryofetal development in mice. The study objectives were to detect potential adverse effects of muS757 on pregnant Crl:CD1 female mice and development of the embryo and fetus consequent to exposure of the female from implantation to closure of the hard palate (Study Number 122517/ eCTD location: Module 4.2.3.5.2).

Timed-mated female mice (22/group) received the vehicle control, 500 or 4500 mg/kg muS757 via IV bolus injection on gestation days (GD) 6 and 13. There were no muS757-related effects on any maternal parameters, including mean maternal body weights or body weight gains. In

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addition, there were no muS757-related macroscopic findings or effects on any ovarian, uterine, or litter parameters at any dose level. Administration of muS757 did not produce any fetal external, visceral, or skeletal malformations or variations.

muS757: An Embryofetal Development Study by Intravenous (Bolus) Injection in Mice / Study Number 122517/ eCTD location: Module 4.2.3.5.2 Study type: Embryofetal development Key Drug-related Adverse Findings: No muS757-related maternal effects were observed at any dose level. There were no muS757-related effects on embryofetal viability or growth, and no muS757-related malformations or variations were observed during external, visceral, or skeletal examination. GLP compliance: Yes

Methods	
Dose and frequency of dosing:	0, 500, 4500 µg/kg on gestation day (GD) 6 and 13
Route of administration:	IV bolus
Formulation/Vehicle:	(b) (4) glutamic acid, (b) (4) sucrose, (b) (4) polysorbate 80, pH 4.2
Species/Strain:	Mouse/ Crl:CD1
Number/Sex/Group:	22/female/group
Age:	72 to 86 days at initiation of dose administration
Satellite groups:	Toxicokinetics: n=9/group (except for the vehicle control, n=3) with dosing on GD 6 and 13
Study design:	- Timed-mated female mice received vehicle control, 500 or 4500 µg/kg muS757 via IV bolus injection on gestation days 6 and 13. - All mice were monitored for: maternal viability, maternal clinical signs, maternal body weights, and maternal body weight changes. - In addition, main study mice were evaluated for macroscopic observations and ovarian and uterine contents (number and distribution of corpora lutea, implantations, live and dead fetuses, and early and late resorptions), and gravid uterine weights. - Fetuses were examined for external, visceral, and/or skeletal abnormalities.

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	- Blood samples were collected from maternal animals on GD 6 at 0.5, 48, and 168 hours post dose and again on GD 13 at 0.5, 48, and 120 hr post dose to determine the serum concentration and toxicokinetics of muS757. - Fetal blood samples were collected on GD 18 to determine fetal muS757 concentrations and the maternal-fetal exposure ratio.
Tabulated TK parameters	Table 11 and Table 12

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Table 11. Applicant – Summary of Toxicokinetic Parameter Estimates of muS757 on GD 6 and 13 after IV Administration of 500 and 4500 µg/kg muS757 in Mice

Dose (µg/kg)	Route	Statistics	GD 6		GD 13	
			C_0 (ng/mL)	AUC_{last} (hr*ng/mL)	C_0 (ng/mL)	AUC_{last} (hr*ng/mL)
500	IV	Mean	9410	451000	4740	149000
4500	IV	Mean	79500	4170000	77000	2300000

AUC_{last} = area under the concentration-time curve from time zero to the time of the last quantifiable concentration (up to 168 hr for GD 6 and 120 hr for GD 13).
C_0 = drug concentration at time zero after an IV bolus dose; GD = gestation day; IV = intravenous

Table 12. Applicant – Summary of Fetal and Female Concentrations and the Fetal-Maternal Ratio of muS757 on GD 13, 120 hr after IV Administration of 500 and 4500 µg/kg muS757 in Mice

Dose (µg/kg)	Route	Statistics	GD 13, 120 hr		
			Fetal Concentration (ng/mL)	Female Concentration (ng/mL)	Fetal-Maternal Ratio
500	IV	Mean	1270	43.1	29.5
4500	IV	Mean	13300	590	22.6

GD = gestation day; IV = intravenous

The FDA's Assessment:

The FDA generally agrees with the Applicant's conclusion and acknowledges that muS757 (a tarlatamab surrogate that binds mouse CD3 and DLL3) crossed the placental barrier. Additionally, there were no signs of toxicity to male or female reproductive organs in the general toxicology studies in monkeys administered repeat doses of tarlatamab.

Tarlatamab is a bispecific T cell engager and causes T cell-dependent depletion of DLL3-expressing cells. Risks associated with T cell activation include cytokine release and associated inflammatory effects. The occurrence of inflammatory adverse events in the mother may adversely affect the pregnancy.

Studies using genetically engineered mice indicate DLL3 plays roles in skeletal development during embryogenesis. DLL3 was found to be expressed intracellularly in the presomitic mesoderm of mouse embryos and to contribute to somitogenesis, a process leading to segmentation in animals that ultimately gives rise to skeletal, muscle, and other connective

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tissues (Chapman et al., 2011). Additional studies have identified DLL3 mRNA transcripts present in unfertilized oocytes and persisting through gastrulation and early organogenesis (Cormier et al., 2004; Dunwoodie et al., 1997). DLL3 loss-of function mutations or deletion of DLL3 in mice leads to delayed and irregular somite formation/segmentation, which results in a phenotype characterized by a disorganized axial skeleton and disruption of vertebral formation, including hemivertebrae associated with disorganized neural arches and rib bifurcations (Dunwoodie et al., 2002, Kusumi et al., 1998)

Further, genetic mutations in DLL3 in humans have been associated with spondylocostal dysostosis, a congenital condition causing segmentation defects of the vertebrae and abnormalities of the ribs that result in a shortened trunk and/or neck (Chapman et al., 2011). Together, these findings suggest that fetal exposure to tarlatamab may increase the risk of abnormal skeletal development.

Given that only DLL3 expressed on the cell surface is expected to be a target for tarlatamab, the intracellular expression pattern of DLL3 noted during fetal development may explain the lack of findings in the EFD study in mice using a mouse tarlatamab surrogate. Though DLL3 has been detected intracellularly during embryogenesis, it remains unknown whether DLL3 is displayed at the cell surface at other timepoints during embryofetal development.

In humans and mice, transfer of IgG antibodies from mother to fetus across the placenta is mediated by the neonatal Fc receptor (FcRn). Tarlatamab can bind the FcRn and may cross the placenta to the developing fetus similarly as an endogenous IgG antibody. Fetal serum concentrations of muS757 were approximately 30-times higher than maternal serum concentrations, indicating potential for tarlatamab to cross the placenta. Additionally, tarlatamab is based on an IgG antibody and may be present in milk; a breastfed child may be exposed to tarlatamab via lactational transfer.

Based on the mechanism of action of tarlatamab, FDA recommends including a Warning for embryo-fetal toxicity and advising females of reproductive potential to use effective contraception during treatment with tarlatamab and for 2 months after the last dose.

5.5.5. Other Toxicology Studies

The Applicant's Position:

No other toxicology studies using tarlatamab or muS757 were conducted.

The FDA's Assessment:

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The FDA agrees.

X	X
Primary Reviewer Melissa A. Pegues	Supervisor Claudia P. Miller

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6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

The Applicant submitted current BLA 761344 for the proposed indication of tarlatamab monotherapy for the treatment of adult patients with advanced small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy. The proposed dosage of tarlatamab is 1 mg on Cycle 1 day 1, followed by 10 mg on Cycle 1 days 8 and 15, and every 2 weeks (Q2W) onward (hereafter referred to as 1/10 mg) administered via a 1-hour intravenous (IV) infusion.

Study 20200491 provides the primary efficacy evidence to support the proposed indication. Part 1 of this trial is a dose randomization study which showed the overall response rate (ORR) of 40% (95% CI: 31%, 51%) in 1/10 mg cohort and 32% (95% CI: 23%, 41%) in 1/100 mg (at the same dosing schedule as 1/10 mg) with 1/10 mg cohort demonstrated a numerically lower rate of any grade neutropenia and Grade 1 and Grade 2 neurotoxicity including immune effector cell-associated neurotoxicity syndrome (ICANS), supporting the selection of 1/10 mg dosage for Part 2 and Part 3 of Study 20200491.

The key review issues are focused on the evaluation of dose selection, drug interaction management and recommendations for restarting therapy after dose delay. The population pharmacokinetics (popPK) analyses found none of the intrinsic or extrinsic covariates including age (32 to 82 years), bodyweight (35 to 149 kg), sex, race (White and Asian), mild or moderate renal impairment, or mild hepatic impairment had a clinically important effect on the pharmacokinetic (PK) of tarlatamab. The exposure-response (E-R) analyses found a positive trend between ORR and exposure with a plateau being achieved at 1/10 mg. A statistically significant positive E-R for safety was also identified for all grade neutropenia and Grade 1 and Grade 2 neurotoxicity including ICANS. The impact of anti-drug antibodies (ADAs) on efficacy, safety, and PK of tarlatamab is unknown due to a low ADA incidence of 3%. Transient elevations of circulating cytokines interleukin (IL)2, IL-6, IL-8, IL-10, and interferon-gamma (INF -γ) were observed at dosages starting at 0.3 mg. The integrated popPK, E-R, pharmacodynamics (PD) analyses along with safety, and efficacy from the Study 20200491 and the dose-finding first in human (FIH) study 20160323 support the proposed tarlatamab 1/10 mg dosing regimen.

Recommendations

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The Office of Clinical Pharmacology has reviewed the information submitted in BLA 761344. This BLA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below in
Table 13.

Table 13: 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 Study 20200491 which demonstrated ORR of 40% (95% CI: 31%, 51%) with the proposed 1/10 mg dosing regimen.
General dosing instructions	The 1/10 mg is selected with the following rationales: • The step-up dose 1 mg mitigated the risk of cytokine release syndrome (CRS), especially ≥ Grade 2 CRS for the subsequent full doses. • CRS grade and incidence for each dose event did not differ significantly across body weight (BW) quartiles, ages or DLL-3 cut-points. • The 1/10 mg dosage showed a numerically higher ORR than 1/100 mg in Study 20200491. • E-R analyses for efficacy with doses up to 100 mg showed ORR plateaued at the selected 1/10 mg. • E-R analyses for safety did not identify major safety concerns with 1/10 mg. A positive E-R safety trend was observed between tarlatamab exposure and any grade neutropenia, Grade 1 and Grade 2 neurotoxicity.
Dosage recommendations for restarting therapy after dose delay	The proposed dosage recommendation for restarting therapy after dose delay aims to mitigate CRS risk and is supported by: • Rebound CRS risk is low and no clear trend for rebound CRS increase with longer dose delays. However, data is limited for longer duration of dose delays. • Based on the totality of data including PK simulation and clinical data, FDA agrees with Applicant's proposed restart therapy recommendation.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dosage adjustment is necessary according to BW, age, sex, race (White and Asian), mild to moderate renal impairment, or mild hepatic impairment, DLL3 target expression. However, limited data on African

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Review Issue	Recommendations and Comments
	American for PK assessment and no data to assess the impact of ethnicity (e.g., Hispanic or Latino) on tarlatamab's PK/PD in the reported clinical trials. See PMC below.
Drug-drug interactions	Tarlatamab causes transient release of cytokines during CRS that may suppress cytochrome (CYP) 450 enzymes and may result in an increased exposure of concomitant CYP substrate; however, based on FDA's evaluation of literature and IL-6 concentrations, the risk of drug interaction for concomitant CYP substrates with tarlatamab appears to be low in the overall patient population. For addition detail, refer section 6.3.1.
Immunogenicity	In Study 20200491, 3.2% (4/124) of patients developed ADA and none of the patients developed neutralizing antibodies (Nab). Because of the low occurrence, the effect of ADA on the PK, PD, safety, and effectiveness of tarlatamab is inconclusive.
Labeling	Overall, the proposed labeling recommendations are acceptable upon Applicant's agreement with the FDA recommended labeling revisions.

Post-marketing Commitment

The following post-marketing commitment (PMC) is being proposed. The PMC study will be included in the Approval Letter with milestones agreed upon after negotiation with the Applicant.

PMC or PMR	Key Issue(s) to be Addressed	Rationale	Key Considerations for Design Features
☒ PMC ☐ PMR	Characterization of PK, in addition to safety and efficacy, in a population representative of the US patient population with SCLC.	Limited data on African American for PK assessment. No data to assess the impact of ethnicity (e.g., Hispanic or Latino) on PK in the reported clinical trials.	Conduct an integrated analysis from ongoing, completed, or planned clinical trials and other potential data sources as appropriate enrolling a sufficient representation of United States (U.S.) racial and ethnic minority patients that is reflective of the U.S. population of patients with SCLC, to further characterize the efficacy, safety and pharmacokinetic of tarlatamab in these patients. In the analysis, include a

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PMC or PMR	Key Issue(s) to be Addressed	Rationale	Key Considerations for Design Features
			sufficient number of patients enrolled in the U.S. and a sufficient number of racial and ethnic minority patients reflective of the incidence of SCLC in each subpopulation to allow for interpretation of the results. The analyses should support comparative efficacy and safety outcome analyses between the aforementioned populations and White patients.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

In Study 20160323 and Study 2020491, tarlatamab exhibited approximate dose-proportional increases in exposures in the evaluated dose range of 0.003 to 100 mg IV administered Q2W and 200 mg Q3W. The steady state in tarlatamab serum concentrations were approximately achieved by the start of cycle 2. The mean (SD) estimated terminal phase elimination half-life at steady state was 5.5 (1.6) days across the evaluated dose range.

Following the proposed dosing regimen of 1 mg on day 1 and 10 mg on day 8, day 15, and Q2W thereafter, tarlatamab geometric mean trough values at steady state (cycle 2 day 15 predose) and peak serum concentrations at steady state (cycle 2 day 15, end of infusion) were 0.44 and 4.3 mg/mL, respectively, based on pooled data across phase 1 and phase 2 studies. There was no indication of time dependent kinetics.

Based on population PK analyses, tarlatamab serum clearance, central volume of distribution, peripheral volume of distribution, and volume of distribution at steady state were estimated to be 0.65 L/day, 3.44 L, 5.06 L, and 8.5 L, respectively for a typical 73 kg White individual. The inter-individual variability for tarlatamab clearance and central volume of distribution were 43.7% and 38.7%, respectively.

At the proposed dosing regimen of 10 mg Q2W, the incidence of treatment-emergent antitarlatamab antibodies was 12% (3 of 25 subjects) for the first-in-human (FIH) Study 20160323 and 3.2% (4 of 124 subjects) for the pivotal phase 2 Study 20200491, for a pooled total of 7 of 149 subjects (4.7%) across the 2 studies. In the pivotal phase 2 Study 20200491, which employed the neutralizing assay, none of the subjects

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developed neutralizing antibodies. Potential impact of antitarlatamab antibodies on the PK, clinical efficacy, and clinical safety of tarlatamab was assessed with the following results:

- Based on the population PK analysis, individuals with positive antitarlatamab antibody binding status at any time during the study were estimated to have approximately 21% higher clearance, which translated to an approximately 24% decrease in serum trough concentrations on average. However, this difference in exposures did not have a clinically relevant impact on efficacy.
- At the proposed dosing regimen, the efficacy measures (including ORR, disease control rate [DCR], and DOR) were similar for antitarlatamab binding antibody positive subjects compared with those who were antitarlatamab antibody negative.
- There was no apparent impact of antitarlatamab antibody development on safety including adverse events.

A detailed description of these analyses can be found in the Integrated Summary of Immunogenicity (Module 5.3.5.3).

The Applicant's Position:

In both Studies 20160232 and 20200491, tarlatamab exhibited approximate dose-proportional increases in exposures in the evaluated dose range. The steady state in tarlatamab serum concentrations were approximately achieved by the start of cycle 2. The mean (SD) estimated terminal phase elimination half-life at steady state was 5.5 (1.6) days, across the evaluated dose range. The incidence of antitarlatamab antibody development was low. There was no meaningful clinical impact of antitarlatamab antibody development on efficacy or safety.

The FDA's Assessment:

The clinical pharmacology program included data from Studies 20160232 and 20200491. FDA agrees that the results of these studies generally provide adequate characterization of tarlatamab PK properties as described below and the PK parameters are presented as geometric mean (CV%) unless otherwise specified:

Dose proportionality: The exposure of tarlatamab increased dose proportionally in the evaluated dose range of 1 mg to 100 mg.

Distribution: Tarlatamab's steady state volume of distribution is 8.6 L (18.3%).

Elimination: Tarlatamab's median elimination half-life (min, max) is 11.2 (4.3 to 26.5) days, and the estimated clearance is 0.65 L/day (44%) in patients with SCLC. Steady state was achieved by Cycle 2 Day 15.

Immunogenicity: 3 % (4/214) of patients tested positive for ADA and none of the patients tested positive for nAb in the pivotal Study 20200491.

Refer to section 6.3.1 and 19.4.1 for details.

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6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:

The proposed dose and dosing regimen for tarlatamab for the treatment of previously treated advanced SCLC is an initial 1 mg dose on cycle 1 day 1, followed by 10 mg on cycle 1 day 8, cycle 1 day 15, and Q2W thereafter, all doses administered via a 1-hour IV infusion. The totality of exposure-response data from the dose exploration and expansion parts of the phase 1 FIH Study 20160323 (dose range 0.003 to 100 mg Q2W and 200 mg Q3W) supported the selection of 2 dose levels of 10 and 100 mg Q2W for further assessment in a randomized manner in Part 1 of the pivotal phase 2 Study 20200491. The analyses from the FIH Study 20160323 demonstrated numerically higher efficacy to be associated with 10 mg exposures relative to lower doses (1 or 3 mg). The analysis also displayed numerical benefit in DCR with exposures associated with the 100 mg Q2W regimen relative to the 10 mg Q2W regimen, therefore supporting the selection of 100 mg as the higher dose level (in addition to 10 mg) to be evaluated in pivotal Study 20200491. Importantly, from a safety and tolerability perspective, a maximal tolerated dose level was not achieved in the ongoing FIH Study 20160323, within the evaluated dose range.

Of the 2 dose levels assessed in Part 1 of pivotal Study 20200491, the 10 mg Q2W regimen was selected at the prespecified interim analysis for further evaluation in Part 2. At the time of interim analysis, measures of efficacy response were similar between the 10 and 100 mg groups. In the 10 mg group, the confirmed ORR (assessed by the investigator) was 34.4% (95% CI: 18.6, 53.2) and the DCR was 75.0% (95% CI: 56.6, 88.5). In the 100 mg group, the confirmed ORR was 35.5% (95% CI: 19.2, 54.6), and the DCR was 64.5% (95% CI: 45.4, 80.8) (Table 12 of Rationale for Recommended Phase 2 Dose [RP2D] (Module 5.3.5.2). At the time of the interim analysis, compared with the 100 mg group, subjects in the 10 mg group experienced fewer treatment-emergent adverse events (Table 19 of Rationale for RP2D). Consistent with the dose-response data, exposure-response analyses demonstrated that exposures with the 10 mg dose regimen were associated with improved tolerability but comparable efficacy relative to the 100 mg dose. Further details of the data available and analysis results at the time of prespecified interim analysis are provided in the Rationale for RP2D (Module 5.3.5.2).

To confirm the selection of 10 mg Q2W regimen, these exposure-response analyses were updated using pooled data from Study 20160323 and Study 20200491 based on the latest cutoff dates of 28 March 2023 and 27 June 2023, respectively. These analyses further confirmed that the proposed dosing regimen of 10 mg Q2W exhibited near maximal efficacy and favorable benefit-risk profile in the intended patient population.

The Applicant's Position:

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Overall, results of exposure-response analysis suggest the proposed dosing regimen of 10 mg Q2W exhibited near maximal efficacy with a limited impact on neutropenia and favorable benefit-risk profile in the intended patient population. None of the covariates evaluated in this analysis resulted in a clinically meaningful change in efficacy or safety and therefore do not warrant a dose adjustment.

The FDA's Assessment:
FDA agrees with the Applicant's position on dose selection of 1/10 mg based on efficacy and safety data from Studies 20200491 and 20160232.

The proposed 1 mg step-dose regimen appears to be acceptable based on the following assessment:

The risk of CRS of an alternative step-up dose for 10 mg target doses is unknown as no alternative step-up regimen was investigated. In Study 20160232, 1 mg step-up was investigated for all target dosages starting at 3 mg. The risk of Grade 2 or above CRS occurrence appeared to be low (≤ 30 %) at all dosages (Table 14). The 1 mg step-up was further evaluated in Study 20200491.

Following administration of 1/10 mg in Study 20200491, in the primary safety population, the majority of CRS incidences were Grade 1 (30%), with the highest rate (40%) observed following the step-up dose 1 mg on Cycle 1 Day 1 (

Table 15 and Figure 3). Grade 3 CRS occurred less frequently in the 1/10 mg cohort (1%) than in the 1/100-mg cohort (6%). The risk of CRS in the subsequent cycles of the 10 mg target doses was mitigated by the initial 1 mg step-up dose. Majority of CRS had a fast onset of 11 to 25 hours, subsequent to 1 mg on Cycle 1 Day 1 and 10 mg on Cycle 1 Days 8. According to the Sunburst plot (Figure 5), incidences of late onset CRS were low. Thirteen patients (9%) who did not experience CRS following the step-up dose 1 mg, developed CRS following the first treatment dose 10 mg on Cycle 1 Day 8; one patient (1%) developed CRS following the second treatment dose on Cycle 1 Day 15 among the patients who did not experience CRS after step-up dose and first treatment dose. For 1/10 mg cohort, a few patients' treatment discontinuation(n=3) and dose interruption (n=4) events might be attributable to CRS occurrence and labeled as no dose events. Other no dose events in Figure 5 and Figure 3 were attributable to other AEs, patient withdrawal and disease progression. Overall, there is no significant CRS concern identified with the 1 mg step-up dose for the 10 mg treatment doses.

In Study 20200491, 1/100 mg dosage resulted in a higher overall CRS rate of 63% and a different CRS dynamics with the highest CRS (49%) including Grade 2 (13%) and Grade 3 (5%) observed following the 100 mg treatment dose on Cycle 1 Day 8 (Figure 4 and

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Table 15). This may be due to immune system is not sufficiently stimulated during the 1 mg step-up dose for the 100 mg treatment dose.

Table 14: FDA – Summary of Response Rates (ORR) and CRS Rate by Grade Following the Different Target Doses With or Without Step-up Regimen in Study 20160232.

Target Dose Levels (mg)	Step Scheme	N[a]	ORR	Any grade CRS	Grade 2 CRS	Grade 3 CRS	Grade 4 CRS
0.003	No step-up	1/1	0	0	0	0	0
0.01	No step-up	1/1	0	0	0	0	0
0.03	No step-up	1/1	0	0	0	0	0
0.1	No step-up	1/1	0	0	0	0	0
0.3	No step-up	9/12	1 (11)	6 (50)	1(8)	0	0
1	No step-up	8/8	1 (13)	3(38)	1(13)	0	0
3	1 mg step-up	9/11	4 (44)	3(27)	1(9)	0	0
10	1 mg step-up	24/54	8 (33)	33 (61)	9(17)	1(2)	1(2)
30	1 mg step-up	8/8	1 (13)	4 (50)	0	1 (13)	0
100	1 mg step-up	76/76	15 (20)	50(66)	14(21)	4 (5)	0

ORR: objective response rate; IV: intravenous administration; SC: subcutaneous administration. CRS: cytokine release syndrome.

a. *Total evaluable efficacy and safety patient population in study 20160232. Monotherapy cohorts include cohorts 1: 0.003 mg, 2: 0.01 mg, 3: 0.03 mg, 4: 0.1 mg, 5: 0.3 mg, 6: 1 mg, 7: 1->3 mg, 9: 1->30 mg; 1->10 mg includes cohorts 8, 32, and 35 and 1->100 mg includes cohorts 10, 11, 30 and 34.*

Source: Reviewer's analysis created from study 20160232 based on dataset ADAEGRD and Applicant's response to IR on 4/10/2024.

Table 15: Summary of CRS Events by Dosing Period in Patients with SCLC Stratified by Dosages in Study 20200491.

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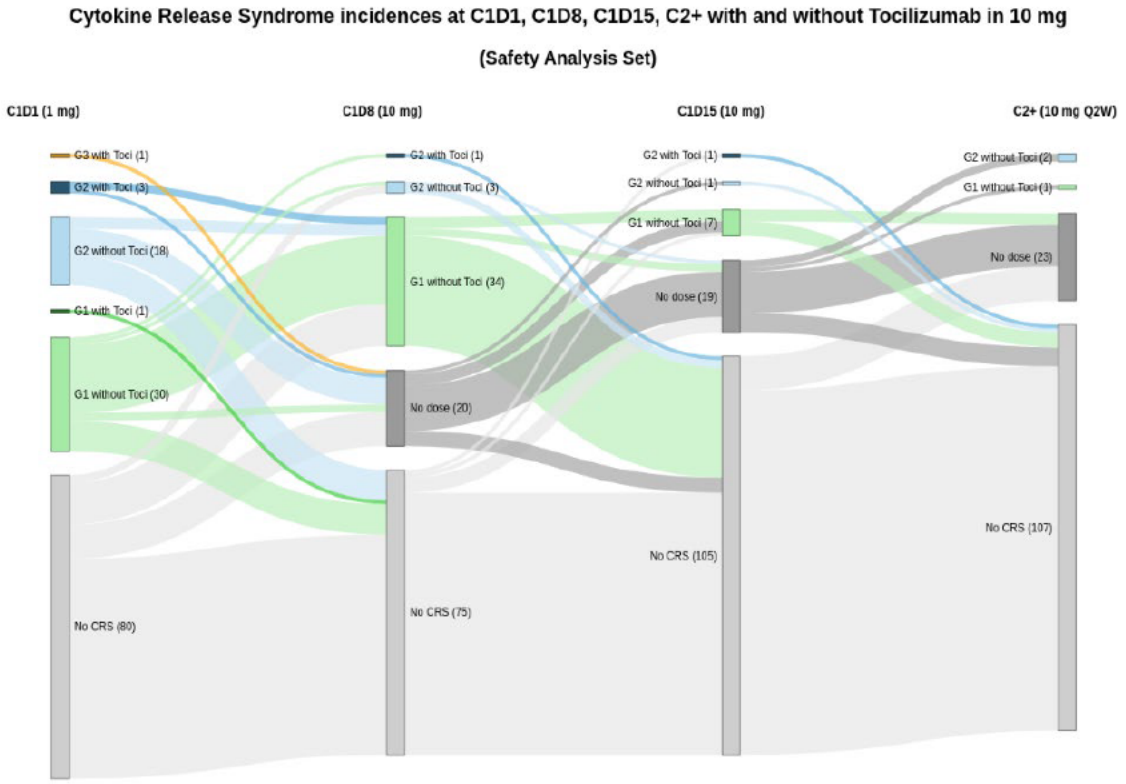
	Step-up Dose 1 Cycle 1 Day 1	First Full Dose Cycle 1 Day 8	Second Full Dose Cycle 1 Day 15	Third Full Dose Cycle 2 Day 1	Forth Full Dose Cycle 2 Day 15	Any Time
	1/10 mg regimen (N=133)					
Patients with ≥1 CRS event	54 (41)	39(30)	10 (7.5)	2 (1.5)	3 (2.3)	70 (53)
Grade 1	32 (24)	35 (26)	8(6)	2 (2)	1 (1)	42(30)
Grade 2	21 (16)	4 (3)	2 (2)	0	1 (1)	27(20)
Grade 3	1 (1)	0	0	0	0	1(1)
	1/100 mg regimen (N=87)					
Patients with ≥1 CRS event	25 (29)	43 (49)	6 (7)	3 (3)	4 (5)	55 (63)
Grade 1	16 (18)	28 (32)	1 (1)	3 (3)	2 (2)	30 (35)
Grade 2	9 (10)	11 (13)	6 (6)	0	2 (2.3)	20(24)
Grade 3	0	4 (5)	0	1 (1)	0	4(5)

Source table: Applicant's response to FDA IR on 3/19/2024 and CSR for study 20200491, Table 14-6.5.401.

Figure 3. Sankey plot for the dosing regimen of 1/10 mg in the pivotal Study 20200491.

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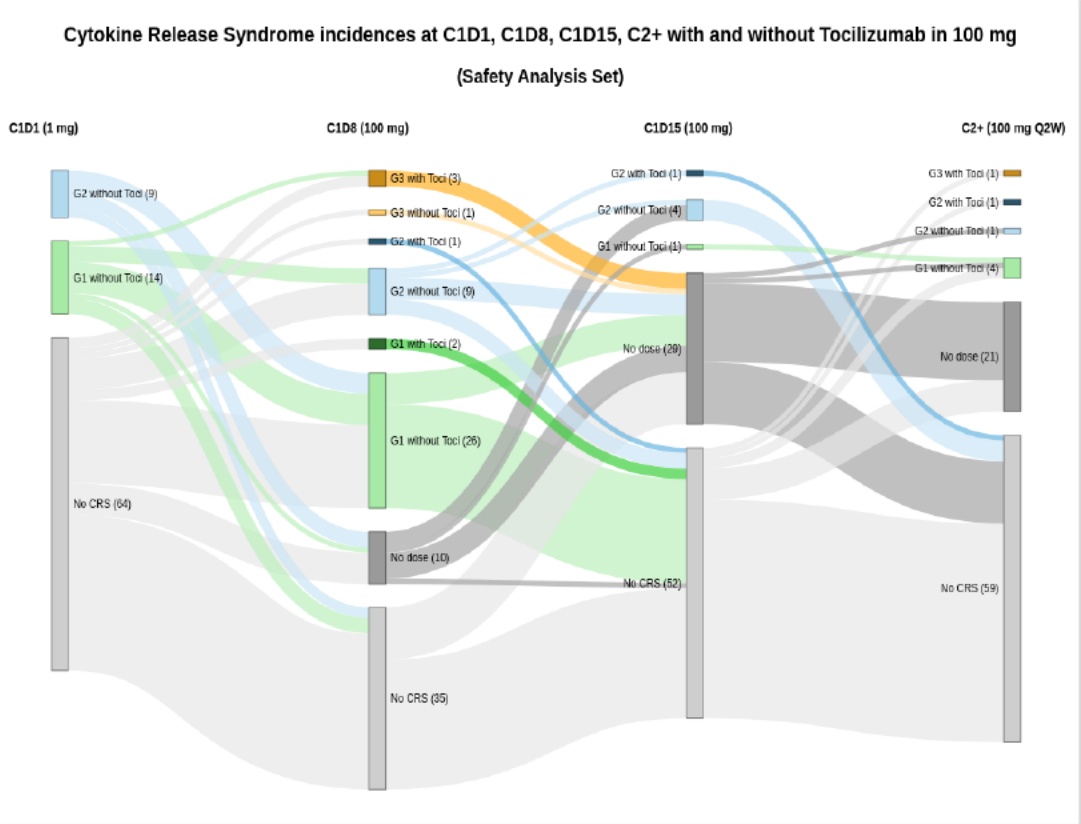
Reference ID: 5382024



A "no dose" category was added to differntiate patients who did not receive a dose from those who received a dose but did not have any CRS events. The worst grade after a dose was used as the CRS grade in the plot. The "C2+" in the plot includes all doses in Cycle 2 and beyond, and the worst grade of all C2+ doses was used. Figure does not include the 2 new Grade 1 CRS events in the 10 mg dose group from updated 90-day safety.

Source: Applicant's response to FDA IR 12/12/2023

Figure 4. Sankey plot for the dosing regimen of 1/100 mg in the pivotal Study 20200491



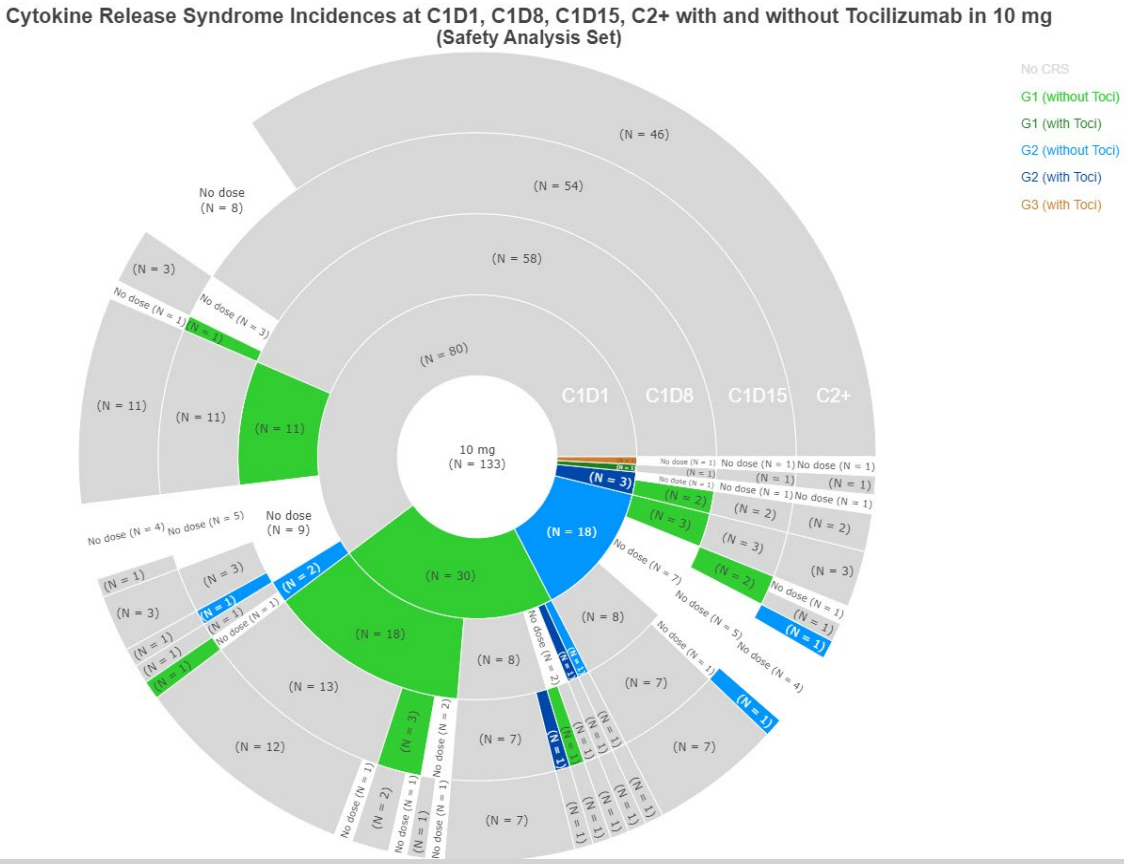
A "no dose" category was added to distinguish patients who did not receive a dose from those who received a dose but did not have any CRS events. The worst grade after a dose was used as the CRS grade in the plot. The "C2+" in the plot includes all doses in cycle 2 and beyond, and the worst grade of all C2+ doses was used. Figure does not include the new CRS events in the 100 mg dose group from updated 90-day safety.

Source: Applicant's response to FDA IR 12/12/2023

Figure 5. Sunburst plots of CRS events by dose event for the proposed 1/10 mg doing regimen in Study 20200491

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A "no dose" category was added to differentiate patients who did not receive a dose from those who received a dose but did not have any CRS events. Figure does not include the 2 new Grade 1 CRS events in the 10 mg dose group from updated 90-day safety.

Source: Applicant's response to FDA IR on 1/10/2024

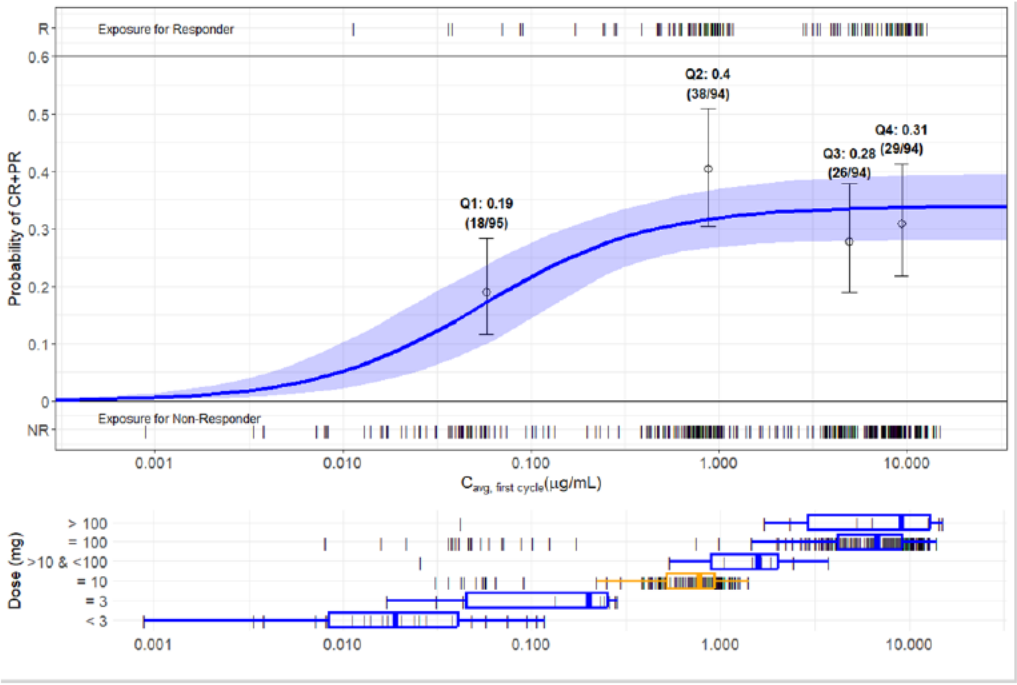
FDA agrees with Applicant's selection of 10 mg treatment doses based on the following assessments:

1) The efficacy data from Study 20160323 indicated that dosages ≥ 3 mg are active (Table 14). Based on the predicted higher antitumor activities and acceptable safety, 1/10 mg and 1/100 mg were selected to expand in Part 1 of Study 20200491 dose randomization study. The 1/10 mg cohorts achieved a numerically higher confirmed ORR than 1/100 mg cohort with fewer all grade neutropenia and ICANs. A benefit-risk assessment based on results from Study 20200491 determined that 1/10 mg achieved a clinically meaningful efficacy with an acceptable safety profile. Refer to section 8.1.7 and 8.2 for detail clinical efficacy and safety summary.

2) FDA agrees that the pertinent E-R analyses appear to be adequate with sufficient number of patients (N = 217) from 1/10 and 1/100 mg cohorts.

Consistent with dose-response (D-R) data in Study 20200491, E-R analyses for efficacy suggested a higher tarlatamab exposure may associate with a higher ORR rate; however, a plateau of efficacy was reached at the exposure of 1/10 mg, supporting the proposed dosage (Figure 6).

Figure 6. Model predicted ORR and observed ORR by tarlatamab Cavg, first cycle quartiles.



Cavg = first cycle model-estimated averaged concentration over the first cycle; ORR = objective response rate. *Source: Figure 8 of Exposure-response Analysis Report*

3) The E-R safety analyses did not identify major safety concerns with the proposed dosage. Positive E-R for safety trends were observed for any grade neutropenia, grade 1 and grade 2 neurotoxicity including ICANs, supporting the lower dosage 1/10 mg. A positive trend was also observed for Grade ≥ 1 CRS and tarlatamab exposure; however, this trend is not conclusive and may be confounded by the effect of step-up dose to subsequent treatment doses. No trends of E-R for safety were identified for Grade 3 AEs, Grade 3 TEAEs, or Grade ≥2 CRS. There were limited data for other AEs. Refer to Appendix 19.4.4 for detailed E-R for safety analyses.

Efficacy and safety data from Study 20200491 together with the E-R analyses for safety and efficacy support the recommended dosage 1/10 mg in patient with SCLC.

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6.2.2.2. Therapeutic Individualization

Data:

The influence of demographic and subject specific characteristics on the PK of tarlatamab were investigated using population PK. Various demographic variables were evaluated in the covariate testing within the population PK analyses framework. Key demographic factors (age, sex, ethnicity), estimates of renal function and liver function, number of prior lines of therapies, baseline disease burden or Eastern Cooperative Oncology Group (ECOG) status, did not affect tarlatamab PK.

Consistent with other biologics, body weight was correlated with tarlatamab clearance, as was positive binding ADA status with increase in body weight or positive ADA binding status associated with increase in clearance. However, at the proposed dosing regimen of 1 mg on day 1 followed by 10 mg on day 8, day 15, and Q2W thereafter, neither body weight nor ADA status had a clinically relevant impact on tarlatamab efficacy as assessed by confirmed ORR or DCR. Race (Asian/Black/Others vs White) was found to be correlated with central volume of distribution; however, race had a negligible impact on exposures. The exposure-response relationship for ORR, DCR, best tumor size response (BTSR), and PFS was not impacted by evaluated intrinsic or extrinsic factors (see Section 6.3.2 and Section 3.5 of Module 2.7.2, Summary of Clinical Pharmacology).

Exposure-response relationships for key efficacy measures (ORR, DCR, BTSR, and PFS) or safety measures were not impacted by any of the evaluated covariates (see Section 6.3.2). Higher sum of tumor lesion diameter at baseline (independent of tarlatamab serum exposures) was significantly associated with higher hazard for OS.

Detailed results are provided in Report 157688 (Population PK Report) (Module 5.3.3.5) and Report 157687 (Exposure-response Analysis Report) (Module 5.3.4.2).

The Applicant's Position:
None of the covariates evaluated in this analysis resulted in clinically meaningful changes in efficacy or safety and therefore do not warrant a dose adjustment.

The FDA's Assessment:

FDA agrees with the Applicant's position that no dose adjustment for tarlatamab is needed for intrinsic and extrinsic factors including age, BW, sex, race (White and Asian), mild to moderate renal impairment, or mild hepatic impairment, as the popPK analyses showed no clinically important effect of these covariates on the PK or E-R efficacy relationship of tarlatamab. Due to limited data, the effects of severe renal impairment, end-stage renal disease, moderate to severe hepatic impairment, ADA, or ethnicity (e.g., Hispanic or Latino) on tarlatamab PK are unknown.

FDA agrees with the Applicant's position that E-R relationships for efficacy and safety

support proposed 1/10 mg dosage. E-R relationship for efficacy suggested a potential trend of higher tarlatamab exposure with higher ORR with responses plateaued at 1/10 mg. Positive E-R for safety trends were observed for any grade neutropenia, Grade 1 and Grade 2 neurotoxicity including ICANs, supporting the lower dosage 1/10 mg. The E-R relationships for safety did not identify major safety concerns on the 1/10 mg dosage as no clear trends were identified for grade ≥ 3 AEs of interest.

Despite a trend toward higher DLL3 H-scores in patients who responded to both the 1/10 and 1/100 mg dosages, partial response observed in a patient lacking DLL3 target expression (H-score=0) supports treatment of patients irrespective of baseline DLL3 expression status.

6.2.2.3. Outstanding Issues

Data:

Not applicable

The Applicant's Position:

None

The FDA's Assessment:

There is limited PK data to assess the impact of PK differences relating to race (e.g., African American) or ethnicity (e.g., Hispanic or Latino) minorities. As described in the PMC that will be issued with the Approval letter, the Applicant should conduct an integrated analysis of data from clinical trial(s) to further characterize the safety, efficacy, PK of tarlatamab among US racial and ethnic minority patients with SCLC. The population should be representative of US population.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:

Pharmacokinetics

Tarlatamab exhibited approximate dose-proportional increases in exposures in the evaluated dose range of 0.003 to 100 mg IV administered Q2W and 200 mg Q3W. The

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mean (SD) estimated terminal phase elimination half-life at steady state was 5.5 (1.6) days across the evaluated dose range.

Following the proposed dosing regimen of 1 mg on day 1 and 10 mg on day 8, day 15, and Q2W thereafter, tarlatamab geometric mean trough values at steady state (cycle 2 day 15 predose) and peak serum concentrations at steady state (cycle 2 day 15, end of infusion) were 0.44 and 4.3 mg/mL, respectively, based on pooled data across phase 1 and phase 2 studies. There was no indication of time dependent kinetics.

Based on population PK analyses, tarlatamab serum clearance, central volume of distribution, peripheral volume of distribution, and volume of distribution at steady state were estimated to be 0.65 L/day, 3.44 L, 5.06 L, and 8.5 L, respectively for a typical 73 kg White individual. The inter-individual variability for tarlatamab clearance and central volume of distribution were 43.7% and 38.7%, respectively.

Various demographic variables were evaluated in the covariate testing within the population PK analyses framework. Key demographic factors (age, sex, ethnicity), estimates of renal function and liver function, number of prior lines of therapies, baseline disease burden or ECOG status, did not affect tarlatamab PK.

Consistent with other biologics, body weight was correlated with tarlatamab clearance, as was positive binding ADA status with increase in body weight or positive ADA binding status associated with increase in clearance. However, at the proposed dosing regimen of 1 mg on day 1 followed by 10 mg on day 8, day 15, and Q2W thereafter, neither body weight nor ADA status had a clinically relevant impact on tarlatamab efficacy as assessed by confirmed ORR or DCR. Race was found to be correlated with central volume of distribution; however, race had a negligible impact on exposures.

At the proposed dosing regimen of 10 mg Q2W, the incidence of treatment-emergent antitarlatamab antibodies was 12% (3 of 25 subjects) for the FIH Study 20160323 and 3.2% (4 of 124 subjects) for the pivotal phase 2 Study 20200491, for a pooled total of 7 of 149 subjects (4.7%) across the 2 studies. In the pivotal phase 2 Study 20200491, which employed the neutralizing assay, none of the subjects developed neutralizing antibodies. Potential impact of antitarlatamab antibodies on the PK, clinical efficacy, and clinical safety of tarlatamab was assessed with the following results:

- Based on the population PK analysis, individuals with positive antitarlatamab antibody binding status at any time during the study were estimated to have approximately 21% higher clearance, which translated to an approximately 24% decrease in serum trough concentrations on average. However, this difference in exposures did not have a clinically relevant impact on efficacy.
- At the proposed dosing regimen, the efficacy measures (including ORR, DCR, and DOR) were comparable for antitarlatamab binding antibody positive subjects compared with those who were antitarlatamab antibody negative.
- There was no apparent impact of antitarlatamab antibody development on safety based on assessment of adverse events.

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Detailed description of these analyses can be found in the Integrated Summary of Immunogenicity (Module 5.3.5.3).

The Applicant's Position:

In both Studies 20160232 and 20200491, tarlatamab exhibited approximate dose-proportional increases in exposures in the evaluated dose range. The steady state in tarlatamab serum concentrations were approximately achieved by the start of cycle 2. The mean (SD) estimated terminal phase elimination half-life at steady state was 5.5 (1.6) days, across the evaluated dose range. The incidence of antitarlatamab antibody development was low. There was no meaningful clinical impact of antitarlatamab antibody development on efficacy and safety.

The FDA's Assessment:

FDA generally agrees with the Applicant's position regarding the characteristics of clinical pharmacology and pharmacokinetics of tarlatamab as summarized in Table 16. The PK parameters are presented as geometric mean (CV%) unless otherwise specified.

Table 16: Tarlatamab General Pharmacology and Pharmacokinetic Characteristics of Tarlatamab Summarized by FDA.

General Information	
PK Bioanalytical assay	An electrochemiluminescent (ECL) assay was used for PK assay. The method validation and in-study performance for plasma samples are acceptable based on the current Bioanalytical Method Validation Draft FDA Guidance for Industry. Refer to section 19.5 for review of analytical method validation.
PK Characteristics	
Steady-state exposure	Steady state in serum exposures were achieved by approximately Cycle 2 Day 15. See Figure 7 and Table 17 for predicted steady-state concentrations and profiles, respectively.
Dose proportionality	Tarlatamab exposure increased dose proportionally in the evaluated dose range of 1mg to 100 mg every 2 week
Distribution	Tarlatamab steady state volume of distribution is 8.6 L (18.3%)
Elimination	Tarlatamab's median terminal half-life (min, max) is 11.2 (4.3 to

	26.5) days, and the estimated clearance is 0.65 L/day (44%) in patients with SCLC.
Specific Population	
Intrinsic Factor	No clinically meaningful differences in the PK were observed based on age (32 to 82 years), BW (35 to 149 kg), sex, race (White and Asian), mild to moderate renal impairment, or mild hepatic impairment. Although BW and race were identified as statistically significant covariates on tarlatamab volume of distribution and clearance, the impacts of these covariates on tarlatamab exposure were not considered clinically relevant. Positive ADA was also identified as a significant time-varying covariate on tarlatamab clearance. Due to low occurrence of ADA, the clinically relevant effect of ADA on tarlatamab's PK, efficacy and safety is not conclusive. None of the covariates evaluated above found to have important effect on E-R relationships for efficacy. Therefore, no dose adjustment is needed based on these intrinsic or extrinsic covariates. No difference in ORR was observed at the DLL3 cut points of < 75% vs ≥ 75% and < 25% vs ≥ 25% at moderate (2+) and strong (3+) staining intensities (see section 8.1.6). These results support treatment of patients at 1/10 mg irrespective of baseline DLL3 expression status. The effects of severe renal impairment, end-stage renal disease, moderate to severe hepatic impairment, ADA, or ethnicity (e.g., Hispanic or Latino) are unknown due to limited or unavailable data.
PD Characteristics	
Pharmacodynamics	Transient elevation of serum cytokines IL-2, IL-6, IL-8, IL-10, and IFN-γ were observed at a tarlatamab dosage of 0.3 mg Q2W and above. Peak elevation of cytokines was generally observed 20-24 hours following the initial dose of tarlatamab at 1 mg on Cycle 1 Day 1 and generally returned to baseline levels prior to the next infusion on Cycle 1 Day 8.
Exposure-Response for	Higher exposures (e.g., $C_{avg,first\ cycle}$) were associated with higher ORR. The efficacy reached a plateau at the higher exposures of target dosage 10 mg Q2W supporting the proposed dosage.

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Efficacy	
Exposure-Response for Safety	Higher tarlatamab exposures (e.g., $C_{avg,first\ cycle}$) were associated with higher incidences of any grade neutropenia, grade 1 and grade 2 neurotoxicity including ICANs. E-R for safety analysis did not identify major safety concerns for the proposed dosage.

Additional Pharmacokinetics Summary

The popPK analysis of tarlatamab was performed using pooled data from Study 20160323 and Study 20200491. Sparse PK samples were collected following end of infusion on C2D15, C3 D1 and C4D1 and pre-infusion on C2D15, C3D1 through C6D1. Based on the PK simulation, geometric mean (% CV) of PK parameters are summarized in Table 17. The popPK simulated tarlatamab PK profile is presented in Figure 7. For additional details, refer to section 19.4.1.

Table 17. Geometric Mean (CV%) Estimate of the Pharmacokinetic Parameters of Tarlatamab

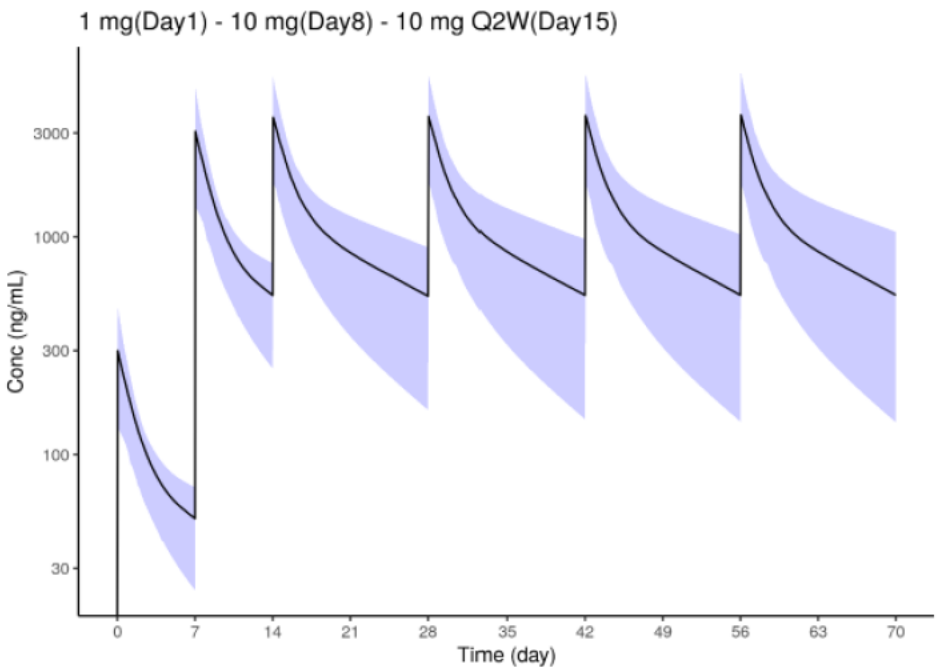
	Parameter			
	C_{avg} (ng/mL)	C_{max} (ng/mL)	C_{trough} (ng/mL)	AUC_{tau} (ng/mL*day)
First step-up dose 1mg	102 (29%)	285 (41%)	47.3 (38%)	711 (28.7%)
First treatment dose 10mg	1050 (29%)	2900 (41%)	502 (39%)	7370 (29%)
Steady state 10mg Q2W	1040 (44.5%)	3400 (40.5%)	495 (73.3%)	14600 (44.5%)

Source: Applicant's response to FDA IR on 1/24/2024

Figure 7. Pharmacokinetic profile of tarlatamab following the proposed dosage of 1/10 mg simulated by PopPK analyses.

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Median is represented by solid black line. 90% prediction interval is represented by the shaded blue area.

Source: Figure 15 in Applicant's Pharmacometrics Report 157688

Cytokine levels

FDA assessed of the potential for drug interactions between tarlatamab and CYP substrates and considered this risk is low. In Study 2020049, cytokine levels were transiently elevated and mostly peaked around 20-24 hours after step-up dose (1 mg) on Cycle 1 Day 1 and returning to baseline around the next target dose (10 mg) on Cycle 1 Day 8 (Figure 8 and Table 18). The concentrations of IL-6 for the total samples, samples without tocilizumab and samples with tocilizumab were summarized in Table 18.

Prior literature and validated physiologically based pharmacokinetic model (PBPK) derived the EC50 values for IL-6 on CY3A4 and CYP3A5 to be 75.2 pg/mL and 51 pg/mL, respectively (Jiang 2016). The median and mean value of peak IL-6 concentrations are 26 pg/mL (Table 18). This peak concentration did not exceed the literature reported EC50 of IL-6, suggesting a clinically relevant interaction between tarlatamab and CYP3A substrates is not expected, and the mean value of IL-6 was lower for tarlatamab than other bispecific drugs including elranatamab and epcoritamab (Table 19). Based on the predicted low drug interaction risk in the general patient population, the information is not included in Section 7 of the USPI.

Figure 10 showed an exploratory analysis, in patients who developed Grade 2 CRS, the peak IL-6 may exceed the EC50 and could potentially lead to suppression of CY3A

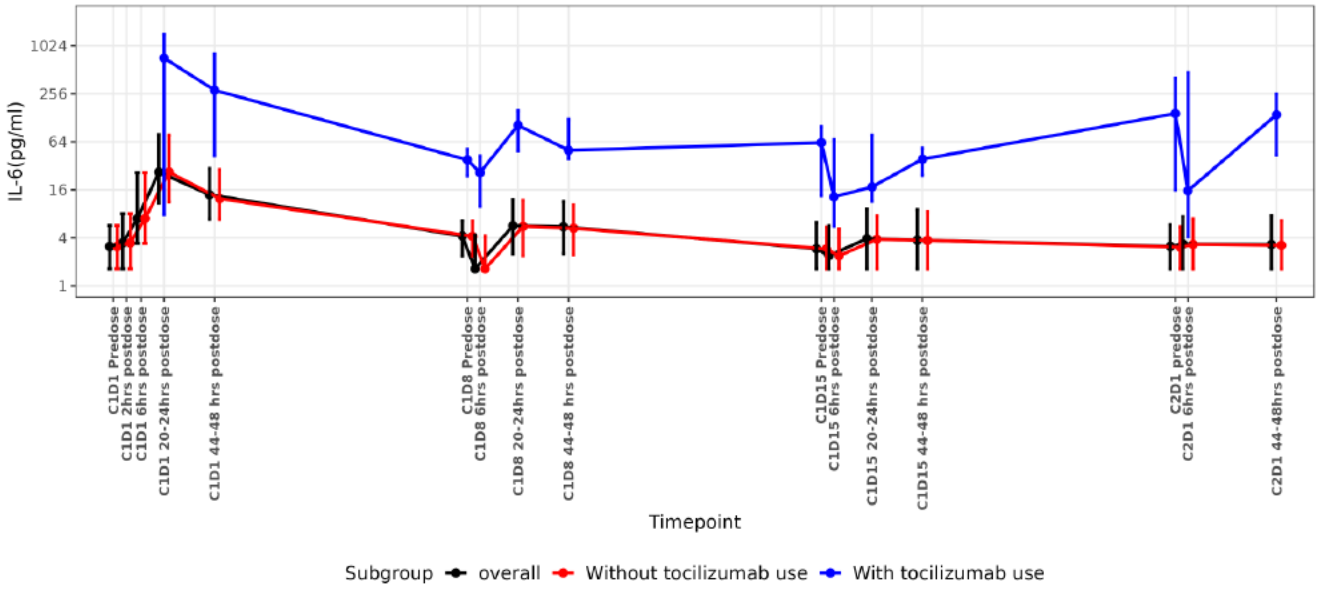
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activity. The risk of drug interaction during and after any CRS cannot be ruled out. Therefore, FDA provided additional language in Section 12 of the USPI that tarlatamab may increase exposure of concomitant CYP substrates during and up to 14 days after occurrence of CRS.

Cytokine release profiles including INF -γ, IL-2, IL-5, IL-10, and tumor necrosis factor alpha (TNF-alpha) in peripheral blood over time without tocilizumab use in Study 2020049 as displayed in Figure 9. Similar time course of cytokine concentrations was also observed for other cytokines except for TNF-alpha. TNF-alpha did not change significantly from the baseline and median concentrations were consistently below 10 pg/mL. For additional details, refer to section 19.4.2.

Figure 8. Observed median IL-6 over time following RP2D 1/10 mg in Study 2020049.



The error bar indicates the 25th, 75th percentile.
Source: Applicant's response to IR on 1/10/2024.

Table 18: Summary of IL-6 by Cycle Day in Study 2020049

Cycle	Dose (mg)	Timepoint	N	Mean (SD)	Median	(25^{th}, 75^{th} percentile)	(2.5^{th}, 97.5^{th} percentile)	Range
C1D1	1mg	predose	128	2 (9.5)	2.1	(0.6, 4.7)	(0.6, 22)	(0.6, 73.4)
	1mg	Predose :with toci	0	NA	NA	NA	NA	NA
	1mg	Predose : without toci	128	2 (9.5)	2.1	(0.6, 4.7)	(0.6, 22)	(0.6, 73.5)

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Cycle	Dose (mg)	Timepoint	N	Mean (SD)	Median	(25^{th}, 75^{th} percentile)	(2.5^{th}, 97.5^{th} percentile)	Range
	1 mg	6 hrs post-dose	127	6 (1104.8)	6.0	(2.4, 25.2)	(0.6, 729.1)	(0.6, 11436.8)
	1 mg	6 hrs post-dose: With toci	0	NA	NA	NA	NA	NA
	1 mg	6 hrs post-dose :Without toci	127	6 (1104.8)	6.0	(2.4, 25.2)	(0.6, 729.1)	(0.6, 11436.8)
	1mg	20-24 hrs post-dose:overall	127	26(741.1)	25.7	(10.0, 78.0)	(0.6, 1116.4)	(0.6,7892.7)
	1mg	20-24 hrs post-dose:With tocilizumab use	2	718 (1006)	718.1	(6.8, 1429.4)	(6.8, 1429.5)	(6.8, 1429.5)
	1mg	20-24 hrs post-dose: without toci	125	**26** (738.4)	**25.7**	(10.2, 76.7)	(0.6, 1038.6)	(0.6, 7892.7)
C1D3	1mg	44-48 hrs post-dose	122	13 (442.9)	12.9	(5.8, 28.6)	(1.3, 556.9)	(0.6, 4728.4)
	1mg	44-48 hrs postdose:With toci	3	283 (386.7)	282.8	(41.9, 798.9)	(41.9, 798.9)	(41.9, 798.9)
	1mg	44-48 hrs post-dose:Without toci	119	11 (443.3)	11.4	(5.8, 27.7)	(1.3, 432.8)	(0.6, 4728.4)

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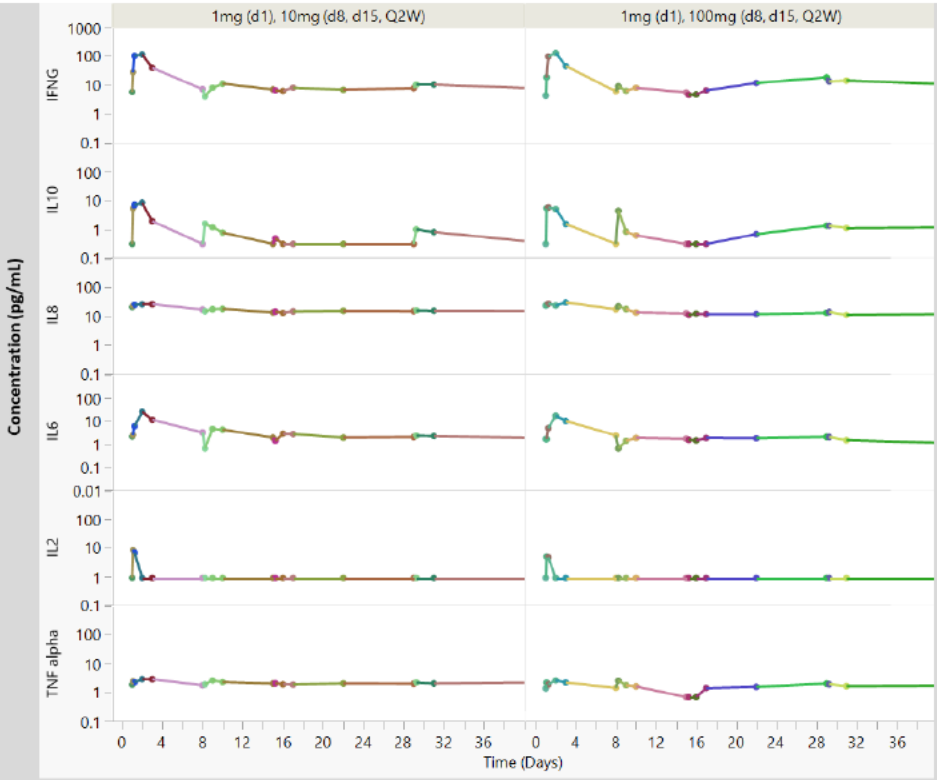
Cycle	Dose (mg)	Timepoint	N	Mean (SD)	Median	(25^{th}, 75^{th} percentile)	(2.5^{th}, 97.5^{th} percentile)	Range
C1D8	10mg	pre-dose	110	3 (9.6)	3.2	(1.4, 5.6)	(0.6, 35.6)	(0.6, 51.0)
	10mg	pre-dose:With toci	2	37 (19.8)	37.0	(23.0, 51.0)	(23.0, 51.0)	(23.0, 51.0)
	10mg	pre-dose:Without toci	108	3 (8.5)	3.2	(1.4, 5.5)	(0.6, 32.4)	(0.6, 50.9)
	10mg	6 hrs post	107	1 (19.3)	0.6	(0.6, 3.4)	(0.6, 32.6)	(0.6, 188.8)
	10mg	6 hrs Post - dose :With toci	2	25 (23.1)	25.3	(9.0, 41.7)	(9.0, 41.7)	(9.0, 42.0)
	10mg	6 hrs post:Without toci	105	1 (19.1)	0.6	(0.6, 3.2)	(0.6, 28.2)	(0.6, 188.8)
C1D10	10mg	44-48 hrs post-dose:overall	105	5 (61.06)	4.5	(1.5, 10.4)	(0.6, 50.9)	(0.6, 615.3)
	10mg	44-48 hrs post-dose:With toci	3	49 (44.8)	49.1	(38.1, 120.6)	(38.1, 120.6)	(38.1, 120.6)
	10mg	44-48 hrs post-dose:Without toci	102	4 (60.9)	4.3	(1.5, 9.3)	(0.6, 41.1)	(0.6, 615.3)
C1D15	10mg	pre-dose:overall	114	2 (45.5)	1.9	(0.6, 5.2)	(0.6, 70.4)	(0.6, 455.8)
	10mg	pre-dose:With toci	3	61 (42.8)	61.3	(12.5, 97.8)	(12.5, 97.8)	(12.5, 97.8)
	10mg	Pre-dose:Without toci	111	2 (45.1)	1.9	(0.6, 4.46)	(0.6, 45.4)	(0.6, 455.8)

Source: Applicant's response to IR on 1/10/2024

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Figure 9. FDA –Median concentration of cytokine over time for 1/10 mg and 1/100 mg dosages in Study 2020049.

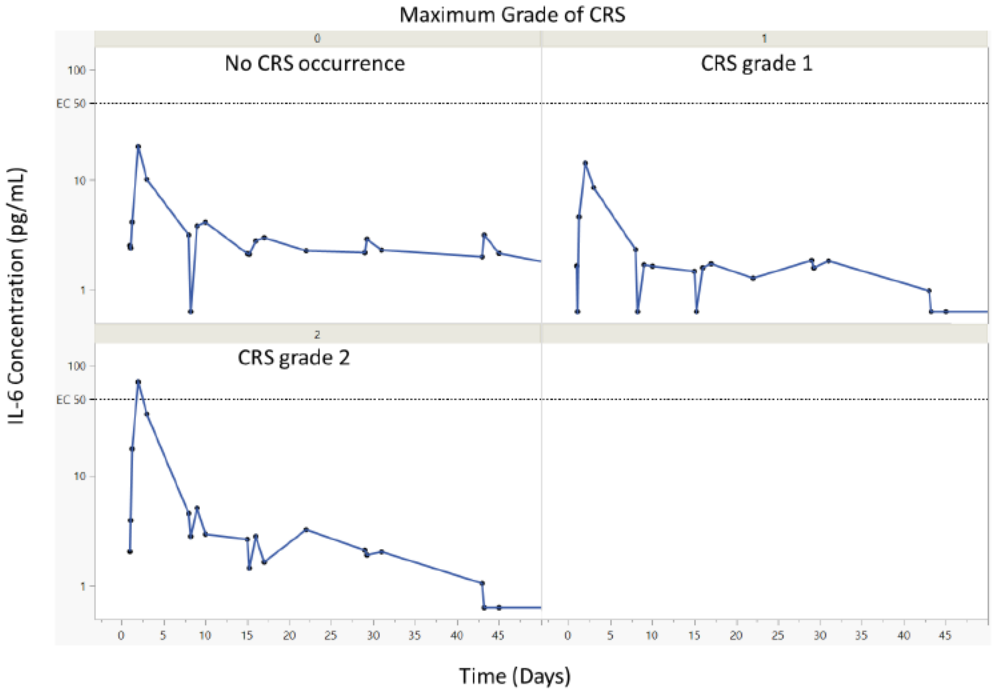


Source: FDA own analysis Applicant's response to IR on 1/10/2024

Figure 10. FDA –Median IL-6 cytokine concentration-time profiles following tarlatamab 1/10 mg dosage in Study 20200491 By maximum CRS grade.

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Each panel represent different maximum CRS occurrence in patients; Lines represent arithmetic median value; IL-6 represents interleukin 6. The median peak IL-6 concentration in patients who had a maximum grade 2 CRS occurrence may exceed EC50 of IL-6. The cytokine profile for patients with Grade 3 CRS is not included due to limited to a single patient data.
Source: FDA's analysis of Applicant's response to IR on 1/10/2024

Table 19. FDA –Summary of Peak IL-6 Level by Different Bispecific.

Drug	Time to Peak	Dose (mg)	N	Mean (SD)	Median	25th, 75th percentile	2.5th, 97.5th percentile	Range
Tarlatamab	C1D2	1mg	127	**26 (741)**	26	10, 78	0.6, 1116	0.6 - 7893
Elranatamab	C1D4	32mg	156	**191 (487)**	25	11, 77	3.2, 1906	1 - 3128
Epcoritamab	C1D15	48mg	126	**208(303)**	58	Unknown	2, 844	2- 844

Source: FDA summary of Applicant's response to IR on 1/10/2024. FDA review of elranatamab BLA 761345 table 13 as well as epcoritamab BLA 761324 table 11.

Immunogenicity

FDA agrees with the Applicant's position that the incidence of ADA was low. In Study 20200491 1/10mg dosage cohort, 3% (4/124) of patients tested positive for ADA and none of the patients developed Nab. All ADAs in 1/10 mg cohort were treatment-induced (Table 20).

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FDA does not agree with the Applicant's position that there is no apparent impact of ADA on tarlatamab's safety or efficacy. Due to the low occurrence of ADA, the impact of ADA on n PK, safety, and effectiveness is inconclusive.

Table 20: Summary of ADA in Study 20200491

N	1/10mg N=124	1/100mg N=87
Overall Incidence	4 (3)	3 (4)
Treatment induced	4 (3)	3 (4)
Treatment-boosted	0	0

Source: CRS study 20200491

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6.3.2. Clinical Pharmacology Questions

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

Data:

Data from Study 20200491 (phase 2) and Study 20160323 (FIH) were included in an integrated exposure-response analysis to support the selection of the proposed dosing regimen (summarized in Section 3.4 of the Clinical Overview and detailed in Section 3.5 of Module 2.7.2, Summary of Clinical Pharmacology). Relationships between tarlatamab exposure and selected measures of response (ORR, DCR, BTSR, PFS, OS, and DOR) were evaluated. The tarlatamab exposure metrics evaluated as predictors of response were model-predicted average concentrations over the first cycle (C_{avg}), peak serum concentrations over the first cycle (C_{max}), and trough serum concentrations at the end of the first cycle on day 28 (C_{trough}), generated using a population PK model. Covariates included in the analyses were demographic factors (age, body weight, sex, race, ethnicity), organ impairment (normal, mild, moderate renal and hepatic function), baseline serum albumin, disease status (ECOG and sum of tumor lesion diameters at baseline), number of prior therapies, and positive ADA status.

With regards to evidence of effectiveness, integrated analysis using pooled data from Study 20160323 and Study 20200491 show that:

- Significant exposure-response relationships were established for key efficacy measures including ORR, DCR, BTSR, PFS, and OS.
- Near maximal efficacy was observed at exposures associated with the proposed clinical regimen of 10 mg Q2W.
- Exposures associated with lower doses are estimated to have lower efficacy.

The Applicant's Position:

Overall, results of exposure-response analysis for efficacy measures suggest the proposed dosing regimen of 10 mg Q2W exhibited near maximal efficacy in the intended patient population, and exposures associated with lower doses are estimated to have lower efficacy. None of the covariates evaluated in this analysis resulted in clinically meaningful changes in efficacy and therefore do not warrant a dose adjustment.

The FDA's Assessment:

FDA agrees with the Applicant's position on that E-R analyses, in addition to the clinical findings from Studies 20200491 and 20160323, supported the proposed 1/10 mg dosing regimen. In Study 20160323 dose escalation, 0.003 to 100 mg Q2W were explored.

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Efficacy analyses suggested a higher response may associate with higher target dosages. 1/10 mg and 1/100 mg were then selected to be evaluated in part I dose randomization study of 20200491. The 1/10 mg demonstrated a numerically higher ORR relative to 1/100 mg in Study 20200491. E-R efficacy suggested a potential trend of higher tarlatamab exposure associated with higher ORR, which plateaued at the 1/10 mg, supporting the proposed dose. Positive E-R for safety trends were observed for any grade neutropenia, Grade 1 and Grade 2 neurotoxicity including ICANs, supporting the lower dosage 1/10 mg.

The 1 mg step-up dose was investigated for all dosages starting at 3 mg and the risk of CRS of an alternative step-up dose for 10 mg is unknown. In Study 20200491, 1 mg step-up dose resulted in more favorable CRS profiles with overall grade CRS occurred primarily after first step-up dose (40%) and first full dose (28%) and only 2% of CRS events for third full dose. Overall, based on a lower incidence of grade ≥2 CRS, as well as the favorable CRS dynamic, the step-up dose appeared to be reasonable.

Refer to section 6.2.2.1 for details regarding justification for the step-up doses and full doses and refer to section 19.4.4 for details regarding the exposure-response relationships for efficacy and safety.

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

Data:

See Section 6.2.2.1, General Dosing

The proposed dose is effective and generally well tolerated in subjects with advanced SCLC. The proposed dosing regimen is supported by the observed efficacy and safety data and demonstrates a favorable benefit-risk profile. In addition to exposure-response analysis for efficacy, analysis correlating tarlatamab exposures with key safety measures using pooled data from Study 20160323 and Study 20200491 were performed. No significant exposure-safety relationships for grade ≥ 3 adverse events, grade ≥ 3 treatment-related adverse events, or grade ≥ 3 adverse events of interest (neurological events, immune effector cell-associated neurotoxicity syndrome [ICANS], and cytokine release syndrome [CRS]) were identified. A shallow trend was observed for higher percentage of subjects experiencing grade ≥ 3 neutropenia with increasing tarlatamab exposures. In addition, no clinically relevant impact on QTc interval was observed at the proposed clinical regimen of 10 mg Q2W.

The Applicant's Position:

Overall, results of exposure-response analysis suggest the proposed dosing regimen of 10 mg Q2W exhibited near maximal efficacy with a limited impact on neutropenia and favorable benefit-risk profile in the intended patient population. None of the covariates

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evaluated in this analysis resulted in clinically meaningful changes in efficacy or safety and therefore do not warrant a dose adjustment.

The FDA's Assessment:
FDA agrees with Applicants' position that the proposed dosage 1/10 mg tarlatamab is acceptable for the patient population for which the indication is being sought. See detailed discussion in section **Error! Reference source not found.**. FDA agrees that no clinically significant QT prolongation was observed, this is consistent with tarlatamab being a protein therapeutic with a molecular weight of 105 KDa, which is not expected to inhibit human ether-a-go-go related gene (hERG) channel function directly.

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6.3.2.1 Dosage Recommendations for Restarting Therapy after Dose Delay

The FDA's Assessment:
FDA agrees with Applicant's proposed recommendations for restarting therapy after dose delay, as outlined in Table 21, based on clinical data and PK simulations. Although CRS associated with tarlatamab treatment occurred primarily with the first dose, risk of CRS re-emerged when a patient was off treatment for a prolong period. This is due to re-sensitization of the immune system and potential rebound of the target cells. Therefore, repeating step-up dose 1 mg at the proposed cutoffs following dose delays is needed to mitigate the risk of rebound CRS.

Table 21. Recommendations for Restarting Therapy After Dosage Delay

Last Dose Administered	Time Since the Last Dose Administered	Action[a]
1 mg Cycle 1 Day 1	2 weeks or less (≤14 days)	Administer IMDELLTRA 10 mg, then resume with the planned dosage schedule.
	Greater than 2 weeks (>14 days)	Administer IMDELLTRA step-up dose 1 mg. If tolerated, increase to 10 mg 1 week later. Then resume with the planned dosage schedule.
10 mg Cycle 1 Day 8	3 weeks or less (≤21 days)	Administer IMDELLTRA 10 mg, then resume with the planned dosage schedule.
	Greater than 3 weeks (>21 days)	Administer IMDELLTRA step-up dose 1 mg. If tolerated, increase to 10 mg 1 week later. Then resume with the planned dosage schedule.

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Last Dose Administered	Time Since the Last Dose Administered	Action[a]
10 mg Cycle 1 Day 15 and onward	4 weeks or less (≤28 days)	Administer IMDELLTRA 10 mg, then resume with the planned dosage schedule.
	Greater than 4 weeks (>28 days)	Administer IMDELLTRA step-up dose 1 mg. If tolerated, increase to 10 mg 1 week later. Then resume with the planned dosage schedule.

[a] Administer required concomitant medications before and after IMDELLTRA infusions and monitor patients accordingly (*see Dosage and Administration [2.1]*).

Source: Table 2, Tarlatamab USPI.

The proposed restart recommendations after dose delay were implemented in Study 20200491. In Study 20200491, there were 6 episodes of repriming with 1 mg step-up dose: 2 episodes of > 21 days of dose delays following the 1 mg step-up dose, 2 episodes of >28 days of dose delay follow the first full dose of 10 mg on Day 8, and 2 episodes of >36 days of dose delay following third and later 10 mg Q2W. No CRS was reported in any of these episodes of repriming.

FDA's assessment on the adequacy of the proposed recommendations for restarting therapy after dose delay, as detailed below, include evaluations of observed rebound CRS data after dose delay and PK simulations following different dosing delay scenarios. In Table 22Table 27, evaluation of rebound CRS events following dose delay in 20200491 indicated that no increase in the risk of CRS following dose delays that were within the proposed cut-off for repriming and no patients experienced Grade 2 or higher CRS upon the resumption of treatment. The overall risk of rebound CRS is assessed to be low. However, there is sparse data to support evaluation of longer dose delay intervals greater than proposed cut-off for repriming. There were three patients experienced dose delays ranging from 15 to 21 days following the first step-up dose with no CRS, a Grade 1 CRS and a Grade 2 CRS, respectively. One patient had dose delay ranging from 22 to 28 days following the first treatment dose and five patients had dose delays great than 28 days following the subsequent full treatment dose. None of these patients developed rebound CRS. The overall clinical data is not concerning regarding rebound CRS or against the proposed re-treatment plan.

Table 22. FDA –Summary of the CRS Events following Dose Delays in Study 20200491.

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Duration	Delayed Dose	No CRS	Grade 1 CRS	Grade 2 CRS
CRS Following Dose Delays Less than or Equal to the Proposed Re-Priming Cut-Offs	**Step-up Dose 1 Delay**	**≤14 days between step-up dose 1 and first full dose**		
		4(57%)	3(42%)	0
	First Full dose Delay	**≤ 21days between first full dose and second full dose**		
	10mg	7 (43%)	3(27%)	0
	Second or Later Dose Delay	**≤ 28 days between full doses ***		
	First 10mg Q2W Dosing	8 (100%)	0	0
	Second or later dose 10mg Q2W	18(100%)	0	0
CRS Following Dose Delays Greater than the Proposed Re-Priming Cut-Offs	**Step-up Dose 1 Delay**	**>14 days between step-up dose 1 and first full dose**		
		1 (33%)	1 (33%)	1 (33%)
	First Full Dose Delay	**>21 days between first full dose and second full dose**		
		1 (100%)	0	0
	Second full Dose Delay	**> 28 days between full doses &**		
	First 10mg Q2W Dosing	0	0	0
	Second or later dose 10mg Q2W	5(100%)	0	0

The summary includes patients who did not receive repriming with 1 mg step-up dose.
Resource: FDA summary of Applicant's response on 1/3/2024

The impact of dose delays on ORR was also assessed. The percentages of responders were comparable in patients with dose interruptions and without dose interruption (Table 23). Dose interruptions did not appear to impact responses in the 1/10 mg cohort.

Table 23. Summary for Responders Who Maintained or Achieved Response With or Without Dose Interruption or Dose Delay in 1/10 mg Cohort in Study 20200491.

	Number of patients included in the assessment (N)	Percentage of patients achieved or maintain response during the treatment period (n/N)
Primary efficacy population		
3 months	70	57.1
6 months	46	69.6
Any period	99	40.4
Patients who had a dose interruption or dose delay		
3 months	46	50.0
6 months	25	64.0
Any period	64	35.9

The analysis set for part 1 and part 2 includes all patients who received at least 1 dosage of 1/10 mg tarlatamab in part 1 and part 2 of the study. The responses used for the analysis were based on BICR assessments using RECIST 1.1 criteria.
Resource: Applicants' response to FDA on 1/26/2024.

PK simulation

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Due to limited clinical data on dose delay, the dosage recommendation for restarting doses or repeating doses were assessed based on a PK simulation. Tarlatamab exposure after each dose delay scenario was simulated with the popPK model and compared to the reference, tarlatamab exposure after the recommended schedules without delays. From a PK perspective, the C_{trough} at the maximum allowed dose delay interval should be similar (20%) or higher than the C_{trough} for next lower dose level (e.g., the step-up doses) to avoid risk of rebound CRS.

Table 24: Simulated Tarlatamab Median C_{trough} for Dose Delay Scenarios

Last Dose Administered	Time Since the Last Dose Administered	Action for Next Dose	Simulated C_{trough} (ng/mL) at End of Dose Delay	Reference C_{trough} (ng/mL)
Step-up dose 1 (1 mg) on day 1	2 weeks or less (≤14 days)	Continue at 10 mg	30 (10-48)	51(24-71)
First Full Dose (10 mg) on day 8	3 weeks or less (≤21 days)	Continue at 10 mg	204 (50-375)	51(24-71)
10 mg day 15 and onward and Q2W	4 weeks or less (≤28 days)	Continue at 10 mg	208 (36.4-461)	51(24-71)

Median and 90% prediction interval are reported; C_{trough} = trough concentration; Q2W = every 2 weeks
Source: Applicant's response to FDA IR on 1/3/2024

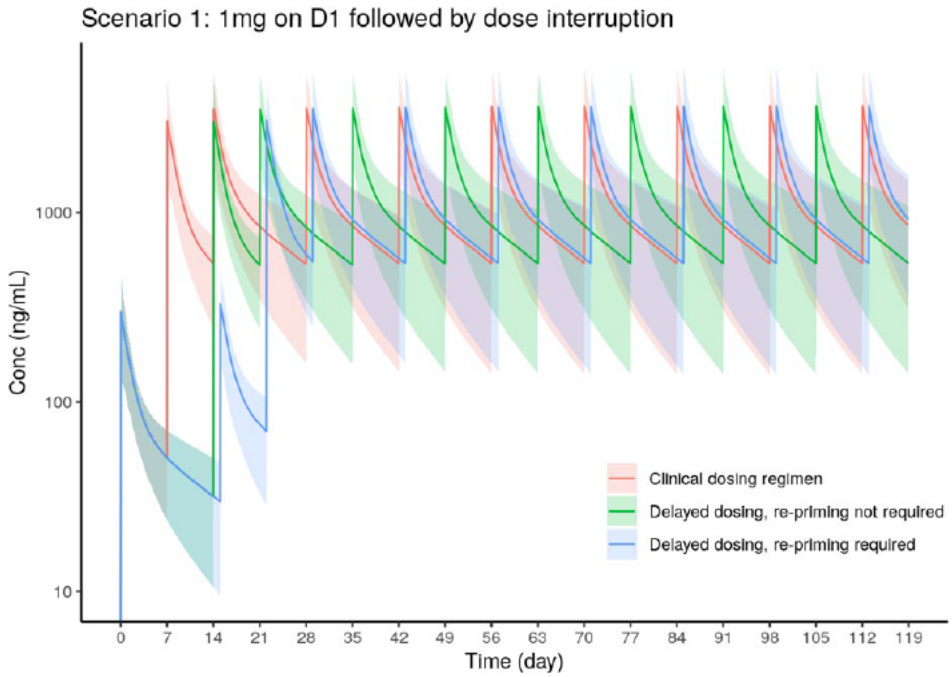
The simulated C_{trough} was higher than reference except in the first dose delay scenario (Table 24). The predicted C_{trough} following the first step-up dose C1D1 dose delay for 14 days was approximately 59% of the reference value. Figure 11 shows when patients received 1 mg on Day 1 and followed by dose interruption, under with and without repriming scenario. Although the initial C_{trough} followed by the dose interruption is lower than the reference, the concentration reaches to that of reference once next target dose is administered. The initial drop in the concentration is not likely to be clinically relevant. The proposed 14 days dose delay cutoff was further supported by safety data observed in study 20160323. During the dose escalation phase, cohort 6 in the dose escalation evaluated the dosing regimen of 1 mg Q2W in 8 patients without a step dose. Overall, CRS was lower than 1/10 mg cohorts, supporting the 14-day cutoff before re-priming in scenario 1 (Table 14).

Based on the simulated PK profile and available clinical data, FDA agrees proceeding with 10 mg doses when the dose interruption ≤ 14 days following the 1 mg step-up dose.

Figure 11. Simulated median PK profiles – Reference (Planned Clinical Dosing Regimen) compared to dosing delay after step-up dose 1 with and without re-priming.

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The line displayed median and shaded area represented the 90% prediction interval, The red line display simulation of planned clinical dosing regimen, which is the reference concentration. The green line displays delayed dosing, re-priming not required (e.g., Dose 1 step-up 1 mg, Day 15 target dose 10 mg, Day 22 target dose 10 mg, followed by planned dosing schedule). The blue line displays dosing, re-priming required, repeat step-dose schedule per Cycle 1 (e.g., simulation of step-up dose 1 1mg, day 16 step up dose 1mg, day 23 target dose 10mg, day 30 target dose 10mg followed by planned dosing schedule).
Source: Applicant's response to FDA IR on 1/5/2024

6.3.2.2 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors (e.g. race, ethnicity, age, performance status, genetic subpopulations, etc.)?

Data:

See Section 6.2.2.2, Therapeutic Individualization.

The Applicant's Position:

None of the covariates evaluated in these analyses resulted in clinically meaningful changes in efficacy or safety and therefore no dose adjustment is recommended.

The FDA's Assessment:

FDA agrees with Applicant's position that there is no need for dose adjustment for the currently proposed indication based on age, BW, sex, race (White and Asian), mild or moderate renal impairment or mild hepatic impairment.

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CRS incidence or severity were generally similar across different BW quartiles following the proposed 1/10 mg tarlatamab (Figure 45 Cytokine Release Syndrome Incidences at C1D1, C1D8, C1D15, C2+ with and without Tocilizumab Stratified by Body Weight Following Administration of 1/10 mg Tarlatamab.**Error! Reference source not found.**). Similarly, there is no clear trend of CRS incidence or severity by age quartiles or DLL3 cut points following the proposed dose (Figure 46, and Figure 47). Therefore, FDA agrees that no step-up dose adjustment is needed in the specific sub-population.

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Due to limited or no available data, the effects of severe renal impairment (eGFR 15 to 29 mL/min), end-stage renal disease (eGFR <15 ml/min), moderate to severe hepatic impairment (total bilirubin >1.5 times ULN and any AST), ADA, or ethnicity (e.g., Hispanic or Latino) on tarlatamab PK are unknown.

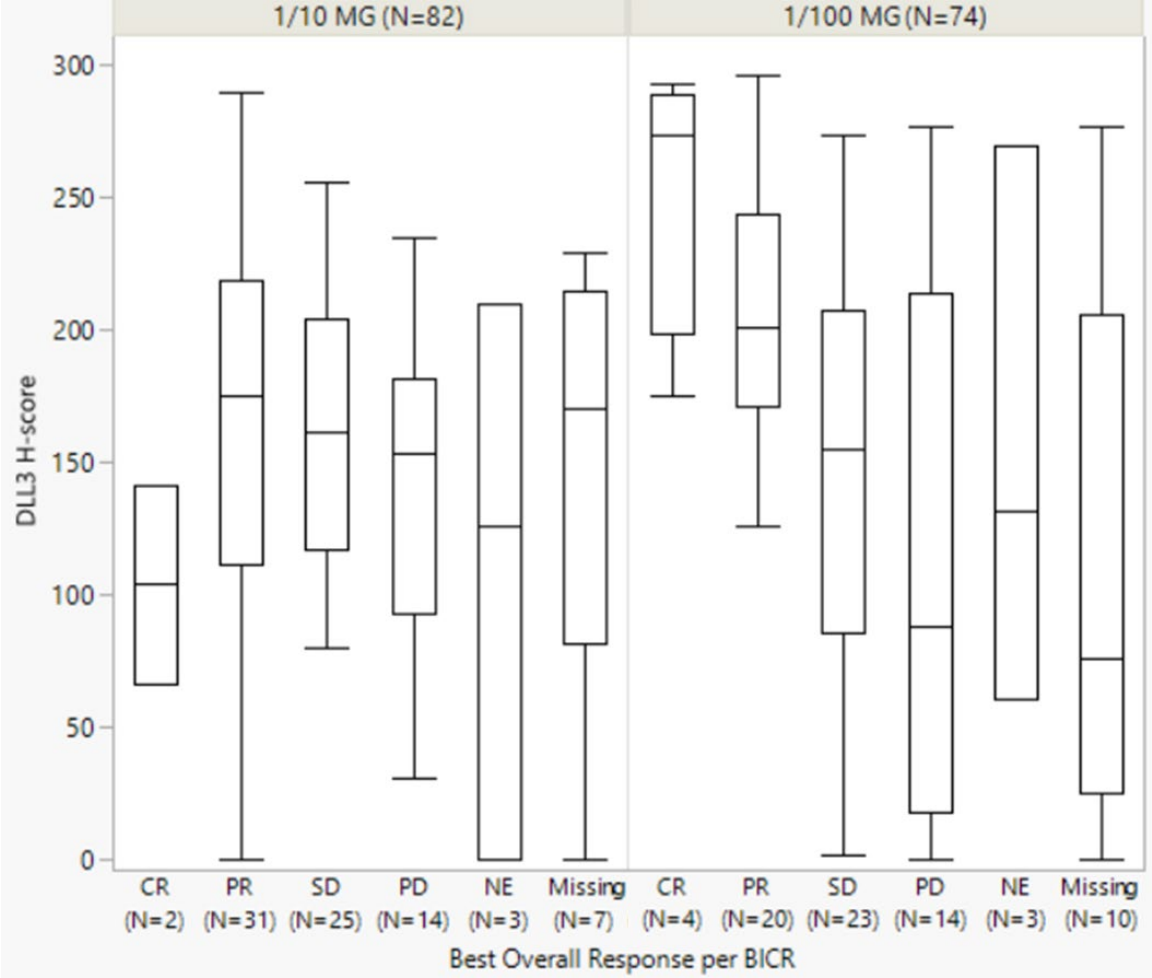
DLL3 expression status

In study 20200491, DLL3 expression was evaluated by immunohistochemistry (IHC) at baseline in fresh or archival tumor tissue samples. For patients with response assessments determined by BICR (N=185), DLL3 expression data was available for 83% of patients (82/99) in the 1/10 mg cohort and 86% of patients (74/86) in the 1/100 mg cohort. Overall response rates in the subset of patients with DLL3 expression data available were consistent with response rates observed in the full Safety Analysis Set for Part 1 and Part 2 (see section 8.1.2). Although there was a general trend toward higher DLL3 H-scores in patients who responded (Figure 12), 1 patient in the 1/10 mg cohort with an H-score of 0 achieved a PR. Additionally, no difference in ORR was observed at the DLL3 cut-points of < 75% vs ≥ 75% and < 25% vs ≥ 25% at moderate (2+) and strong (3+) staining intensities, as assessed by the Applicant (see section 8.1.6). These results support treatment of patients irrespective of baseline DLL3 expression status.

Figure 12. FDA – DLL3 H-score by Best Overall Response per BICR in the 1/10 MG and 1/100 MG Cohorts (Subset of Safety Analysis Set for Part 1 and Part 2 with Available DLL3 H-score Results)

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Data cutoff date: October 2, 2023.
Source: FDA reviewer's analyses.

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

Data:

Based on molecular size and route of administration of tarlatamab, no formal food-drug or drug-drug interaction studies were required and therefore not performed.

The Applicant's Position:

Not applicable

The FDA's Assessment:

FDA agrees with Applicant on that a food effect is not anticipated given tarlatamab is a large molecule and is administered intravenously.

FDA agrees with Applicant's position on that no formal drug-drug interaction studies are required. Based on FDA's evaluation of literature and understanding of postulated mechanism of IL-6 mediated CYP suppression, the drug interaction risk between CYP substrates and tarlatamab is low. Cytokine levels peaked 24 hours after the tarlatamab first dose administration with peak median concentration around 26 pg/mL. However, the risk of drug interaction during and after any CRS cannot be ruled out. Therefore, additional labeling language is provided in Section 12.3 of USPI that tarlatamab may increase exposure of concomitant CYP substrates during and up to 14 days after occurrence of CRS. Refer to section 6.3.1 and 19.4.2**Error! Reference source not found.** for review of the cytokine analyses.

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Primary Reviewer	Team Leader
Yue Xiang	Hong Zhao
Jianghong Fan	Youwei Bi
Sarah Dorff	Sarah Dorff

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7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:
The clinical studies supporting the marketing application for the intended indication in SCLC are provided in Table 25. The primary study to support efficacy and safety is the pivotal phase 2 Study 20200491.

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Reference ID: 5382024

Table 25. Applicant – Table of Clinical Studies

Study Type and Protocol Number	Study Objectives	Study Design and Type of Control	Treatment(s) Administered	Number of Subjects Enrolled (Actual/Planned)	Key Entry Criteria	Study Duration Per Protocol	Study Status/ Report Type[a]
Uncontrolled Studies (Module 5.3.5.2)							
20160323 (IND 134859)	PK, safety, tolerability; MTD or RP2D and preliminary antitumor activity	Phase 1 • nonrandomized • dose exploration • dose expansion • open-label • multicenter	Tarlatamab 0.003, 0.01, 0.03, 0.1 or 0.3 mg (no step); 1 mg on Day 1 (step dose) and 3 mg, 10 mg, 30 mg or 100 mg on Days 8 and 15 and Q2W IV thereafter; or 1 mg on Day 1 and 100 mg on Day 8 then 100 or 200 mg on Day 15 and Q3W thereafter IV; 0.1 or 0.3 mg tarlatamab on Days 1 and 15 then Q2W with pembrolizumab 200 mg IV from cycle 1 day 15 then Q3W; Dexamethasone 8 mg PO on cycle 1 day 1 prior to tarlatamab step dose for Part D (cohort 11)	238/392 as of 02 October 2023 Duration of treatment: until disease progression	Subjects ³ 18 years with R/R SCLC who progressed or recurred following at least 1 platinum-based regimen	Approximately 4 years	Ongoing/Interim Analysis CSR

Footnotes defined on last page of table.

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Table 25. Applicant – Table of Clinical Studies

Study Type and Protocol Number	Study Objectives	Study Design and Type of Control	Treatment(s) Administered	Number of Subjects Enrolled (Actual/Planned)	Key Entry Criteria	Study Duration Per Protocol	Study Status/ Report Type[a]
20200491 (IND 134859)	Efficacy, safety, tolerability, PK	Phase 2 • randomized dose evaluation • nonrandomized dose expansion • open-label (BICR endpoint) • multicenter		222/220 as of 02 October 2023 Duration of treatment: until disease progression	Adult subjects [3] 18 years of age with confirmed R/R SCLC who have progressed treatment with platinum containing therapy, and at least 1 additional line of therapy	Approximately 24 months	Ongoing/ Primary Analysis CSR
Part 1			Tarlatamab 1 mg on Day 1, then 10 or 100 mg on Day 8, Day 15 and Q2W IV thereafter	176/180 as of 02 October 2023			
Part 2			Tarlatamab 1 mg on Day 1, then 10 mg (based on an interim analysis of Part 1) on Day 8, Day 15 and Q2W IV thereafter	12/10 at selected dose (total of 100 subjects at selected dose inclusive Part 1 enrollment)			
Part 3	Modified Monitoring Cohort		Tarlatamab 1 mg on Day 1, then 10 mg on Day 8, Day 15 and Q2W IV thereafter	34/30			

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Table 25. Applicant – Table of Clinical Studies

Study Type and Protocol Number	Study Objectives	Study Design and Type of Control	Treatment(s) Administered	Number of Subjects Enrolled (Actual/Planned)	Key Entry Criteria	Study Duration Per Protocol	Study Status/ Report Type[a]
Other Studies (Module 5.3.5.4)							
20200439 (IND 134859)	PK, safety, tolerability; antitumor activity and RP2D	Phase 1b • nonrandomized, • dose exploration • dose expansion • open-label • multicenter	[redacted]	[redacted]	[redacted]	[redacted] (b) (4)	Ongoing/Study Summary Report
20200040 [redacted] (b) (4)	PK, safety, tolerability; MTD or RP2D and preliminary antitumor activity	Phase 1b • nonrandomized • dose exploration • dose expansion • open-label • multicenter					Ongoing/Study Summary Report

Footnotes defined on last page of table.

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Table 25. Applicant – Table of Clinical Studies

Study Type and Protocol Number	Study Objectives	Study Design and Type of Control	Treatment(s) Administered	Number of Subjects Enrolled (Actual/Planned)	Key Entry Criteria	Study Duration Per Protocol	Study Status/ Report Type[a]
20200469 (b) (4)	PK, safety, tolerability; MTD or RP2D and preliminary antitumor activity	Phase 1b • nonrandomized • dose exploration • dose expansion • open-label • multicenter	(b) (4)				

Footnotes defined on last page of table.

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Reference ID: 5382024

Table 25. Applicant – Table of Clinical Studies

Study Type and Protocol Number	Study Objectives	Study Design and Type of Control	Treatment(s) Administered	Number of Subjects Enrolled (Actual/Planned)	Key Entry Criteria	Study Duration Per Protocol	Study Status/ Report Type[a]
Controlled Studies (Module 5.3.5.1)							
20210004 (IND 134859)	Efficacy, safety, tolerability, PROs, PK	Phase 3 • randomized • active-controlled • open-label • multicenter	[redacted] (b) (4)				

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[redacted] (b) (4)

SCLC = small cell lung cancer.

[a] Status at the time of the marketing application.

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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The Applicant's Position:
All studies pertinent to the evaluation of efficacy and safety for the intended indication are summarized above in Table 25. The primary support for the efficacy of the proposed indication is based on the results from Part 1 and Part 2 of the pivotal phase 2 Study 20200491 in subjects with advanced SCLC who had progressed or recurred following 1 platinum-based regimen (with or without immune checkpoint inhibitor) and at least 1 other line of therapy.

The FDA's Assessment:
FDA generally agrees with the Applicant's position. Results from Parts 1 and 2 of Study 20200491 comprise the primary efficacy population to support efficacy evaluation of this application. Efficacy data from Part 3 of Study 20200491 and from patients who received the proposed tarlatamab dose from Study 20160323 were considered as supportive data for efficacy.

Results from Study 20200491 (n=159) and 20160323 (n=27) comprise the primary safety population use to support he safety evaluation of this Application.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Pivotal Study 20200491

Trial Design

The Applicant's Description:

Study 20200491 is an ongoing phase 2, open-label, registrational study evaluating tarlatamab for the treatment of subjects with recurrent SCLC who had progressed or recurred following 1 platinum-based regimen (with or without immune checkpoint inhibitor) and at least 1 other line of therapy (retreatment with a platinum-based regimen was considered a second line of therapy) (Figure 13).

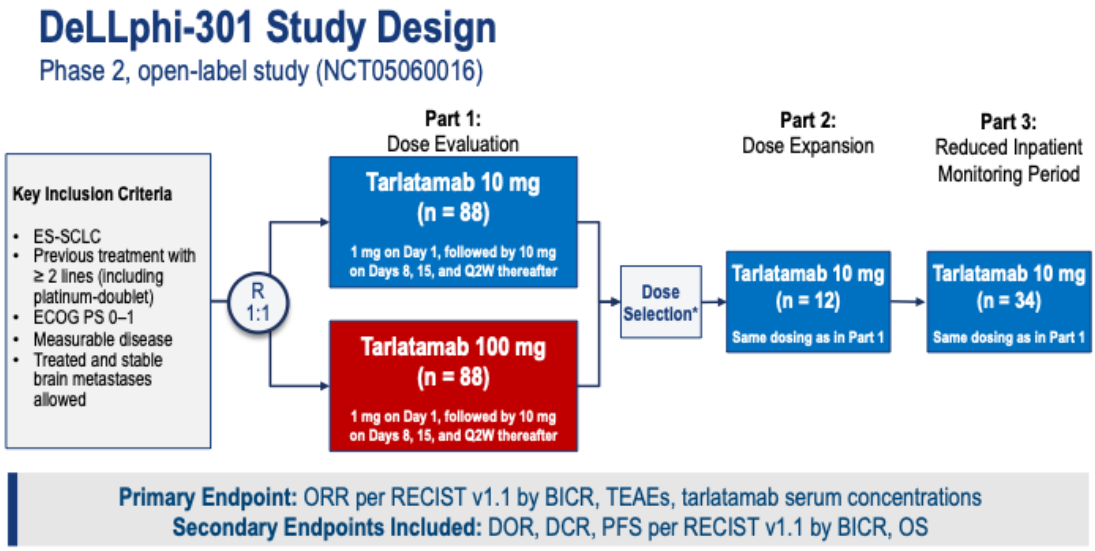
This study was conducted in 3 parts. Part 1 evaluated 2 dose levels of tarlatamab in which approximately 180 eligible subjects were planned to be enrolled and randomized 1:1 to either treatment with a target dose of 10 or 100 mg tarlatamab. To select a dose for expansion, an interim analysis was performed after 30 subjects in each group in Part 1 had opportunity to confirm an objective response after the first posttreatment scan, or up to 13 weeks of follow-up, whichever occurred first. Enrollment continued in a randomized fashion until dose selection was finalized. Part 2 was a dose expansion phase at the selected dose based on the interim

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analysis of Part 1 and enrolled until approximately 100 subjects (from Parts 1 and 2 combined) had been enrolled at the selected dose level. Part 3 was initiated after completing enrollment of Parts 1 and 2**,** to enroll up to approximately 30 additional subjects at the selected dose, with modified cycle 1 monitoring criteria.

Figure 13. Applicant – Schema of Study 20200491



*Once 30 subjects per dose level had the opportunity to confirm an objective response after the first post-treatment scan or ³ 13 weeks of follow-up, whichever occurred first.
BICR = blinded independent central review; DCR = disease control rate; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; ES-SCLC = extensive-stage small cell lung cancer; ITT = intention-to-treat; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; Q2W = every 2 weeks; R = randomization; RECIST = Response Evaluation Citeria in Solid Tumors; TEAE = treatment-emergent adverse event

The FDA's Assessment:

FDA generally agrees with the Applicant's description of the trial design of Study 20200491.

Eligibility Criteria

The Applicant's Description:

Study 20200491
Eligible subjects were men or women (≥ 18 years of age [or legal adult age within country]) with histologically or cytologically confirmed relapsed or refractory SCLC who progressed or recurred following 1 platinum-based regimen and at least 1 other prior line of therapy (Note: [1] re-treatment with a platinum-based regimen was considered a second line of therapy; [2] platinum-based regimen followed by immune checkpoint/PD-L1 inhibitor as maintenance

therapy was considered 1 line of therapy; [3] in countries where standard of care first-line systemic treatment included platinum-containing chemotherapy in combination with PD-L1 inhibitor, it was required for subjects to have failed or be ineligible for PD-L1 inhibitor as part of their first-line systemic treatment).

The FDA's Assessment:

FDA generally agrees with the Applicant's description of key eligibility criteria for Study 20200491. Additional key inclusion criteria include patients having an ECOG performance status of 0 or 1 and at least one measurable lesion as defined by RECIST v1.1. Key exclusion criteria included symptomatic brain metastases, evidence of interstitial lung disease or non-infectious pneumonitis and active immunodeficiency.

Study Endpoints

The Applicant's Description:

Study 20200491
The primary objectives of the study were to:

- evaluate safety and efficacy (per RECIST 1.1 by investigator) of 2 dose levels of tarlatamab (Part 1 only)
- evaluate antitumor activity of tarlatamab as determined by ORR per RECIST 1.1 by blinded independent central review (BICR) (Parts 1 and 2)
- evaluate safety of reduced mandatory monitoring period in cycle 1 at selected dose of tarlatamab (Part 3)

Secondary objectives for all parts of the study included other measures of efficacy (endpoints of DOR, DCR, PFS, and OS), safety, PK, and immunogenicity.

The FDA's Assessment:

FDA agrees with the Applicant's description of the endpoints in Study 20200491. FDA considers ORR an appropriate efficacy endpoint to support accelerated approval, where ORR is of sufficient magnitude and duration with a corresponding 95% confidence interval excluding clinically irrelevant response rates for the proposed dose (10 mg dose). Additionally, while the statistical analysis plan included summary statistics of PFS and OS as secondary efficacy endpoints, FDA does not consider time to-event endpoints interpretable in the context of a single arm trial for the purposes of regulatory decision-making.

Statistical Analysis Plan and Amendments

The Applicant's Description:

Study 20200491: There were 5 amendments to the original statistical analysis plan (SAP) before the data snapshot date of this report (18 July 2023), as summarized in Table 26. Within these

SAP amendments, there were no changes to the protocol-specified analyses. The efficacy endpoints and the corresponding statistical methods of analysis for Study 20200491 are summarized in Table 27.

Table 26. Applicant – Summary of Statistical Analysis Plan Amendments (Study 20200491)

Amendment	Changes
Original (v1.0) 21 January 2022	Not applicable
Amendment 1 (v2.0) 11 April 2022	• updated baseline and safety analyses • updated Appendix B for BOR calculation
Amendment 2 (v3.0) 31 May 2022	• updated based on protocol amendment 3 • added definitions and efficacy analyses for DLL3 subgroups
Amendment 3 (v4.0) 02 September 2022	• updated analysis set definition for interim efficacy, DLL3 subgroups and efficacy analyses
Amendment 4 (v5.0) 19 April 2023	updated the below sections per protocol amendment 5: • updated Study Schema • added objective and endpoints for primary endpoint (Part 3) and updated secondary and exploratory endpoints • updated enrolled subjects for Part 1 and Part 2 • updated study design for Part 3 and sample size for all parts of study • updated definition for Full Analysis Set, added definition for Interim Efficacy Analysis Set for primary analysis and removed definition of DLL3 analysis sets • updated follow-up time threshold for primary analysis • updated confidence level for ORR, added Part 3 in subject accountability, updated analysis sets in efficacy analyses, updated for events of interest, exposure to IP, and exposure to other protocol-required therapy • updated Appendix B (BOR calculation algorithm) and Appendix C (PFS calculation and censoring rule)
Amendment 5 (v6.0) 28 June 2023	• updated definition for treatment-emergent adverse event, to specify that events directly related to small cell lung cancer or disease progression (including, but not limited to, preferred terms “small cell lung cancer,” “disease progression,” etc) were excluded from analysis

BOR = best overall response; DLL3 = delta-like ligand 3; IP = investigational product; ORR = objective response rate; PFS = progression-free survival

Table 27. Applicant –Statistical Methods for Study 20200491

Endpoint	Study 20200491 (Pivotal)
ORR	Clopper Pearson exact 97.5% CIs (Clopper and Pearson, 1934) (subjects without a postbaseline tumor assessment were considered nonresponders) Plot of percent change from baseline in target lesion sum of diameters
DCR	Clopper Pearson exact 95% CI
DoDC, DOR, PFS, OS	Kaplan-Meier estimates for median and selected quantiles with 95% CI calculated using the Brookmeyer and Crowley method (Brookmeyer and Crowley, 1982) Rates for selected time points were reported along with 95% CI using the Greenwood formula to estimate the standard error in CI calculation (Kalbfleisch and Prentice, 1980)

BICR = blinded independent central review; DCR = disease control rate; DoDC = duration of disease control; DOR = duration of response; ORR = objective response rate; OS = overall survival; PFS = progression-free survival
ORR, DCR, DoDC, and PFS assessments were assessed by BICR and by investigator and OS by investigator.

The FDA's Assessment:

FDA agrees with the Applicant's descriptions of the statistical analysis plan. In addition, during the pre-BLA meeting dated September 8, 2023, FDA requested that the Applicant provide a 95% CI of ORR using the Clopper-Pearson exact method, and FDA also commented that the as-treated population, which includes all patients who received at least one dose of tarlatamab, should be the primary efficacy analysis population. In the BLA submission, the Applicant provided 95% CI and included results of a post-hoc analysis of ORR and DOR in the as-treated population. FDA and the Applicant also agreed that it would be acceptable to provide updated efficacy data in the 90-day safety update report, which were provided during the review cycle.

Protocol Amendments

The Applicant's Description:

Changes in the conduct of pivotal Study 20200491 that were implemented by protocol amendments are described in the protocol. Major changes in the conduct of the study are described in Table 28.

Table 28. Applicant – Protocol Amendment Summary (Study 20200491)

Amendment	Major Changes	No. Subjects Enrolled Under Amendment
Original Protocol 24 June 2021	Not applicable	25
Amendment 1 01 October 2021	• added neutropenia as an identified risk of tarlatamab • updated the statistical analysis of objective response rate based on feedback from the US FDA • clarified collection of serious and nonserious adverse events during long-term follow-up based on feedback from the European Union Voluntary Harmonisation Procedure • incorporated patient input on the study design • added siltuximab as a CRS rescue medication if tocilizumab is unavailable • added stopping criteria for siltuximab use and subgroup analysis for subjects who receive siltuximab • updated the medical resource utilization and health economics data to be collected and analyzed • corrected timing of antitarlatamab antibody sample collection	0
Amendment 2 06 December 2021	• added option for subjects to continue on investigational product after radiologic disease progression • replaced circulating tumor cell collection with ctDNA collection and provided details of collection in Section 8.8.1 • added dose selection committee language, and clarified that the data review team oversaw futility and safety interim analyses • added time points for collection of serum markers • clarified that all subjects needed a brain MRI/CT at screening • clarified criteria for evaluating treatment with siltuximab	122

Footnotes are defined on the last page of the table.

Table 28. Applicant – Protocol Amendment Summary (Study 20200491)

Amendment	Major Changes	No. Subjects Enrolled Under Amendment
Amendment 3 12 May 2022	• replaced the independent confirmation of progression group with efficacy readers, who performed the assessment • added testing of DNA/RNA by PCR as needed as a part of viral serology in the local laboratory • allowed the option of dose reduction for grade 2 TLS and grade 4 non-febrile neutropenia and to discontinue tarlatamab permanently if grade 2 TLS repeated • removed PK subgroup analysis in the statistical analysis section for subjects who received siltuximab • clarified that the central imaging vendor must communicate radiologic disease progression results to study site and Sponsor within a targeted date of 5 business days after receiving images	41
Amendment 4 18 November 2022	• see superseding amendment 4 for changes	See superseding amendment 4

Footnotes are defined on the last page of the table.

Table 28. Applicant – Protocol Amendment Summary (Study 20200491)

Amendment	Major Changes	No. Subjects Enrolled Under Amendment
Superseding Amendment 4 13 December 2022	• incorporated an additional Modified Monitoring substudy (Part 3) to be conducted after Part 2 had completed enrollment, to evaluate safety of reduced inpatient monitoring • included a synopsis of benefit-risk assessment • updated the objectives and endpoints of the study: – added primary objectives and endpoints for Part 3 – updated exploratory objectives and endpoints regarding treatment effect on subjects receiving tarlatamab for all parts of the study • updated the overall design of the study to: – inform that the study would be conducted in 3 parts – update the number of additional subjects per arm from 30 subjects to 60 subjects – update the total number of subjects participating in the study from approximately 160 subjects to approximately 220 subjects – inform that up to approximately 30 additional subjects would be enrolled in Part 3 of the study • removed eligibility requirement of no acute symptoms of COVID-19 within 14 days prior to first dose of tarlatamab from exclusion criteria • removed COVID-19 from tarlatamab dose modifications guidelines for adverse events table • updated that the safety follow-up visit would be performed approximately 42 (**+** 5) days after the last dose of tarlatamab • updated the end of study section to inform that the study duration for subjects would be approximately up to 24 months, to be extended as needed to ensure all subjects had the opportunity to be followed in long-term follow-up for at least 1 year after the last subject's last dose of tarlatamab • included specific exclusions to Part 3 of the study • included hospitalization and monitoring guidance for cycle 1 of Part 3 of the study • updated tarlatamab dose modification guidelines for neurologic events and CRS • included CRS and ICANS in the safety assessments section	34

Footnotes are defined on the last page of the table.

Table 28. Applicant – Protocol Amendment Summary (Study 20200491)

Amendment	Major Changes	No. Subjects Enrolled Under Amendment
Amendment 5 23 March 2023	• changed the time of the follow-up from 6 months to 24 weeks from the first scheduled post baseline tumor • clarified that in Part 1, subjects were randomized to either the target dose of 10 mg or 100 mg tarlatamab IV • added that assessments performed as standard of care prior to informed consent, but within the protocol-specified window, could be used for screening • removed a sentence that primary analysis excluded Part 3 data from the efficacy analysis • clarified and confirmed that assessment of relatedness for nonserious adverse events to study procedures was not required	0

CRS = cytokine release syndrome; CT = computed tomography; ctDNA = circulating tumor DNA; FDA = Food and Drug Administration; ICANS = immune effector cell-associated neurotoxicity syndrome; MRI = magnetic resonance imaging; PCR = polymerase chain reaction; PK = pharmacokinetics; TLS = tumor lysis syndrome; US = United States

The FDA's Assessment:

FDA generally agrees with the Applicant's description of the protocol amendments with one clarification below.

On November 18, 2022, the study was amended (amendment 4) to incorporate a Part 3 that would be conducted after enrollment to Part 2 was completed. The purpose of Part 3 of the study was to evaluate the safety of reduced inpatient monitoring during Cycle 1 administration of tarlatamab.

8.1.2. Study Results – Study 20200491

Compliance with Good Clinical Practices

Data:

Audits of Study 20200491 were included as part of the independent Amgen Quality, Compliance, and Audit program performed by Amgen. The audit certificate is provided in Section 16.1.8 of Study 20200491 clinical study reports (CSRs).

Amgen has been closely monitoring the evolving COVID-19 situation across the globe and has, therefore, taken proactive steps to maintain the safety of study participants and support staff, including Amgen representatives, at all clinical study centers, and to maintain study data integrity while maintaining compliance with good clinical practice (GCP). Guidelines on study conduct during the COVID-19 period were documented in the respective study protocols.

The Applicant's Position:

Study 20200491 was conducted in accordance with the Code of Federal Regulations (CFR) governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) in accordance with GCP. Study 20200491 was conducted under Investigational New Drug 134859.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. Findings were noted from the GCP site inspections as described in Section 4.1. The Applicant conducted a 100% SDR/SDV for all clinical sites that participated in Study 20200491 which yielded updated data for efficacy and safety that did not impact FDA's interpretation of the trial results in a meaningful way. This updated data was used in labeling. Based on the information provided in this application, the conduct of Study 20200491 was consistent with the International Council for Harmonization guidelines for Good Clinical Practice, U.S. Federal regulations and requirements by other applicable regulatory authorities.

Financial Disclosure

Data:

See Appendix 19.2.

The Applicant's Position:

Study 20200491 was an Amgen-sponsored clinical study. Financial interests or arrangements with clinical investigators have been disclosed (see Appendix 19.2).

The FDA's Assessment:

FDA reviewed the financial disclosure information provided by the Applicant. Refer to FDA's assessment of this information in Appendix 19.2.

Patient Disposition

Study 20200491: Overall, as of the data cutoff date of 27 June 2023, 222 subjects were randomized (Part 1) or enrolled (Parts 2 and 3) and 220 subjects received at least 1 dose of tarlatamab, including 99 subjects in the 10 mg target dose group across Parts 1 and 2, 87 subjects in the 100 mg target dose group in Part 1, and 34 subjects in the Part 3 modified safety monitoring 10 mg target dose group.

As of the data cutoff date, 32.0% of subjects overall were continuing treatment with tarlatamab: 29.0% from the 10 mg group (Parts 1 and 2), 25.0% from the 100 mg group (Part 1), and 58.8% from Part 3 (10 mg with modified monitoring). Overall, 67.1% of subjects had discontinued tarlatamab: 70.0% from the 10 mg group (Parts 1 and 2), 73.9% from the 100 mg group (Part 1), and 41.2% from Part 3 (10 mg with modified monitoring). The most common reason for discontinuation of tarlatamab was disease progression (46.8%), followed by adverse event (6.8%), death (5.9%), and subject request (5.9%). As of the data cutoff date, 43.2% of subjects had discontinued the study; the most common reasons for study discontinuation were death (32.9%) and withdrawal of consent (9.0%) (Table 14-1.1.1 of Study 20200491).

The Applicant's Position:

As of the data cutoff dates for the Biologics License Application (BLA), 220 subjects were enrolled and received tarlatamab in Study 20200491 (99 at the 10 mg dose from Parts 1 and 2; 34 at the 10 mg dose with modified safety monitoring from Part 3). The primary analysis for the pivotal study was based on the BICR Full Analysis Set which included subjects who were randomized (Part 1) or enrolled (Part 2), received at least 1 dose of tarlatamab, and had 1 or more measurable lesions at baseline as assessed by BICR using RECIST 1.1. Safety analyses included subjects who received ³ 1 dose of investigational product.

The FDA's Assessment:

FDA generally agrees with the Applicant's description of patient disposition for Study 20200491. As previously discussed, although the Applicant presented data from the 10 and 100 mg doses for tarlatamab throughout this application, FDA review of efficacy focused on the proposed indicated dose (10 mg) for tarlatamab.

As of the data cutoff date, the most common reason for discontinuation of tarlatamab 10 mg was disease progression (52%), followed by adverse event (7%), death (3%), and subject request (6%). In addition, 43% of subjects had discontinued the study; the most common reasons for study discontinuation were death (35%) and withdrawal of consent (7%)

An information request was also sent to the Applicant to clarify the details for 8% of patients who discontinued safety follow-up with the reason "other". The Applicant clarified that the majority of patients refused the safety follow-up visit.

Protocol Violations/Deviations

Data:

Study 20200491: As of the data cutoff date of 27 June 2023, a total of 81 subjects (36.8%) had at least 1 important protocol deviation (IPD) (Section 9.2 of Study 20200491). Overall, the most frequently reported (> 10% of subjects overall) IPDs were other GCP deviations (19.5%) and missing predose assessments during treatment period (10.5%). No IPDs due to COVID-19 control measures were reported. Details for all important protocol deviations are provided by subject in Listing 16-2.2.1 of Study 20200491.

The Applicant's Position:

The above mentioned IPDs did not affect the overall results of the study.

The FDA's Assessment:

FDA reviewed the full list of protocol deviations provided by the Applicant. For the tarlatamab 10 mg dose, 32% of patients had at least one important protocol deviation. Overall, the most frequently reported (> 10% of subjects overall) IPDs were other GCP deviations (20.2%) and missing predose assessments during treatment period (10.1%). Deviations listed under the "other GCP deviations" category were generally in regard to samples being collected without consent being obtained, samples being erroneously collected that were not required per protocol or late SAE reporting.

There were also 2 patients who received the incorrect dose of study treatment. Review of these protocol deviations showed that 1 patient received 1 mg of tarlatamab instead of 10 mg of tarlatamab and a second patient received 10 mg of tarlatamab instead of 1 mg. Lastly, there were 4 patients who had eligibility criteria violations. Two patients received prior anticancer therapy within 30 days of the first dose of tarlatamab; one was within 28 days and the other was within 29 days. Two additional patients did not receive at least 2 prior lines of treatment (only received 1 prior line with platinum and PD-(L)1 therapy); one of these patients had a response to treatment.

In addition, as noted in the summary from the Office of Scientific Inspections, 1 patient who received the tarlatamab 10 mg dose was found ineligible following inspection of (b) (4) (patient (b) (6)). The patient was noted to have a partial thrombosis of the abdominal aorta at screening which violates the exclusion criteria of having a history of arterial thrombosis within 12 months of the first dose of tarlatamab treatment. The patient had a response to tarlatamab treatment, but FDA assessed that this eligibility violation is unlikely to have had an impact on response to tarlatamab treatment as the violation was in relation to a criteria related to patient safety. The eligibility violation did not appear to have an impact on the patient's safety.

From review of the above, FDA's assessment is that the important protocol deviations are

unlikely to have impacted the study's results in a meaningful way.

Table of Demographic Characteristics

Data:

Study 20200491: Baseline demographics and disease characteristics were generally consistent across the 10 and 100 mg dose groups (Table 29). Overall, across all parts, 70.9% of subjects were men, and the majority were White (62.7%) and not Hispanic or Latino (61.4%). The median (range) age was 64 (34 to 82) years, and the majority of subjects were younger than 65 years (52.7%).

Table 29. Applicant – Baseline Demographics (Safety Analysis Set – Study 20200491)

	Parts 1 and 2		Part 3	
	1->10 mg (N = 99)	1->100 mg (N = 87)	1->10 mg Modified Safety Monitoring (N = 34)	Overall (N = 220)
Sex - n (%)				
Male	71 (71.7)	61 (70.1)	24 (70.6)	156 (70.9)
Female	28 (28.3)	26 (29.9)	10 (29.4)	64 (29.1)
Race - n (%)				
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	41 (41.4)	36 (41.4)	2 (5.9)	79 (35.9)
Black (or African American)	0 (0.0)	0 (0.0)	1 (2.9)	1 (0.5)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
White	57 (57.6)	50 (57.5)	31 (91.2)	138 (62.7)
Ethnicity - n (%)				
Hispanic or Latino	1 (1.0)	2 (2.3)	0 (0.0)	3 (1.4)
Not Hispanic or Latino	56 (56.6)	48 (55.2)	31 (91.2)	135 (61.4)
Multiple	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (1.0)	1 (1.1)	0 (0.0)	2 (0.9)
Age (years)				
N	99	87	34	220
Mean	63.6	62.5	65.5	63.4
SD	8.6	9.9	8.1	9.1
Median	64.0	62.0	65.5	64.0
Q1, Q3	58.0, 70.0	57.0, 69.0	60.0, 72.0	57.0, 70.0
Min, Max	35, 82	34, 80	49, 80	34, 82
Age group - n (%)				
18 - 64 years	51 (51.5)	51 (58.6)	14 (41.2)	116 (52.7)
65 - 74 years	38 (38.4)	26 (29.9)	14 (41.2)	78 (35.5)
75 - 84 years	10 (10.1)	10 (11.5)	6 (17.6)	26 (11.8)
³ 85 years	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Data snapshot date: 01 March 2024. Data cutoff date: 27 June 2023.
Source: Table 14-2.1.1 of Study 20200491

Reference ID: 5382024

The Applicant's Position:

Overall, the subjects with SCLC enrolled in Study 20200491 had baseline characteristics indicative of subjects with advanced SCLC. Thus, the patient population evaluated in the efficacy studies is considered representative of the overall population of patients with advanced SCLC and supportive of the proposed indication.

Data from racial and ethnic minorities such as American Indian or Alaska Native, Black or African American, and Native Hawaiian or Other Pacific Islander are limited.

The FDA's Assessment:

The median age of patients enrolled is consistent with that of the US patient population with SCLC. A higher proportion of male patients were enrolled compared with female patients (71% vs. 28%) which does not align with the known distribution of sex for SCLC in the US. However, the ORR was similar between both groups of patients (38% for males vs. 46% for females).

Patient enrollment into the efficacy population was multi-regional and global; the countries with the highest enrollment/randomization included: South Korea (30%), Spain (18%) and Japan (11%). Of the overall study population, no Black/African American patients were enrolled and only one patient was Hispanic/Latino. The distribution underrepresents the incidence of SCLC in these racial and ethnic minority groups. Despite these limitations, FDA agrees that the submitted data is supportive of the proposed indication for the US population. However, a postmarketing commitment (PMC) will be issued for analyses from ongoing or planned clinical trials enrolling a sufficient representation of U.S. racial and ethnic minority patients that is reflective of the US population of patients with SCLC to further characterize the safety and efficacy of tarlatamab in these patients.

Reference ID: 5382024

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

Data:

20200491

A total of 220 subjects received tarlatamab in this study with 99 subjects receiving 10 mg IV Q2W across Part 1 and Part 2 (combined), and treatment continued until disease progression or unacceptable toxicity. Tumor assessments were performed every 6 weeks for the first 48 weeks and every 12 weeks thereafter. Overall across all parts of the study, subjects had a median (range) of 2 (1 to 8) prior lines of therapy, including prior PD-1 or PD-L1 inhibitor therapy (74.1%) and prior radiotherapy (79.1%) (Table 30). Time to progression after first-line platinum therapy was < 90 days for 51 subjects (23.2%), 90 to < 180 days for 47 subjects (21.4%), 180 days or more for 47 subjects (21.4%), and unknown for 75 subjects (34.1%). Most subjects had metastatic disease (95.5%), with no brain metastases (73.6%) or liver metastases (64.1%), and an ECOG score of 1 (72.7%). In the 10 mg group, 99 subjects (100%) received prior platinum therapy, 20.2% received prior topotecan therapy, and 69.7% received prior anti-PD-L1 therapy. Baseline characteristics were generally consistent across the dose groups.

A post hoc platinum sensitivity analysis was performed for Parts 1 and 2 for progression-free interval after first-line platinum therapy, in which the interval was defined as time from end of platinum therapy in the first line to date of progression or start date of subsequent therapy, whichever came first. Of 185 subjects, progression-free interval was < 90 days for 60 subjects (38 subjects at 10 mg dose), ≥ 90 days for 109 subjects (55 subjects at 10 mg dose), and unknown for 16 subjects (6 subjects at 10 mg dose) (Table 22 of Module 2.7.3, SCE).

A post hoc sensitivity analysis was also performed for Parts 1 and 2 for prior lines of therapy representing global standard of care. Of 185 subjects, the number of subjects who received the following therapies at any line were 41 for topotecan, 96 for any topoisomerase 1 inhibitor (topotecan or belotecan or irinotecan), 13 for lurbinectedin, and 17 for amrubicin (Table 23 of Module 2.7.3, SCE).

Reference ID: 5382024

Table 30. Applicant – Baseline Disease Characteristics (Safety Analysis Set – Study 20200491)

	Parts 1 and 2		Part 3	
	1->10 mg (N = 99)	1->100 mg (N = 87)	1->10 mg Modified Safety Monitoring (N = 34)	Overall (N = 220)
ECOG status at baseline[a] – n (%)				
0	26 (26.3)	24 (27.6)	10 (29.4)	60 (27.3)
1	73 (73.7)	63 (72.4)	24 (70.6)	160 (72.7)
Smoking history – n (%)				
Never	8 (8.1)	5 (5.7)	1 (2.9)	14 (6.4)
Current	18 (18.2)	10 (11.5)	5 (14.7)	33 (15.0)
Former	73 (73.7)	72 (82.8)	28 (82.4)	173 (78.6)
Prior lines of therapy – n (%)				
1	2 (2.0)	2 (2.3)	0 (0.0)	4 (1.8)
2	65 (65.7)	47 (54.0)	22 (64.7)	134 (60.9)
3	18 (18.2)	22 (25.3)	6 (17.6)	46 (20.9)
> 3	14 (14.1)	16 (18.4)	6 (17.6)	36 (16.4)
Number of prior lines of therapy				
Mean	2.5	2.8	2.6	2.6
SD	1.0	1.3	1.0	1.1
Median	2.0	2.0	2.0	2.0
Q1, Q3	2.0, 3.0	2.0, 3.0	2.0, 3.0	2.0, 3.0
Min, Max	1, 6	1, 8	2, 6	1, 8
Prior PD-1 or PD-L1 – n (%)				
Yes	73 (73.7)	62 (71.3)	28 (82.4)	163 (74.1)
No	26 (26.3)	25 (28.7)	6 (17.6)	57 (25.9)
Prior radiotherapy for current malignancy – n (%)				
Yes	77 (77.8)	73 (83.9)	24 (70.6)	174 (79.1)
No	22 (22.2)	14 (16.1)	10 (29.4)	46 (20.9)

Footnotes are defined on the last page of the table.

Reference ID: 5382024

Table 30. Applicant – Baseline Disease Characteristics (Safety Analysis Set – Study 20200491)

	Parts 1 and 2		Part 3	
	1->10 mg (N = 99)	1->100 mg (N = 87)	1->10 mg Modified Safety Monitoring (N = 34)	Overall (N = 220)
Disease stage at screening - n (%)				
Stage 0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage I	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage II	1 (1.0)	0 (0.0)	2 (5.9)	3 (1.4)
Stage III	5 (5.1)	10 (11.5)	1 (2.9)	16 (7.3)
Stage IV	87 (87.9)	73 (83.9)	28 (82.4)	188 (85.5)
Unknown/Missing	6 (6.1)	4 (4.6)	3 (8.8)	13 (5.9)
Metastatic at baseline - n (%)				
Yes	97 (98.0)	81 (93.1)	32 (94.1)	210 (95.5)
No	2 (2.0)	6 (6.9)	2 (5.9)	10 (4.5)
Platinum sensitivity[b] - n (%)				
< 90 days	27 (27.3)	17 (19.5)	7 (20.6)	51 (23.2)
³ 90 and < 180 days	22 (22.2)	18 (20.7)	7 (20.6)	47 (21.4)
³ 180 days	20 (20.2)	18 (20.7)	9 (26.5)	47 (21.4)
Unknown	30 (30.3)	34 (39.1)	11 (32.4)	75 (34.1)
Brain metastases at baseline - n (%)				
Yes	22 (22.2)	32 (36.8)	4 (11.8)	58 (26.4)
No	77 (77.8)	55 (63.2)	30 (88.2)	162 (73.6)
Liver metastases at baseline - n (%)				
Yes	38 (38.4)	29 (33.3)	12 (35.3)	79 (35.9)
No	61 (61.6)	58 (66.7)	22 (64.7)	141 (64.1)

-> = step dose to target dose (eg, 1 -> 10 mg = 1 mg step dose to 10 mg target dose); ECOG = Eastern Cooperative Oncology Group; PD-1 = programmed cell death 1; PD-L1 = programmed death ligand 1

[a] 0 = Fully active, able to carry on all pre-disease performance without restriction. 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work.

[b] Platinum sensitivity was calculated as end of first-line platinum therapy to date of first progression.

Data snapshot date: 01 March 2024. Data cutoff date: 27 June 2023.

Source: Table 14-2.1.2 of Study 20200491

Reference ID: 5382024

The Applicant's Position:

Overall, the subjects with SCLC enrolled in Study 20200491 had baseline characteristics indicative of subjects with advanced SCLC. Thus, the patient population evaluated in the efficacy studies is considered representative of the overall population of patients with advanced SCLC and supportive of the proposed indication.

The FDA's Assessment:

FDA generally agrees with the Applicant's characterization of the baseline characteristics of patients who were enrolled in Study 20200491. Through information requests, the Applicant clarified that all patients who received 10 mg tarlatamab from Parts 1 and 2 of Study 20200491 had ES-SCLC, 97% of patients had metastatic disease and 73 patients (74%) had received prior anti-PD-(L)1 therapy. Of these 73 patients, 58 (59%) received anti-PD-(L)1 therapy in combination with platinum-based chemotherapy in the first line setting which is representative of frontline standard of care treatment in the US. In addition, 50 patients (51%) received prior topoisomerase-I inhibitors including 20% of patients who received prior topotecan. Of the 49 patients who did not receive a topoisomerase I inhibitor, the majority (89%) received treatments that are considered standard of care options in the US, including platinum-based chemotherapy rechallenge, lurbinectedin, CAV, temozolomide, paclitaxel. Other treatments received include amrubicin, PD-(L)1 in combination with experimental agents and gemcitabine in combination with paclitaxel. A table of all second line therapies received in patients who did not receive a prior topoisomerase-I inhibitor is summarized below.

Table 31 Summary of second line therapies for patients who did not receive a prior topoisomerase-I inhibitor

Therapy	**N (n=47)[a]**
Amrubicin	5
CAV	10
Gemcitabine + Paclitaxel	1
Lurbinectedin	3
Paclitaxel	1
PD-(L)1 +/- experimental drug[b]	4
Platinum +/- PD-(L)1[c]	20
Temozolomide + PARP	3

a. 2 patients did not receive second line treatment (considered important protocol deviations)
b. experimental drugs include anti-ATR, CTLA-4, and LAG-3 medicines
c. 2 patients received anti-PDL1 therapy + platinum after receiving platinum treatment as adjuvant treatment or as

radical treatment

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Treatment Compliance

Study 20200491: When subjects were dosed at the site, they received tarlatamab directly from the investigator or designee, under medical supervision. The date and time of each dose administered were recorded in the source documents and in the electronic case report form (eCRF). Additional details on the method used to assess treatment compliance are provided in Protocol Section 6.5.

Concomitant Medications

Throughout the study, investigators could prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Protocol Section 6.1.6 of Study 20200491.

Study 20200491: Overall, concomitant medication use was reported for 217 subjects (98.6%). The concomitant medications (used in ≥ 10% of subjects) are presented in Table 12-15 of Study 20200491. Of these, the most common (≥ 20% of subjects) were paracetamol (82.3%), dexamethasone (42.3%), sodium chloride (29.1%), magnesium oxide (25.5%), omeprazole (22.7%), lactulose (22.3%), and metoclopramide (20.0%). Concomitant CRS medication use by preferred term is provided in Table 14-8.11 of Study 20200491.

Rescue Medication

Not applicable

The Applicant's Position:

No formal treatment compliance measurements were planned. Analyses for exposure demonstrated that, the median relative dose intensity of tarlatamab was 93% and 90% for the 10 and 100 mg dose groups, respectively, in Study 20200491. Concomitant medication use was consistent with protocol-specified criteria.

The FDA's Assessment:

FDA agrees with the Applicant's description of treatment compliance along with concomitant and rescue medications. In addition, pretreatment with dexamethasone 1 hour prior to administration of tarlatamab on Cycle 1 Day 1 and Day 8 and treatment with 1 liter of normal saline over 4 to 5 hours following all tarlatamab doses in Cycle 1 was required for all patients per protocol.

Reference ID: 5382024

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Study 20200491

A total of 185 and 186 subjects were included in the BICR or Investigator Full Analysis/Safety Analysis Set, respectively. The key efficacy results for tumor response from the phase 2 Study 20200491 (safety analysis set) Part 1 and 2 are provided in Table 32.

Objective response was defined as a best overall response of either complete response or partial response per RECIST 1.1. Of the 186 evaluable subjects in the Safety Analysis Set for Parts 1 and 2 (10 and 100 mg), 7 subjects (3.8%) had a confirmed complete response and 63 subjects (33.9%) had a confirmed partial response. The ORR (95% CI) by BICR was 41.4% (31.6, 51.8) for subjects who received the 10 mg target dose and 33.3% (23.6, 44.3) for subjects who received the 100 mg target dose. Within the 10 mg dose, the lower limit of the 95% CI excluded the prespecified benchmark ORR of 15%. The overall ORR (95% CI) by BICR was 37.6% (30.7, 45.0) (Table 32).

Duration of response was defined as time from first evidence of complete response or partial response to disease progression or death due to any cause, whichever occurred first. For Parts 1 and 2 overall (10 and 100 mg), the median (95% CI) DOR among confirmed responders as assessed by BICR was 8.3 (6.9, not estimable [NE]) months, and the median (95% CI) follow-up time for DOR was 9.5 (8.2, 9.7) months (Table 8 of Module 2.7.3, SCE). The median (range) time to objective response was 1.4 (1.1 to 9.6) months. In the 10 mg group, the median (95% CI) DOR was not reached (5.9, NE months) (range: 2.4-12.4+ months). In the 100 mg group, it was 7.6 (5.6, NE months) (range: 1.4+ to 12.6+). The median (95% CI) follow-up time for DOR was 8.3 (7.2, 9.6) months in the 10 mg group and 9.7 (8.2, 9.9) months in the 100 mg group. The overall median time to objective response was 1.4 months in both dose groups (Table 8 of Module 2.7.3, SCE).

Of the 41 responders in the 10 mg target dose group, 23 subjects (56.1%) and 10 subjects (24.4%) had a DOR of at least 6 and 9 months, respectively. As of 27 June 2023, 22 of 41 responders (53.7%) in the 10 mg target dose group were still having ongoing responses (on treatment without disease progression or death), including 18 subjects (43.9%) whose responses reached at least 6 months and still had ongoing response (Table 14-4.3.2 of Study 20200491).

Of the 33 subjects in the BICR Interim RECIST Analysis Set for Part 3, 4 subjects (12.1%) had a confirmed partial response. As of the data cutoff date, 5 subjects (15.2%) had an unconfirmed partial response awaiting a confirmatory scan. The overall ORR by BICR using a 97.5% CI was 12.1% (2.8%, 30.6%) for confirmed responders and

27.3% (11.9%, 48.0%) for confirmed and unconfirmed responses awaiting a confirmatory scan (Table 14-4.7.2 of Study 20200491).

Reference ID: 5382024

Table 32. Applicant – Summary of Objective Response as Assessed by BICR (Study 20200491 Safety Analysis Set for Part 1 and Part 2)

	1->10 mg (N = 99)	1->100 mg (N = 87)	Part 1 and Part 2 Overall (N = 186)
Best overall response[a] - n (%)			
Confirmed complete response	1 (1.0)	6 (6.9)	7 (3.8)
Confirmed partial response	40 (40.4)	23 (26.4)	63 (33.9)
Stable disease	29 (29.3)	26 (29.9)	55 (29.6)
Progressive disease	19 (19.2)	14 (16.1)	33 (17.7)
Not evaluable	3 (3.0)	4 (4.6)	7 (3.8)
No post-baseline scan	7 (7.1)	14 (16.1)	21 (11.3)
Objective response rate - n (%)	41 (41.4)	29 (33.3)	70 (37.6)
95% CI[b]	(31.6, 51.8)	(23.6, 44.3)	(30.7, 45.0)
Disease control rate - n (%)	70 (70.7)	55 (63.2)	125 (67.2)
95% CI[b]	(60.7, 79.4)	(52.2, 73.3)	(60.0, 73.9)
Any tumor shrinkage - n (%)			
Yes[c]	72 (72.7)	53 (60.9)	125 (67.2)
At least 30% tumor shrinkage[d]	47 (47.5)	36 (41.4)	83 (44.6)
No	19 (19.2)	18 (20.7)	37 (19.9)
Missing	8 (8.1)	16 (18.4)	24 (12.9)

-> = step dose to target dose (eg, 1 -> 10 mg = 1 mg step dose to 10 mg target dose); BICR = blinded independent central review; RECIST = Response Evaluation Criteria in Solid Tumors

The Safety Analysis Set for Part 1 and Part 2 included all subjects who received at least 1 dose of tarlatamab.

Objective response rate was defined as the proportion of subjects with a best overall response of complete response or partial response as defined by RECIST 1.1.

Disease control rate was defined as the proportion of subjects with a best overall response of complete response or partial response or stable disease as defined by RECIST 1.1.

c Included subjects who had any tumor shrinkage in the target lesions at postbaseline assessment.

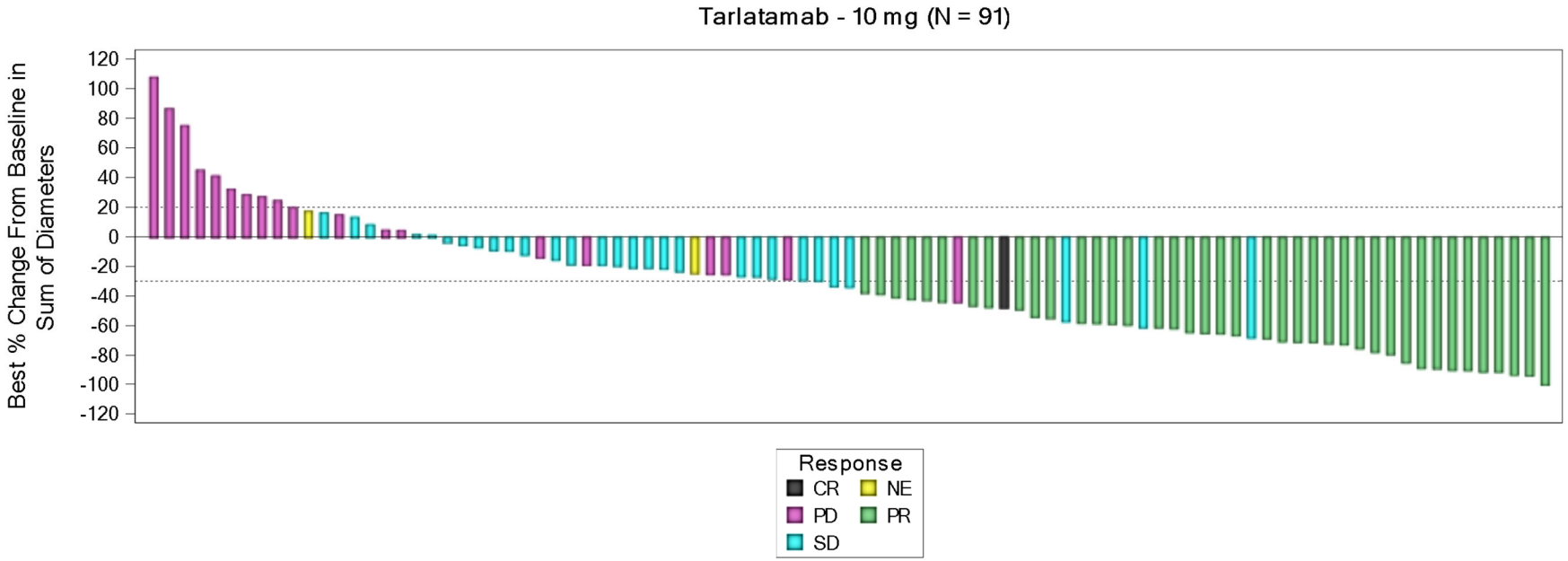
d Included subjects who had at least 30% tumor shrinkage in the target lesions at postbaseline assessment.

Data snapshot date: 01 March 2024. Data cutoff date: 27 June 2023.

Source: Table 14-4.1.402 of Study 20200491

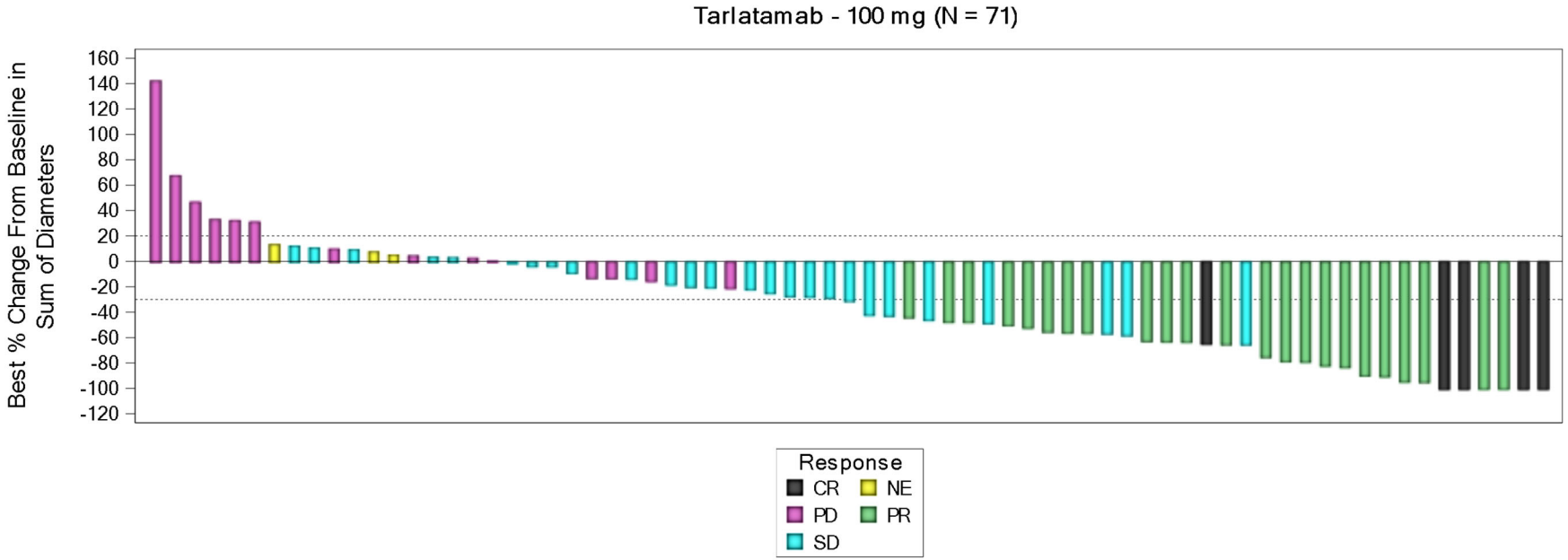
Reference ID: 5382024

Figure 14. Applicant – Waterfall Plot for Best Percentage Change From Baseline by Treatment Group as Assessed by BICR (Study 20200491 BICR Full Analysis Set for Part 1 and Part 2)



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Figure 14. Applicant – Waterfall Plot for Best Percentage Change From Baseline by Treatment Group as Assessed by BICR (Study 20200491 BICR Full Analysis Set for Part 1 and Part 2)



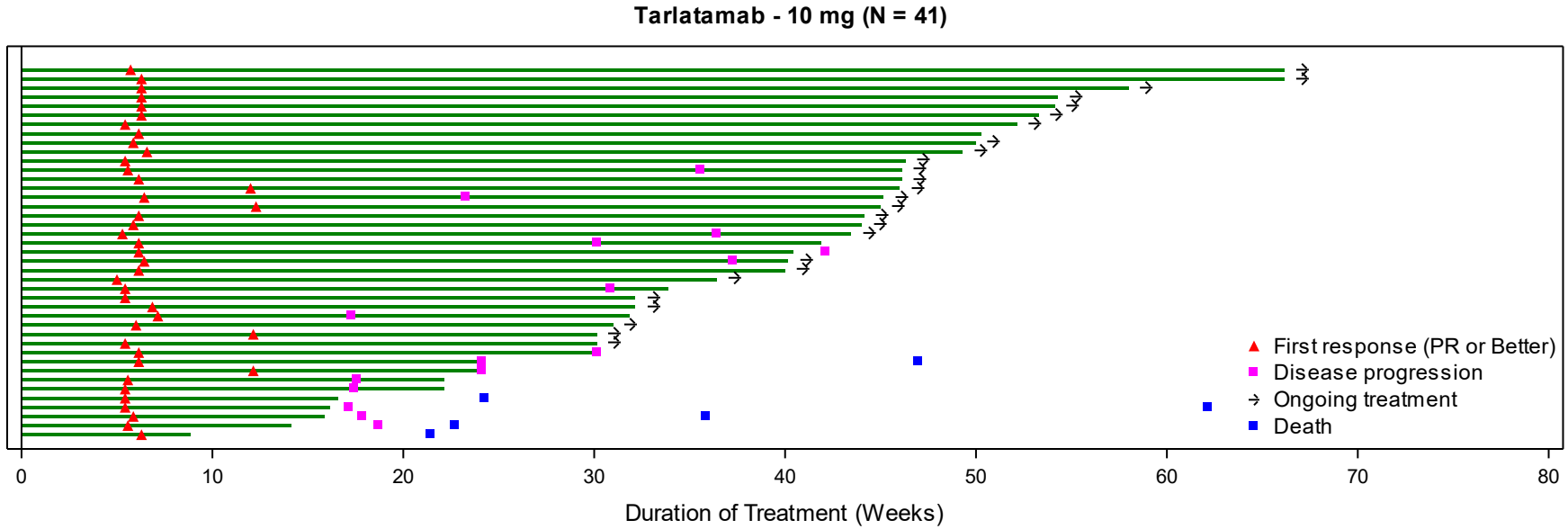
BICR = blinded independent central review; CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease

The BICR Full Analysis Set for Part 1 and Part 2 consisted of all subjects who were randomized (Part 1) or enrolled (Part 2), received at least 1 dose of tarlatamab, and had 1 or more measurable lesions at baseline as assessed by BICR using RECIST 1.1 criteria.

Data snapshot date: 01 March 2024. Data cutoff date: 27 June 2023.

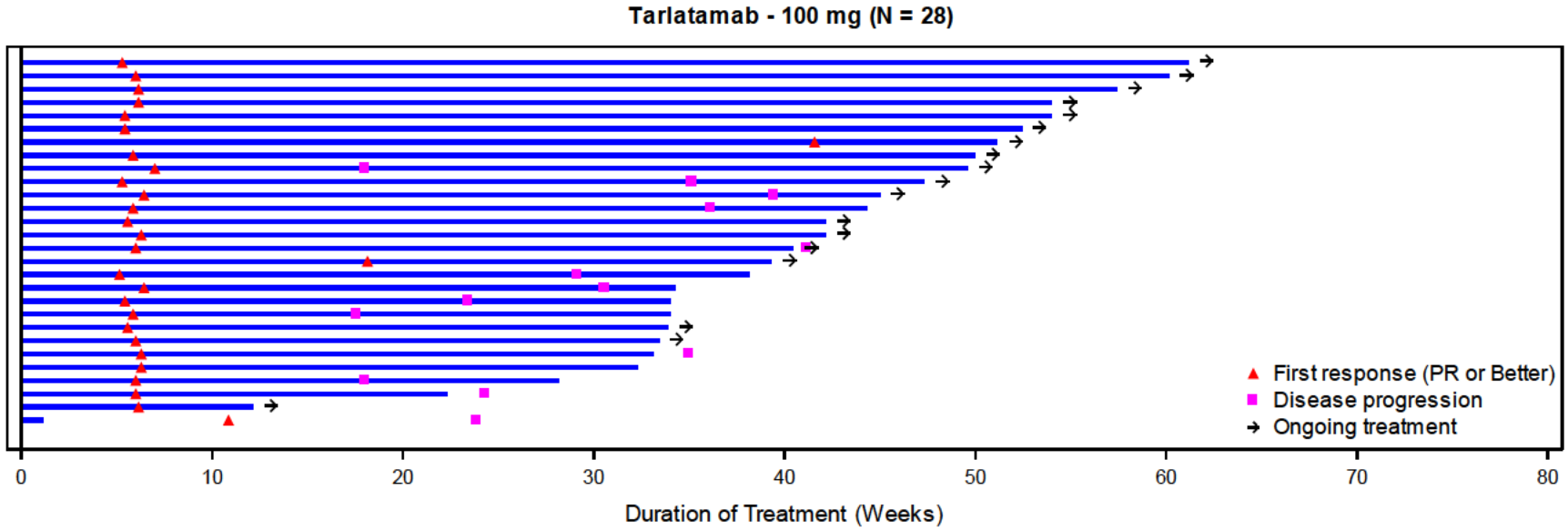
Source: Figure 14-4.1.2 of Study 20200491

Figure 15. Applicant – Swimmer Plot for Time to Response and Duration of Study Treatment Among Confirmed Responders as Assessed by Blinded Independent Central Review (Study 20200491 BICR Full Analysis Set for Part 1 and Part 2)



Footnotes are defined on the next page.

Figure 15. Applicant – Swimmer Plot for Time to Response and Duration of Study Treatment Among Confirmed Responders as Assessed by Blinded Independent Central Review (Study 20200491 BICR Full Analysis Set for Part 1 and Part 2)



BICR = blinded independent central review; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors
The BICR Full Analysis Set for Part 1 and Part 2 consisted of all subjects who were randomized (Part 1) or enrolled (Part 2), received at least 1 dose of tarlatamab, and had 1 or more measurable lesions at baseline as assessed by BICR using RECIST 1.1 criteria.
Assessment of disease response was determined based on RECIST 1.1 guidelines.
Data snapshot date: 01 March 2024. Data cutoff date: 27 June 2023.
Source: Figure 14-4.2.2 of Study 20200491

Efficacy Update as of 02 October 2023

As of the data cutoff date 02 October 2023, of the 186 subjects in the Safety Analysis Set for Parts 1 and 2, 8 subjects (4.3%) had a confirmed complete response and 62 subjects (33.3%) had a confirmed partial response as assessed by BICR (Table 33.). The overall ORR (95% CI) by BICR was 37.6% (30.7%, 45.0%). The ORR (95% CI) was 41.4% (31.6%, 51.8%) for subjects who received the 10 mg target dose and 33.3% (23.6%, 44.3%) for subjects who received the 100 mg target dose (Table 33. and Figure 16). These results are consistent with those from the primary analysis (Table 32).

In Parts 1 and 2 as assessed by investigator, no subject had a confirmed complete response and 70 subjects (37.6%) had a confirmed partial response. The ORR (95% CI) was 41.4% (31.6%, 51.8%) for subjects who received the 10 mg target dose and 33.3% (23.6%, 44.3%) for subjects who received the 100 mg target dose. The overall ORR (95% CI) by investigator assessment was 37.6% (30.7%, 45.0%) (90-day Table 14-4.1.1 of Study 20200491 and 90-day Figure 14-4.1.1 of Study 20200491).

Analyses were conducted for best overall response to evaluate concordance between assessments by BICR (primary endpoint) and the study center investigator (secondary endpoint). The concordance rate between BICR and investigator assessment for responder (complete response or partial response) vs nonresponder was 89.0% (90-day Table 14-4.2 of Study 20200491).

For Parts 1 and 2 overall, the median (95% CI) DOR among confirmed responders as assessed by BICR was 9.7 (6.9, NE) months (8.3 [6.9, NE] months at primary analysis). In the 10 mg target dose group (Parts 1 and 2), the response appears rapid and durable with median (range) time to response (TTR) of 1.4 (1.1 to 2.8) months and a median (95% CI) DOR of 9.7 (5.9, NE) months. Of the 41 responders in the 10 mg target dose group, 27 subjects (65.9%) and 17 subjects (41.5%) had a DOR of at least 6 and 9 months, respectively; 11 subjects (26.8%) had a DOR of at least 12 months, all increased since primary analysis. As of 02 October 2023,
19 of 41 responders (46.3%) in the 10 mg target dose group were still having ongoing responses (on treatment without disease progression or death), including 15 subjects (36.6%) whose responses reached at least 9 months and were still ongoing (an increase from 10 subjects at primary analysis) (90-day Table 14-4.3.2 of Study 20200491).

Table 33. Applicant – Summary of Objective Response as Assessed by BICR (Safety Analysis Set for Part 1 and Part 2) (Study 20200491 90-Day Efficacy Update)

	1->10 mg (N = 99)	1->100 mg (N = 87)	Part 1 and Part 2 Overall (N = 186)
Best overall response[a] - n (%)			
Confirmed complete response	2 (2.0)	6 (6.9)	8 (4.3)
Confirmed partial response	39 (39.4)	23 (26.4)	62 (33.3)
Stable disease	29 (29.3)	26 (29.9)	55 (29.6)
Progressive disease	19 (19.2)	14 (16.1)	33 (17.7)
Not evaluable	3 (3.0)	4 (4.6)	7 (3.8)
No post-baseline scan	7 (7.1)	14 (16.1)	21 (11.3)
Objective response rate - n (%)	41 (41.4)	29 (33.3)	70 (37.6)
95% CI[b]	(31.6, 51.8)	(23.6, 44.3)	(30.7, 45.0)
Disease control rate - n (%)	70 (70.7)	55 (63.2)	125 (67.2)
95% CI[b]	(60.7, 79.4)	(52.2, 73.3)	(60.0, 73.9)
Any tumor shrinkage - n (%)			
Yes[c]	72 (72.7)	53 (60.9)	125 (67.2)
At least 30% tumor shrinkage[d]	47 (47.5)	36 (41.4)	83 (44.6)
No	19 (19.2)	18 (20.7)	37 (19.9)
Missing	8 (8.1)	16 (18.4)	24 (12.9)

-> = step dose to target dose (eg, 1 -> 10 mg = 1 mg step dose to 10 mg target dose); BICR = blinded independent central review; RECIST = Response Evaluation Criteria in Solid Tumors

The safety analysis set for Part 1 and Part 2 includes all subjects who received at least 1 dose of tarlatamab in Part 1 and Part 2 of the study.

Objective response rate was defined as the proportion of subjects with a best overall response of complete response or partial response as defined by RECIST 1.1.

Disease control rate was defined as the proportion of subjects with a best overall response of complete response or partial response or stable disease as defined by RECIST 1.1.

[a] Assessment of disease response was determined based on RECIST 1.1 guidelines.

[b] Exact confidence interval was calculated using the Clopper Pearson method.

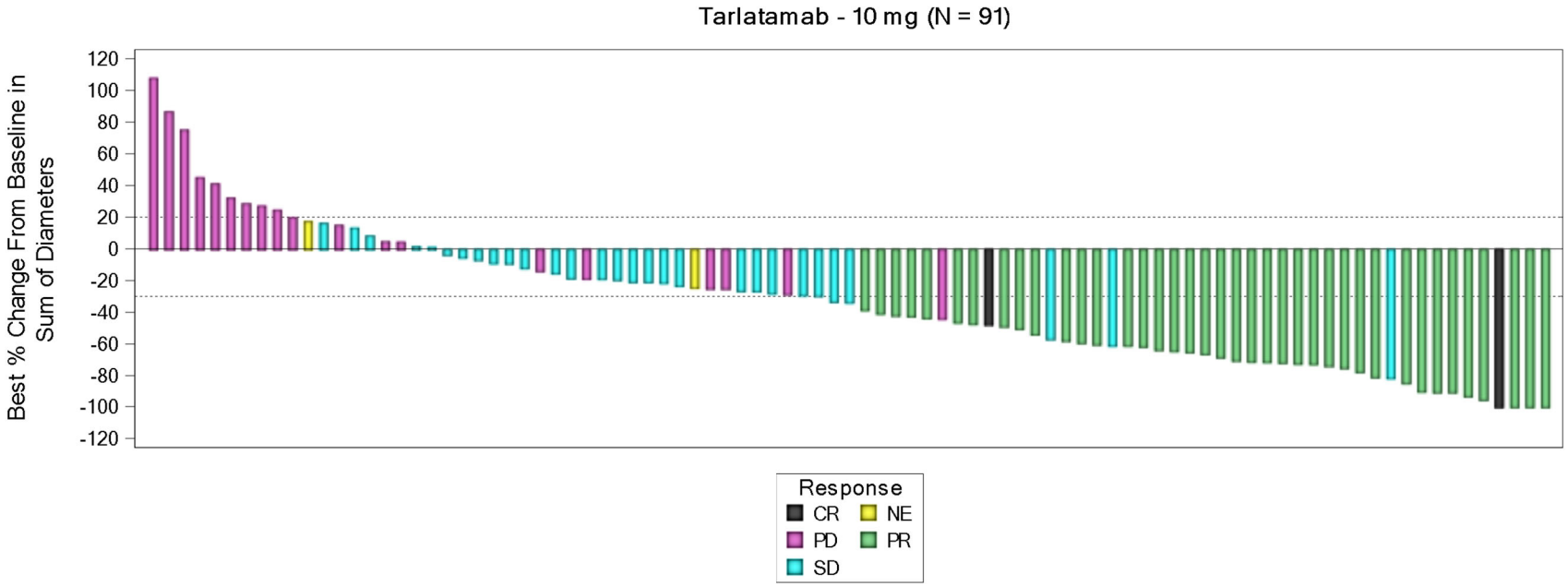
[c] Includes subjects who had any tumor shrinkage in the target lesions at postbaseline assessment.

[d] Includes subjects who had at least 30% tumor shrinkage in the target lesions at postbaseline assessment.

Data snapshot date: 01 March 2024; data cutoff date: 02 October 2023

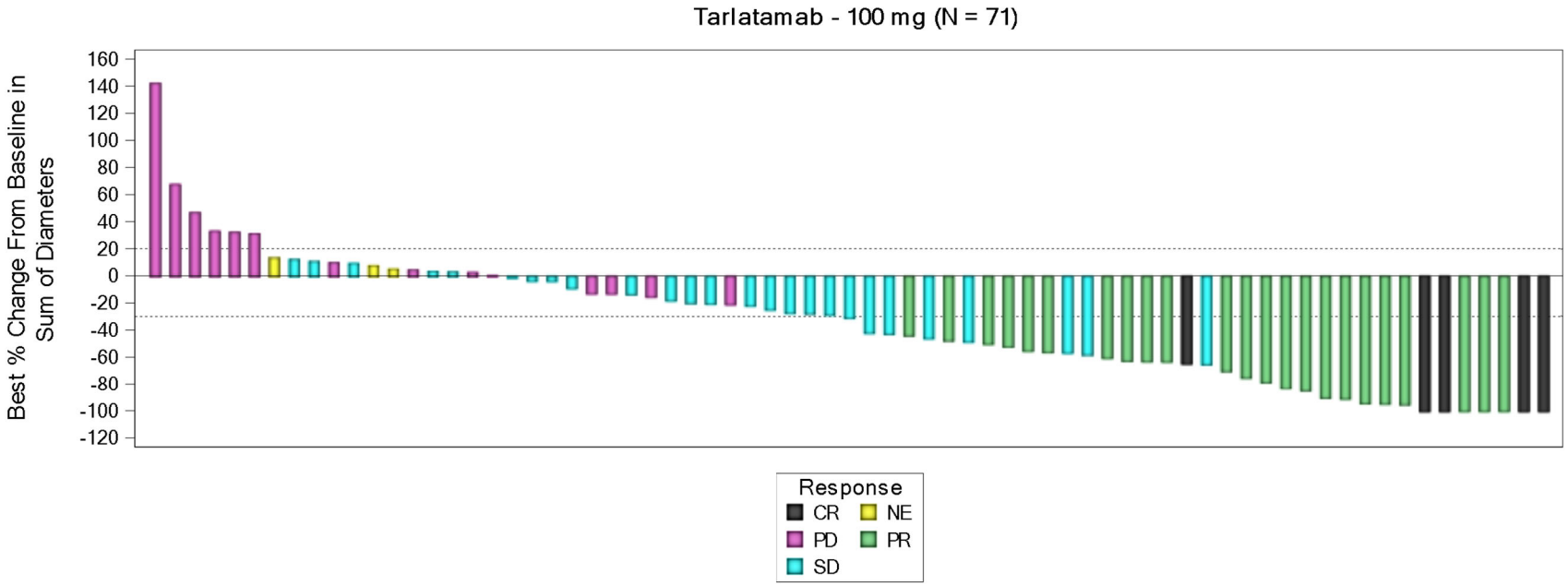
Source: 90-day Table 14-4.1.2 of Study 20200491

Figure 16. Applicant – Waterfall Plot for Best Percentage Change From Baseline by Treatment Groups as Assessed by BICR (Safety Analysis Set for Part 1 and Part 2) (Study 20200491 90-Day Efficacy Update)



Footnotes are defined on the last page of the figure.

Figure 16. Applicant – Waterfall Plot for Best Percentage Change From Baseline by Treatment Groups as Assessed by BICR (Safety Analysis Set for Part 1 and Part 2) (Study 20200491 90-Day Efficacy Update)



BICR = blinded independent central review; CR = complete response; N = number of subjects in treatment group with evaluable postbaseline assessments; NE = not estimable; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease

The safety analysis set for Part 1 and Part 2 includes all subjects who received at least 1 dose of tarlatamab in Part 1 and Part 2 of the study.

Data snapshot date: 01 March 2024; data cutoff date: 02 October 2023

Source: 90-day Figure 14-4.1.2 of Study 20200491

The Applicant's Position:

The observed ORR in the pivotal study, which was rapid and durable, represents a clinically meaningful benefit when considering the intended patient population with life-threatening disease and limited available therapies (Section 2).

The FDA's Assessment:

FDA considers the ORR endpoint by BICR as the primary endpoint, while DoR is a supportive secondary endpoint. Note that analysis of DCR and proportion of tumor shrinkage is generally considered exploratory since the DCR is not a well-established measure of clinical benefit.

FDA disagrees with the Applicant's summary of the efficacy results above since the results were updated from re-adjudication of previous target lesion assessments and none of the 25 previously unsubmitted scans submitted for BICR factored into any update of response (see Section 4.1 for details). In the updated data submitted to FDA on March 15, 2024, by the Applicant, the best overall response of patient (b) (6) was changed from stable disease to partial response, and the ORR by BICR was consequently updated from 40% to 41%. In the FDA's analyses, the number of responders by BICR in the 10 mg target dose group in Parts 1 and 2 remains 40, and the ORR by BICR was 40% (95% CI: 31%, 51%). Among the 40 responders in the 10 mg target dose group in Parts 1 and 2, the median DoR was not reached at the data cutoff date of October 2, 2023 (90-day update). To better characterize the DoR, the data was summarized with additional follow-up time, as requested by FDA. At the latest data cutoff date of January 12, 2024, the median DoR was 9.7 months (95% CI: 6.9, NE and range: 2.7, 20.7+); and 68% and 40% of the responders had an observed DoR ≥6 months and ≥12 months, respectively. The median follow-up time for DoR was 15.1 months (estimated using the reverse Kaplan-Meier Method). See Table 34 for the FDA's summary of the efficacy results.

Table 34. FDA – Summary of ORR and DoR as Assessed by BICR (Safety Analysis Set for Part 1 and Part 2)

	1->10 mg (N = 99)
Best overall response[a] - n (%)	
Confirmed complete response	2 (2)
Confirmed partial response	38 (38)
Confirmed ORR - n (%)	40 (40)
95% CI[b]	(31, 51)
DoR (in responders) – months	**N = 40**
Median[c] (95% CI)	9.7 (6.9, NE)
Range	2.7, 20.7+
Duration ≥ 6 months[d]	68%
Duration ≥ 9 months[d]	50%
Duration ≥ 12 months[d]	40%
Median follow-up time[e]	15.1

a Assessment of disease response was determined based on RECIST 1.1 guidelines.
b Exact 95% confidence interval was calculated using the Clopper Pearson method.
c Base on Kaplan-Meier method.
d Based on observed duration of response.
e Based on reverse Kaplan-Meier method.
NE=Not estimable.
+: censored.
Data cutoff date: January 12, 2024.
Source: FDA reviewer's analyses.

Data Quality and Integrity

Data:

See Section 8.2.3.

The Applicant's Position:

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

The FDA's Assessment:

Overall, outside of the issues identified from the GCP inspections described in Section 4.1 that FDA assessed as being adequately addressed, there were no significant data quality or integrity

issues identified during the review of this BLA.

Efficacy Results – Secondary and other relevant endpoints

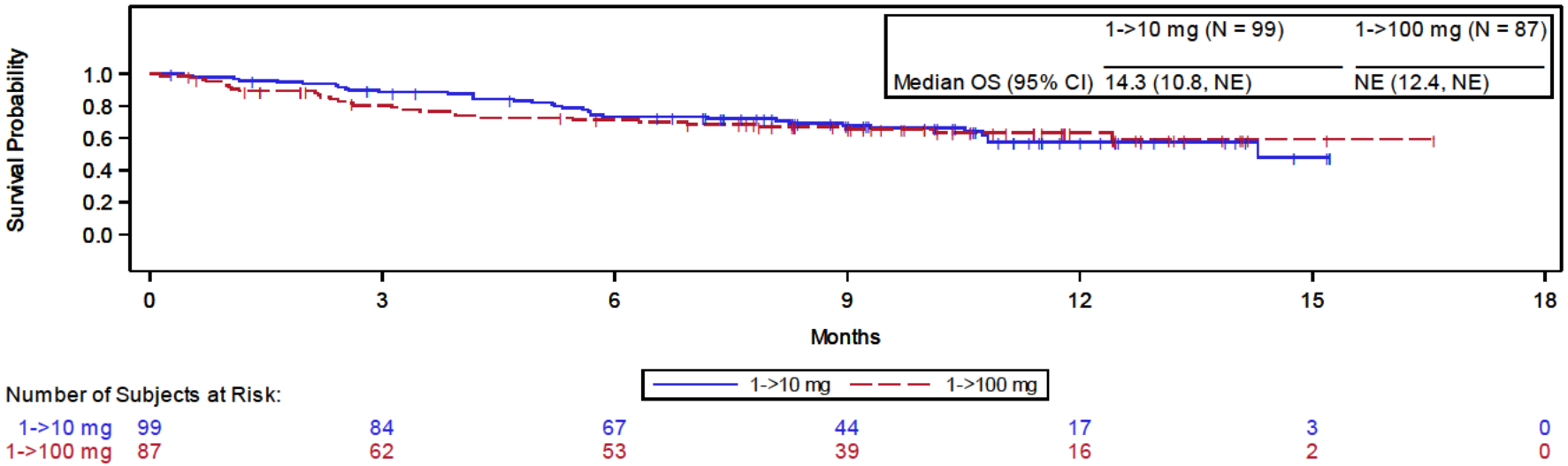
Data:

Study 20200491

The PFS and OS results provide additional evidence of the efficacy of tarlatamab. In Study 20200491 Parts 1 and 2 overall, the median (95% CI) PFS by BICR was 4.0 (2.9, 5.4) months, with a median follow-up time of 9.7 months, and Kaplan-Meier estimates for PFS of 36.1% at 6 months and 23.4% at 12 months (Table 14-4.5.2 of Study 20200491 and Section 2.1.4.4 of Module 2.7.3, SCE). Results for the 10 and 100 mg dose groups (Parts 1 and 2) were comparable: in the 10 mg dose group, the median (95% CI) PFS by BICR was 4.3 (3.0, 5.6) months, with a median follow-up time of 9.7 months, and Kaplan-Meier estimates for PFS of 39.7% at 6 months and 25.7% at 12 months; in the 100 mg dose group, the median (95% CI) PFS by BICR was 3.2 (2.6, 4.2) months, with a median follow-up time of 10.8 months, and Kaplan-Meier estimates for PFS of 31.9% at 6 months and 20.7% at 12 months.

Median (range) follow-up time for OS for Parts 1 and 2 overall was 10.6 (9.7 to 11.3) months, and the median (95% CI) OS was not reached (12.4 to NE months); the Kaplan-Meier estimate for OS at 6 months was 72.5% and 59.8% at 12 months, with similar results for the 10 and 100 mg dose groups (Table 14-4.6.1 of Study 20200491 and Section 2.1.4.5 of Module 2.7.3, SCE). As of the data cutoff date, 101 of the 186 subjects (54.3%) were alive at last follow-up visit, 19 (10.2%) had withdrawn consent, 1 (0.5%) was lost to follow-up, and 65 (34.9%) had died (Table 14-4.6.1 of Study 20200491).

Figure 17. Applicant – Kaplan-Meier Plot for Progression-free Survival as Assessed by BICR (Study 20200491 BICR Full Analysis Set for Part 1 and Part 2)



-> = step dose to target dose (eg, 1 -> 10 mg = 1 mg step dose to 10 mg target dose); BICR = blinded independent central review; KM = Kaplan-Meier; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors

The BICR Full Analysis Set for Part 1 and Part 2 consisted of all subjects who were randomized (Part 1) or enrolled (Part 2), received at least 1 dose of tarlatamab, and had 1 or more measurable lesions at baseline as assessed by BICR using RECIST 1.1 criteria.

Progression-free survival per RECIST 1.1 was defined as the interval from the date of first dose of tarlatamab to the earlier of progressive disease per RECIST 1.1 or death due to any cause.

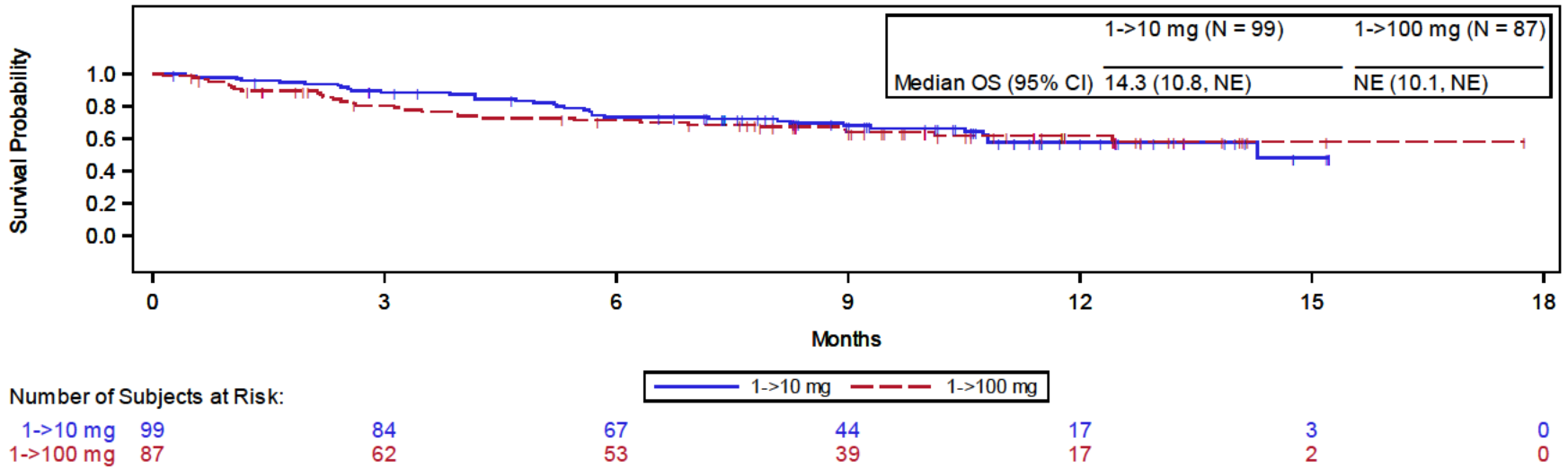
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The survival curves and median PFS were estimated using KM method and their 95% CI were estimated using log-log transformation of KM survival estimate by Brookmeyer and Crowley (1982) method.

Data snapshot date: 01 March 2024. Data cutoff date: 27 June 2023.

Source: Figure 14-4.4.6 of Study 20200491

Figure 18. Applicant – Kaplan-Meier Plot for Overall Survival (Safety Analysis Set for Part 1 and Part 2) (Study 20200491 Primary Analysis)



Number of Subjects at Risk:

1->10 mg	99	84	67	44	17	3	0
1->100 mg	87	62	53	39	17	2	0

-> = step dose to target dose (eg, 1 -> 10 mg = 1 mg step dose to 10 mg target dose); KM = Kaplan-Meier; NE = not estimable; OS = overall survival; RECIST = Response Evaluation Criteria in Solid Tumors

The safety analysis set included all subjects who received at least 1 dose of tarlatamab.

Overall survival was defined as the interval from the date of first dose of tarlatamab to the event of death due to any cause. Subjects still alive was censored at the date last known to be alive. If the date last known to be alive was after the date that triggered the analysis (ie, the data cutoff date), the subject was censored at the analysis trigger date.

Censor indicated by vertical bar |.

The survival curves and median OS were estimated using KM method and their 95% CI were estimated using log-log transformation of KM survival estimate by Brookmeyer and Crowley (1982) method.

Data snapshot date: 01 March 2024. Data cutoff date: 27 June 2023.

Source: Figure 14-4.4.7 of Study 20200491

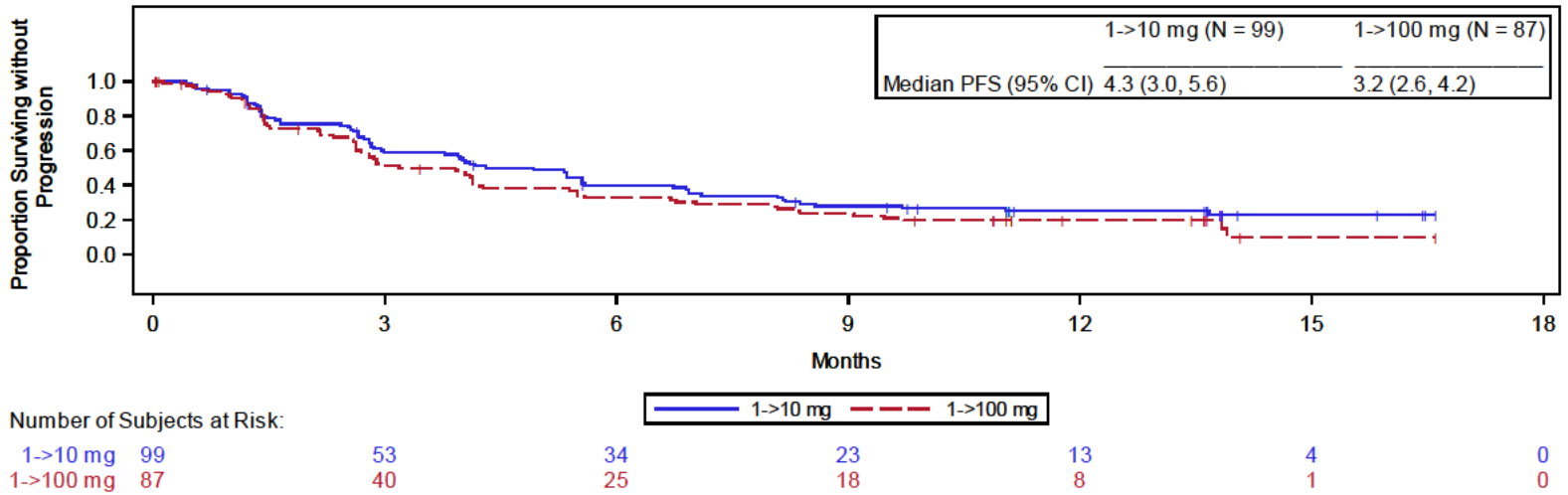
Efficacy Update as of 02 October 2023

In Study 20200491 Parts 1 and 2 overall, the Kaplan-Meier estimate of median (95% CI) PFS by BICR was 4.0 (2.9, 5.4) months (90-day Table 14-4.5.2 of Study 20200491). In the 10 mg dose group (Parts 1 and 2), median (95% CI) PFS based on BICR was 4.3 (3.0, 5.6) months, with a median follow-up time of 13.6 months (90-day Table 14-4.5.2 of Study 20200491 and Figure 19). The Kaplan-Meier estimates for PFS at 6 and 12 months were 39.7% and 25.2%, respectively. In the 100 mg target dose group, median (95% CI) PFS based on BICR was 3.2 (2.6, 4.6) months, with a median follow-up time of 11.8 months (90-day Table 14-4.5.2 of Study 20200491 and Figure 19). The Kaplan-Meier estimates for PFS at 6 and 12 months were 32.8% and 19.7%, respectively. Except for a longer median follow-up time, these results are similar to those from the primary analysis (Table 14-4.6.1 of Study 20200491).

For Parts 1 and 2 overall, median (range) follow-up time for OS was 13.6 (12.9, 14.3) months, and the median (95% CI) OS was 15.2 (12.3, NE) months (previously not reached at primary analysis). In the 10 mg dose group (Parts 1 and 2), median (95% CI) OS was 15.2 (10.8, NE) months, with a median follow-up time of 13.8 months (90-day Table 14-4.6.1 of Study 20200491 and Figure 20). In comparison, at the primary analysis, the median OS was lower (14.3 months) and the median follow-up time shorter (10.6 months). The Kaplan-Meier estimates for OS at 6 and 12 months were 73.4% and 56.7%, respectively. In the 100 mg dose group, median (95% CI) OS was 15.1 (10.1, NE) months (previously not reached), with a median follow-up time of 13.3 months (previously 10.6 months) (90-day Table 14-4.6.1 of Study 20200491 and Figure 20). The Kaplan-Meier estimates for OS at 6 and 12 months were 71.4% and 61.8%, respectively.

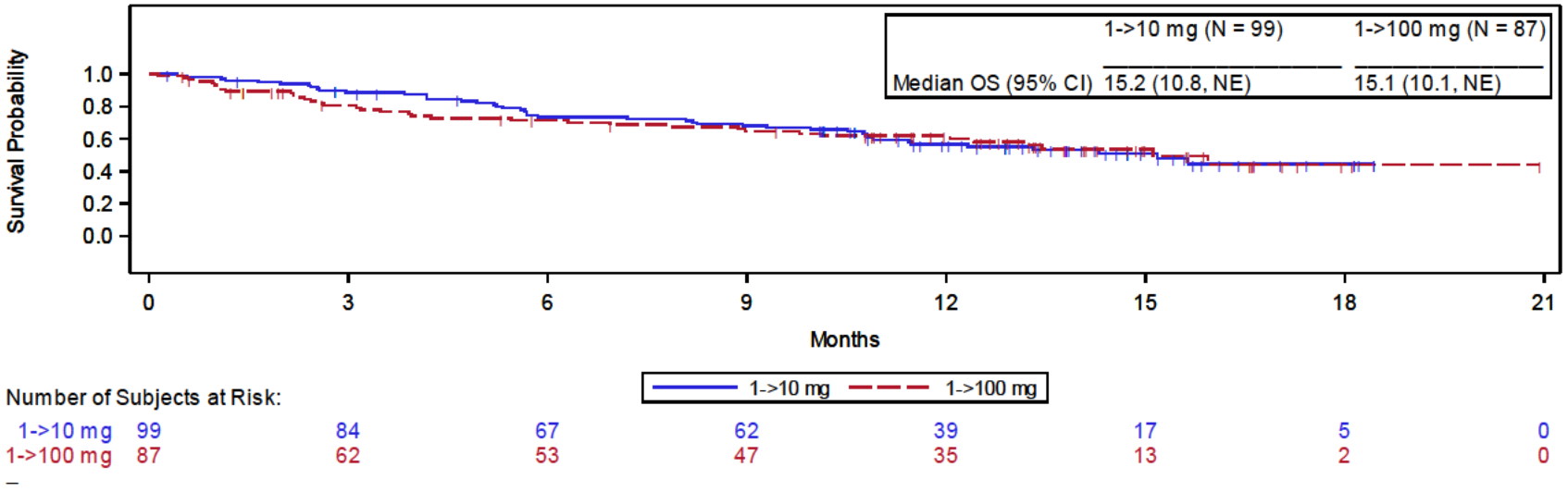
As of data cutoff date 02 October 2023, 48 subjects (48.5%) and 38 subjects (43.7%) in the 10 and 100 mg groups, respectively, were alive at last follow-up (90-day Table 14-4.6.1 of Study 20200491). This number is decreased from the number of subjects alive at the primary analysis (57 and 44 in the 10 and 100 mg groups, respectively). Except for a longer median follow-up time and fewer subjects alive at last follow-up, these results are similar to those from the primary analysis.

Figure 19. Applicant – Kaplan-Meier Plot for Progression-free Survival as Assessed by BICR (Safety Analysis Set for Part 1 and Part 2) (Study 20200491 90-Day Efficacy Update)



-> = step dose to target dose (eg, 1 -> 10 mg = 1 mg step dose to 10 mg target dose)
BICR = blinded independent central review; KM = Kaplan-Meier; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors
The safety analysis set for Part 1 and Part 2 includes all subjects who received at least 1 dose of tarlatamab in Part 1 and Part 2 of the study.
Progression-free survival per RECIST 1.1 was defined as the interval from the date of first dose of tarlatamab to the earlier of progressive disease per RECIST 1.1 or death due to any cause.
Censor indicated by vertical bar |.
The survival curves and median PFS were estimated using KM method and their 95% CI were estimated using log-log transformation of KM survival estimate by Brookmeyer and Crowley (1982) method.
Data snapshot date: 01 March 2024; data cutoff date: 02 October 2023
Source: 90-day Figure 14-4.4.6 of Study 20200491

Figure 20. Applicant –Kaplan-Meier Plot for Overall Survival (Safety Analysis Set for Part 1 and Part 2) (Study 20200491 90-Day Efficacy Update)



-> = step dose to target dose (eg, 1 -> 10 mg = 1 mg step dose to 10 mg target dose)
KM = Kaplan-Meier; NE = not estimable; OS = overall survival; RECIST = Response Evaluation Criteria in Solid Tumors
The safety analysis set included all subjects who received at least 1 dose of tarlatamab.
Overall survival was defined as the interval from the date of first dose of tarlatamab to the event of death due to any cause. Subjects who were still alive were censored at the date last known to be alive. If the date last known to be alive was after the date that triggered the analysis (ie, the data cutoff date), the subject was censored at the analysis trigger date.
Censor indicated by vertical bar |.
The survival curves and median OS were estimated using KM method and their 95% CI were estimated using log-log transformation of KM survival estimate by Brookmeyer and Crowley (1982) method.
Data snapshot date: 01 March 2024; data cutoff date: 02 October 2023
Source: 90-day Figure 14-4.4.7 of Study 20200491

The Applicant's Position:

The PFS and OS results in the pivotal study provides additional evidence of the efficacy of tarlatamab. No notable differences were observed among various subgroups for ORR, DOR, DoDc, PFS, or OS. However, subgroup analysis interpretation may be limited because of the small sample size of each subgroup.

The FDA's Assessment:

DoR was also a secondary endpoint for the study; FDA's assessment of the DoR endpoint is summarized above along with assessment of data from the ORR endpoint. FDA reviewed the summary of the PFS and OS data above. However, FDA disagrees with the Applicant's position regarding the interpretation of PFS and OS results as evidence for treatment effect. These endpoints are difficult to interpret in the absence of an appropriate control arm.

The interpretation of the comparison of the PFS and OS results between the 10 mg dose group and 100 mg dose group in the BICR Full Analysis Set and Safety Analysis Set are also limited, as the two groups of patients were not fully randomized (the 10 mg group included patients in Part 2 who enrolled after dose selection and thus were not randomized).

Dose/Dose Response

See Section 6.3.2, Clinical Pharmacology Questions

The Applicant's Position:

The proposed dose of 10 mg Q2W is effective and generally well tolerated in subjects with advanced SCLC. The proposed dosing regimen is supported by the observed efficacy and safety data and demonstrates a favorable benefit-risk profile. Overall, results of exposure-response analysis for efficacy measures suggest the proposed dosing regimen of 10 mg Q2W exhibited near maximal efficacy in the intended patient population, and exposures associated with lower doses are estimated to have lower efficacy. None of the covariates evaluated in the exposure-response analysis resulted in clinically meaningful changes in efficacy and therefore do not warrant a dose adjustment.

The FDA's Assessment:

FDA generally agrees with the Applicant's position that E-R analyses, in addition to the clinical findings from Studies 20200491 and 20160323, support the proposed 1/10 mg dosing regimen. Please see Section 6.2.2.1 for FDA's full assessment on the proposed tarlatamab dose.

Durability of Response

Data:

See Efficacy Results – Primary Endpoint (Including Sensitivity Analyses) for data.

The Applicant's Position:

Tarlatamab monotherapy demonstrated a clinically meaningful and durable objective response among subjects with advanced SCLC in pivotal Study 20200491. Using the safety analysis set, the ORR (95% CI) by BICR was 41.4% (31.6, 51.8) for subjects who received the 10 mg target dose and 33.3% (23.6, 44.3) for subjects who received the 100 mg target dose. The overall ORR (95% CI) by BICR was 37.6% (30.7, 45.0). Results for the efficacy update as of 02 October 2023 were comparable to those at primary analysis.

The FDA's Assessment:

DoR was a secondary endpoint for the study; FDA's assessment of the DoR endpoint is summarized above along with assessment of data from the ORR endpoint.

Persistence of Effect

Data:

No long-term efficacy data with the exception of those presented in the preceding sections are available at the time of this application.

The Applicant's Position:

Not applicable

The FDA's Assessment:

FDA agrees with the Applicant's position.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:

An exploratory objective of the phase 2 Study 20200491 was to investigate the subject experience with tarlatamab treatment using patient-reported outcome instruments. Although exploratory, a trend toward improvement or stabilization was observed in the severity of key lung cancer symptoms of cough, dyspnea, and chest pain across both doses (10 and 100 mg in Part 1 and Part 2) when compared with baseline (Section 10.4 and Section 16.1.13.8 of Study 20200491). A consistent trend toward improvement was also observed for global health status. Most subjects reported no or little degree of bother due to treatment-related side effects associated with tarlatamab.

The Applicant's Position:

Although exploratory, subjects overall showed a trend toward improvement or stabilization was observed in the severity of key lung cancer symptoms of cough, dyspnea, and chest pain when compared with baseline.

The FDA's Assessment:

FDA reviewed the summary of the PRO data above. However, treatment effect on these endpoints is difficult to interpret in the absence of an appropriate control arm.

Additional Analyses Conducted on the Individual Trial

Data:
Not applicable

The Applicant's Position:

Not applicable

The FDA's Assessment:

FDA agrees with the Applicant's position.

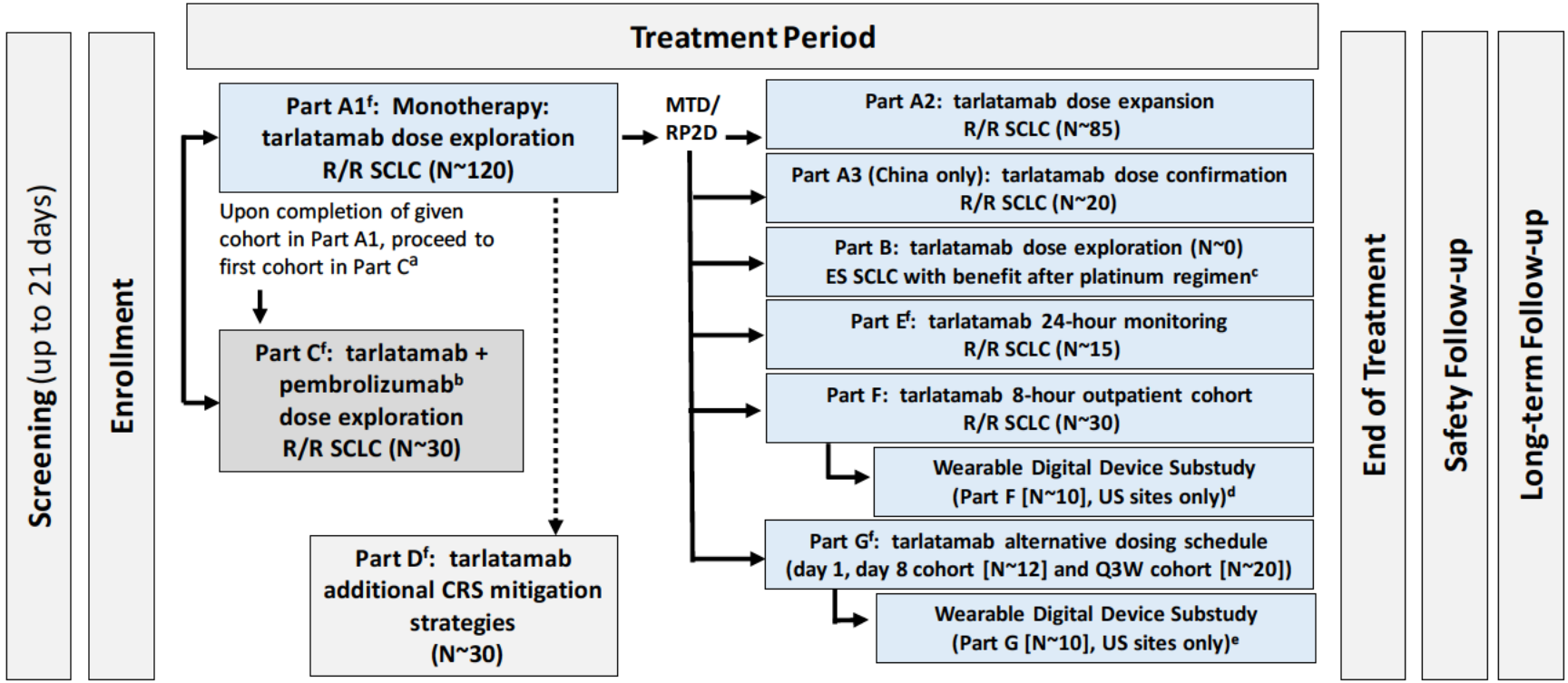
8.1.3. Supportive Study 20160323

Trial Design

The Applicant's Description:

Study 20160323 is an ongoing, phase 1, FIH, open-label, ascending, multiple-dose study evaluating tarlatamab as monotherapy and in combination with anti-PD-1 therapy (Figure 21). Tarlatamab is administered as an IV infusion Q2W or Q3W (in Part G) (with or without step dosing) in subjects with advanced SCLC that progressed or recurred after at least 1 platinum-based regimen. The study consists of multiple parts designed to evaluate the safety and tolerability of tarlatamab alone (Parts A, D, E, and G) or in combination with pembrolizumab (Part C) and to determine the maximum tolerated dose or recommended phase 2 dose of tarlatamab alone (Part A1) or in combination with pembrolizumab (Part C). Secondary objectives were to characterize the PK and evaluate preliminary antitumor activity of tarlatamab alone or in combination with pembrolizumab (Figure 21). See Section 8.1 of Study 20160323 for full details of the study design.

Figure 21. Applicant – Schema of Study 20160323



CRS = Cytokine Release Syndrome; ES = extensive stage; IV = intravenous; MTD = maximum tolerated dose; Q2W = every 2 weeks; RP2D = recommended phase 2 dose; R/R = relapsed/refractory; SCLC = small cell lung cancer; US = United States

Tarlatamab was administered as a short-term IV dose Q2W beginning in cycle 2. In cycle 1, step dosing may be implemented.

[a] Depending on the observed safety data, a second cohort will be enrolled to test an increased dose.

[b] Tarlatamab and pembrolizumab was administered using a staggered dosing schedule, with tarlatamab administered Q2W starting on day 1, and pembrolizumab administered Q3W starting on day 15.

[c] Part B will not be opened.

[d] Among the 30 subjects in Part F, 10 subjects from US sites only may be enrolled in the wearable digital device substudy.

[e] Among the 32 subjects in Part G, 10 subjects from US sites only may be enrolled in the wearable digital device substudy.

[f] Enrollment has been completed.

The FDA's Assessment:

FDA agrees with the Applicant's description of the study design.

Eligibility Criteria

The Applicant's Description:

Study 20160323

Eligible subjects were ³18 years of age with relapsed or refractory SCLC who progressed or recurred following at least 1 platinum-based regimen. Subjects must have had measurable disease per modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, an ECOG performance status of 0 to 2, and adequate organ function. Eligibility criteria included adequate cardiac, pulmonary, kidney, and liver function. Subjects with acute and/or uncontrolled active systemic infection, active hepatitis B or C, or human immunodeficiency virus infection or COVID-19 infection were excluded.

The FDA's Assessment:

FDA agrees with the Applicant's description of the eligibility criteria.

Study Endpoints

The Applicant's Description:

Study 20160323: The primary objectives of the study were to evaluate the safety and tolerability of tarlatamab and to determine the maximum tolerated dose or recommended phase 2 dose of tarlatamab. Secondary objectives included characterizing the PK of tarlatamab and evaluating preliminary antitumor activity of tarlatamab.

The FDA's Assessment:

FDA agrees with the Applicant's description of the study endpoints.

Statistical Analysis Plan and Amendments

The Applicant's Description:

Study 20160323: There were 3 amendments to the original SAP before the data cutoff date of 28 March 2023 for this study as summarized in Table 8-8 of Study 20160323. Full statistical methods for this supportive study are provided in Section 8.8 of Study 20160323.

The FDA's Assessment:

FDA agrees with the Applicant's above descriptions of the statistical analysis plan and amendments.

8.1.4. Study Results – Study 20160323

Compliance with Good Clinical Practices

Data:

Audits of Study 20160323 were included as part of the independent Amgen Quality, Compliance, and Audit program performed by Amgen. The audit certificates are provided in Section 16.1.8 of Study 20160323 clinical study reports.

Amgen has been closely monitoring the evolving COVID-19 situation across the globe and has, therefore, taken proactive steps to maintain the safety of study participants and support staff, including Amgen representatives, at all clinical study centers, and to maintain study data integrity while maintaining compliance with GCP. Guidelines on study conduct during the COVID-19 period were documented in the respective study protocols.

The Applicant's Position:

Study 20160323 was conducted in accordance with the CFR governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) in accordance with GCP. Study 20160323 was conducted under Investigational New Drug 134859.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Financial Disclosure

Data:

See Appendix 19.2.

The Applicant's Position:

Study 20160323 was an Amgen-sponsored clinical study. Financial interests or arrangements with clinical investigators have been disclosed (see Appendix 19.2).

The FDA's Assessment:

FDA agrees with the Applicant's position. See Appendix 19.2 for full review.

Patient Disposition

Study 20160323: Overall, as of the data cutoff date of 28 March 2023, 208 subjects were enrolled in Study 20160323, and 205 subjects received at least 1 dose of tarlatamab, including 27 subjects in the 10 mg Q2W dose group, 63 subjects in the 100 mg Q2W dose group, and 13 subjects in the 100 mg Q2W dose group with modified safety monitoring. As of the data

cutoff date, 180 subjects (86.5%) discontinued tarlatamab. The most frequent reason for discontinuation was disease progression (68.8%) (Table 14-1.1 of Study 20160323).

The Applicant's Position:

As of the data cutoff dates for the Biologics License Application (BLA), 205 subjects were enrolled and received tarlatamab in Study 20160323 (27 at the 10 mg dose).

The FDA's Assessment:

FDA agrees with the Applicant's description of patient disposition. The focus of FDA's review for this study will be based upon the patients who received tarlatamab at the proposed indicated dose (10 mg dose).

Protocol Violations/Deviations

Data:

Study 20160323: As of the data cutoff date 28 March 2023, a total of 158 subjects (77.1%) had at least 1 IPD. Important protocol deviations were consistent across groups, with the exception of subjects in the 10 mg monotherapy dose group who had a more than 10% higher rate of IPDs (88.9%) than the overall population and subjects in the 100 mg dose with 24-hour monitoring group who had a more than 10% lower rate of IPDs (53.8%) than the overall population (Section 9.2 of Study 20160323). Overall, the most frequently reported (> 10% of subjects) IPDs were missing data (65.9%) and received the wrong treatment or incorrect dose (10.2%).

The Applicant's Position:

The above mentioned IPDs did not affect the overall results of the study.

The FDA's Assessment:

FDA agrees with the Applicant's position. From the 27 patients who received the tarlatamab 10 mg dose, 24 patients (89%) reported at least one IPD. The most frequently reported (>10% of patients) IPDs were missing data 70.4% and receiving the wrong treatment or incorrect dose (11.4%) in the 10 mg dose group.

Table of Demographic Characteristics

Data:

Study 20160323: In the overall population (N= 205), more than half of subjects (56.1%) were men, mostly White (78.0%), and not Hispanic or Latino (77.6%). The median (range) age was 63 (32 to 80) years, with more than half of all subjects younger than 65 years (60.5%) (Table 35).

Table 35. Applicant – Baseline Demographics (Safety Analysis Set– Study 20160323)

	≤ 3 mg (N = 35)	1->10 mg (N = 27)	1->30 mg (N = 8)	1->100 mg (N = 63)	1->100 mg 24-Hr Outpatient (N = 13)	eIV Cohorts (N = 32)	Alternative Dosing Cohorts (N = 19)	Combination Cohorts (N = 8)	Overall (N = 205)
Sex - n (%)									
Male	21 (60.0)	10 (37.0)	7 (87.5)	38 (60.3)	7 (53.8)	17 (53.1)	10 (52.6)	5 (62.5)	115 (56.1)
Female	14 (40.0)	17 (63.0)	1 (12.5)	25 (39.7)	6 (46.2)	15 (46.9)	9 (47.4)	3 (37.5)	90 (43.9)
Race - n (%)									
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	2 (5.7)	3 (11.1)	1 (12.5)	11 (17.5)	1 (7.7)	0 (0.0)	4 (21.1)	0 (0.0)	22 (10.7)
Black or African American	1 (2.9)	1 (3.7)	0 (0.0)	1 (1.6)	3 (23.1)	0 (0.0)	1 (5.3)	0 (0.0)	7 (3.4)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
White	31 (88.6)	21 (77.8)	6 (75.0)	45 (71.4)	9 (69.2)	28 (87.5)	12 (63.2)	8 (100.0)	160 (78.0)
Ethnicity - n (%)									
Hispanic/Latino	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Not Hispanic/Latino	31 (88.6)	21 (77.8)	6 (75.0)	44 (69.8)	9 (69.2)	28 (87.5)	12 (63.2)	8 (100.0)	159 (77.6)
Multiple	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (2.9)	2 (7.4)	1 (12.5)	6 (9.5)	0 (0.0)	4 (12.5)	2 (10.5)	0 (0.0)	16 (7.8)
Age (years)									
N	35	27	8	63	13	32	19	8	205
Mean	61.9	64.4	61.4	61.0	58.8	61.5	62.8	64.1	61.8
SD	8.9	9.6	12.7	7.9	8.7	8.4	8.0	8.8	8.6
Median	63.0	67.0	64.0	62.0	60.0	63.0	64.0	63.0	63.0
Q1, Q3	55.0, 70.0	57.0, 71.0	61.5, 68.0	56.0, 67.0	52.0, 62.0	58.0, 68.0	57.0, 68.0	58.0, 70.0	57.0, 69.0
Min, Max	44, 74	43, 80	32, 72	42, 76	41, 74	43, 74	45, 78	52, 79	32, 80
Age group - n (%)									
< 65 years	20 (57.1)	11 (40.7)	6 (75.0)	41 (65.1)	10 (76.9)	21 (65.6)	11 (57.9)	4 (50.0)	124 (60.5)
³ 65 years	15 (42.9)	16 (59.3)	2 (25.0)	22 (34.9)	3 (23.1)	11 (34.4)	8 (42.1)	4 (50.0)	81 (39.5)

Footnotes provided at the end of this table.

Reference ID: 5382024

-> = step dose to target dose (eg, 1 -> 10 mg: 1 mg step dose to 10 mg target dose); eIV = extended intravenous infusion; N = Number of subjects in analysis set; n = Number of subjects with observed data; Q1 = first quartile. Q3 = third quartile; Q3W = once every 3 weeks

The safety analysis set consisted of all subjects who enrolled and received at least 1 dose of tarlatamab for monotherapy cohorts, and received at least 1 dose of tarlatamab or pembrolizumab for combination cohorts.

£ 3 mg includes cohorts 1-7; 1->10 mg includes cohorts 8 and 32; 1->30 mg includes cohort 9; 1->100 mg includes cohort 10, 30 and 11 only: tarlatamab + dexamethasone; 1->100mg 24 Hr Outpatient includes cohort 34; eIV Cohorts include cohort 26: 30 mg eIV ->100 mg and cohorts 27 and 31: 100 mg eIV->100mg; Alternative Dosing Cohorts include 2-step cohort 23: 1->25->100 mg, 2-step cohort 37: 1->100->200 mg Q3W, and cohort 38: 1->100 mg D1/D8; Combination Cohorts includes cohort 15: tarlatamab 0.1 mg + pembrolizumab and cohort 16: tarlatamab 0.3 mg + pembrolizumab.

Snapshot date: 22 May 2023; Data cutoff date: 28 March 2023

Source: Table 14-2.1 of Study 20160323

The Applicant's Position:

Overall, the subjects with SCLC enrolled across the study had baseline characteristics indicative of subjects with advanced SCLC. Thus, the patient population evaluated in the efficacy studies is considered representative of the overall population of patients with advanced SCLC and supportive of the proposed indication.

Data from racial and ethnic minorities such as American Indian or Alaska Native, Black or African American, and Native Hawaiian or Other Pacific Islander are limited.

The FDA's Assessment:

FDA reviewed the results presented above for the demographics but did not verify the results since this study was supportive and the results were not included in labeling. In general, FDA agrees with the Applicant's position but notes the small number of patients enrolled who received tarlatamab at the proposed indicated dose.

Reference ID: 5382024

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

Data:

Study 20160323

Overall, subjects had a median (range) of 2.0 (1 to 7) prior lines of therapy, including prior PD-1 or PD-L1 inhibitor therapy (61.0%). Most subjects had received prior radiotherapy for current malignancy (77.1%). Most subjects had metastatic disease (92.2%) and an ECOG performance score of 1 (61.5%). Prior to tarlatamab treatment, subjects' response to their most recent platinum-based anticancer treatment was as follows:

- 47.3% of subjects were sensitive to the most recent platinum-based therapy, defined as best response of stable disease or better and an interval of ³ 90 days between the date of the last dose of platinum in the most recent platinum-containing prior line and the start date.
- 28.3% of subjects were refractory, defined as a best response of progressive disease to most recent line of platinum-based chemotherapy.
- 20.0% of subjects were resistant, defined as a best response of stable disease or better and a treatment-free interval of < 90 days between the date of most recent line of platinum-based chemotherapy and the start date of the next line of treatment.

Baseline characteristics for Study 20160323 are provided in Table 13 of Module 2.7.3, SCE.

The Applicant's Position:

Overall, the subjects with SCLC enrolled across phase 1 and 2 studies had baseline characteristics indicative of subjects with advanced SCLC. Thus, the patient population evaluated in the efficacy studies is considered representative of the overall population of patients with advanced SCLC and supportive of the proposed indication.

The FDA's Assessment:

FDA reviewed the results presented above for the other baseline characteristics but did not verify the results since this study was supportive and the results were not included in labeling.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Treatment Compliance

Reference ID: 5382024

Study 20160323: Investigational products were administered at the study center by a qualified staff member. A physician must have been available at the time of administration of investigational products (Protocol Section 6.2). The date, time, package lot number, dose, and the start and stop time of infusion were recorded (Protocol Section 6.2.5).

Concomitant Medications

Throughout the study, investigators could prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Protocol Section 6.9 of Study 20160323.

Overall, concomitant medication use was reported for 204 of 205 subjects (99.5%). The concomitant medication categories with the highest incidence rates (> 10% of subjects) are presented in Table 12-14 of Study 20160323. Overall, the most frequently reported concomitant medications (≥ 25% of subjects) were paracetamol (85.9%), dexamethasone (82.4%), sodium chloride (56.6%), ondansetron (32.2%), and omeprazole (28.3%).

Rescue Medication

Not applicable

The Applicant's Position:

No formal treatment compliance measurements were planned. Analyses for exposure demonstrated that regardless of dose, the median relative dose intensity of tarlatamab was 100% in Study 20160323. Concomitant medication use was consistent with protocol-specified criteria.

The FDA's Assessment:

FDA agrees with the Applicant's description of compliance, concomitant and rescue medication.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Study 20160323

At the 10 mg monotherapy target dose (N = 24 evaluable subjects in the Interim Efficacy Analysis Set), 8 subjects had a confirmed response, including 2 subjects (8.3%) with a complete response and 6 subjects (25.0%) with a partial response. The confirmed ORR (95% CI) based on investigator assessment was 33.3% (15.6%, 55.3%). In addition, 1 subject had an unconfirmed partial response awaiting confirmatory scan for a confirmed and unconfirmed ORR (95% CI) of 37.5% (18.8%, 59.4%). The response was rapid and durable, with a median (range) time to response of 1.7 (1.6 to 11.3) months and a median (95% CI) DOR of 14.9 (3.0, NE) months. The median (95% CI) follow-up time for DOR was 18.8 (1.0, NE) months.

Reference ID: 5382024

At the 100 mg monotherapy target dose (N = 76 evaluable subjects in the Interim Efficacy Analysis Set), 15 subjects had a confirmed response, including 2 subjects (2.6%) with a complete response and 13 subjects (17.1%) with a partial response. The ORR (95% CI) based on investigator assessment was 19.7% (11.5%, 30.5%). In addition, 2 subjects had unconfirmed partial responses awaiting confirmatory scan for a confirmed and unconfirmed ORR (95% CI) of 22.4% (13.6%, 33.4%). The median (range) time to response was 1.8 (1.6 to 3.7) months; the median (95% CI) DOR was not reached (5.6, NE) months. The median (95% CI) follow-up time for DOR was 18.7 (12.8, 23.8) months.

Efficacy Update as of 02 October 2023

As of the 02 October 2023 data cutoff date, tarlatamab monotherapy and combination therapy for SCLC subjects at multiple doses resulted in confirmed ORR (95% CI) of 22.2% (16.9%, 28.2%), including 3 additional subjects with confirmed responses since the original cutoff date (49 subjects [02 October 2023] vs 46 subjects [28 March 2023]). One additional subject had an unconfirmed partial response and was awaiting confirmatory scan. The ORR (95% CI) for the 49 subjects with confirmed response and 1 subject with unconfirmed partial response awaiting confirmatory scan was 22.6% (17.3%, 28.7%). The DCR (95% CI) was 52.5% (45.7%, 59.2%) (90-day Table 14-4.1.1 of Study 20160323). These updated results are consistent with the results presented in the primary analysis (Section 2.2.3 of Module 2.7.3, Summary of Clinical Efficacy).

The median DOR (95% CI) was 11.2 (6.6, 14.9) months for the 49 confirmed responders (90-day Table 14-4.2.1 of Study 20160323).

Updated Kaplan-Meier plot for DOR is provided in 90-day Figure 14-4.3.1. An updated waterfall plot of best overall response is provided in 90-day Figure 14-4.1 of Study 20160323. An updated swimmer plot of time to response and duration of treatment among confirmed responders in the Interim Analysis Efficacy Set is provided in 90-day Figure 14-4.2 of Study 20160323.

These results are consistent with the interim analyses presented in the initial marketing application (Section 2.2.3 of Module 2.7.3, Summary of Clinical Efficacy), and this updated efficacy information aligns with the overall study conclusions as originally presented (Study 20160323 Interim Analysis CSR).

The Applicant's Position:

These efficacy results from phase 1 were supportive of those observed in the phase 2 study. The FIH efficacy results across all dose cohorts are summarized in Section 2.2.3 of Module 2.7.3, SCE; full results are provided in the Study 20160323 clinical study report.

The FDA's Assessment:

At the time of the original BLA submission, 27 patients had enrolled and 24 were evaluable for

efficacy. Of the 24, there 8 responses (ORR 33%). FDA reviewed the efficacy results presented above but did not verify the results since this study was supportive and the results were not included in labeling.

Data Quality and Integrity

Data:
See Section 8.2.3.

The Applicant's Position:
No issues were identified regarding data integrity or submission quality that had an effect on the efficacy review.

The FDA's Assessment:

FDA did not assess the data quality and integrity of this study since the study was supportive and the results were not included in labeling.

Efficacy Results – Secondary and other relevant endpoints

Data:
Study 20160323

In the 10 mg target dose group, median (95% CI) PFS based on investigator review was 3.5 (1.9, 11.0) months, with a median follow-up time of 20.5 months. The Kaplan-Meier estimates for PFS at 6 and 12 months were 36.3% and 24.2%, respectively. Median (95% CI) OS was 20.3 (5.1, NE) months, with a median follow-up time of 12.6 months. The Kaplan-Meier estimates for OS at 6 and 12 months were 61.8% and 54.9%, respectively.

In the 100 mg target dose group, median (95% CI) PFS based on investigator review was 3.7 (1.9, 4.5) months, with a median follow-up time of 18.8 months. The Kaplan-Meier estimates for PFS at 6 and 12 months were 32.1% and 18.6%, respectively. Median (95% CI) OS was not reached (11.0, NE) months, with a median follow-up time of 12.0 months. The Kaplan-Meier estimates for OS at 6 and 12 months were 79.3% and 60.4%, respectively.

Efficacy Update as of 02 October 2023

The Kaplan-Meier estimate of median (95% CI) PFS of all subjects was 3.3 (2.0, 3.7) months (90-day Table 14-4.3.1 of Study 20160323). At the time of the data cutoff, the Kaplan-Meier estimate of median (95% CI) OS was 12.8 (10.9, 20.3) months (90-day Table 14-4.4.1 of Study 20160323). These results are consistent with the interim analyses presented in the initial marketing application (Section 2.2.3 of Module 2.7.3, Summary of Clinical Efficacy), and this updated efficacy information aligns with the overall study conclusions as originally presented (Study 20160323 Interim Analysis CSR).

The Applicant's Position:

The PFS and OS results in the phase 1 study provide additional evidence of the efficacy of tarlatamab.

The FDA's Assessment:

FDA reviewed the efficacy results presented above but did not verify the results since this study was supportive and the results were not included in labeling. FDA does not agree with the Applicant's position on PFS and OS results since these time-to-event endpoints are difficult to interpret in the absence of an appropriate control arm.

Persistence of Effect

Data:

No long-term efficacy data with the exception of those presented in the preceding sections are available at the time of this application.

The Applicant's Position:

Not applicable

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.1.5. Integrated Review of Effectiveness

The FDA's Assessment:

Efficacy data from Parts 1 and 2 of Study 20200491 in patients who received the tarlatamab 10 mg proposed dose comprise the primary dataset to support this application. See Section 8.1.2 for detailed discussion of these results. Efficacy data from Part 3 of Study 20200491 and in patients who received the tarlatamab 10 mg dose in Study 20160323 were evaluated as supportive evidence of effectiveness for this application.

The proposed indication by the Applicant (SCLC with disease progression on or after platinum-based chemotherapy) differs from the population studied in the 20200491 study (SCLC with disease progression after receiving previous treatment with platinum-based chemotherapy and at least one other line of prior therapy). To evaluate the appropriateness of the Applicant's proposal, FDA performed analyses of efficacy subgroups by prior therapies from Study 20200491 which are further described in Section 8.1.7.

8.1.6. Assessment of Efficacy Across Trials

Primary Endpoints

Data:

See Efficacy Results – Primary Endpoint (Including Sensitivity Analyses).

The Applicant's Position:

The primary evidence for efficacy for this marketing application is the evaluation of the data for 222 subjects with advanced SCLC who received tarlatamab monotherapy (10 or 100 mg) in the pivotal phase 2 Study 20200491, as reflected in a durable objective response in a large percentage of subjects and supported by the totality of clinically significant response measures.

The efficacy results from the 208 subjects enrolled in FIH Study 20160323 provided supportive efficacy data.

The FDA's Assessment:

FDA generally agrees with the Applicant's position, with the exception that this review did not rely on efficacy data from patients treated at the 100 mg dose. As described in Section 8.1.5, the primary evidence for efficacy for this marketing application is from the evaluation of data from 99 patients with ES-SCLC who received tarlatamab 10 mg from Parts 1 and 2 of Study 20200491. The efficacy results from Part 3 of Study 20200491, along with those from the 24 efficacy evaluable patients who received the tarlatamab 10 mg dose in Study 20160323 provide supportive efficacy data.

Secondary and Other Endpoints

Data:

See Efficacy Results – Secondary and other relevant endpoints.

The Applicant's Position:

Overall, efficacy data for the phase 1 study (20160323) are consistent with the phase 2 efficacy results (from Study 20200491) in subjects with advanced SCLC treated with tarlatamab 10 mg monotherapy.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. The ORR results from the 24 efficacy

evaluable patients from Study 20160323 are generally consistent with the Study 20200491 efficacy results.

Additionally, in Study 20200491, 34 patients received tarlatamab at the proposed dosing regimen in Part 3 of the study, which was primarily intended to evaluate the safety of tarlatamab under reduced monitoring criteria for CRS. The confirmed BICR ORR per RECIST v1.1 was 32% (95% CI: 17%, 51%). The DoR estimate is premature as 73% of the patients who had responses were censored for the DoR analysis. These ORR results are generally consistent with the results observed in Parts 1 and 2 (40% vs. 32%).

Subpopulations

Analyses for ORR, DOR, DoDC, PFS, and OS in Study 20200491 Parts 1 and 2 (10 and 100 mg) were conducted to explore the consistency of tarlatamab treatment effect across subgroups of age, race, region, number of prior lines of anticancer therapy, prior PD-1 or PD-L1 therapy, sum of diameters of target lesions at baseline, platinum sensitivity, presence of brain or liver metastasis at baseline, and DLL3 cut points. No notable differences were observed among these subgroups for ORR (Figures 7 and 8 of Module 2.5, Clinical Overview), DOR, DoDc, PFS, or OS. However, subgroup analysis interpretation may be limited because of the small sample size of each subgroup.

A post hoc analysis performed for Parts 1 and 2 (10 and 100 mg) of the progression-free interval after first-line platinum therapy, which included time to next therapy for subjects with unknown progression dates after first-line platinum therapy, showed that efficacy was observed across all subgroups. Objective response rate, DOR, DoDC, PFS, and OS across these subgroups by progression-free interval after first-line platinum treatment were generally consistent with the primary analyses (Table 4 of Module 2.5 [Clinical Overview] for ORR and DOR).

A post hoc analysis performed for Parts 1 and 2 (10 and 100 mg) of prior lines of therapy showed that efficacy was observed across subgroups of subjects who had (or had not) received a variety of prior lines of therapy representing global standard of care, including topotecan, lurbinectedin, and amrubicin. Objective response rate, DOR, PFS, and OS across these subgroups by prior line of therapy were generally consistent with the primary analyses (Table 5 of Module 2.5 [Clinical Overview] for ORR and DOR).

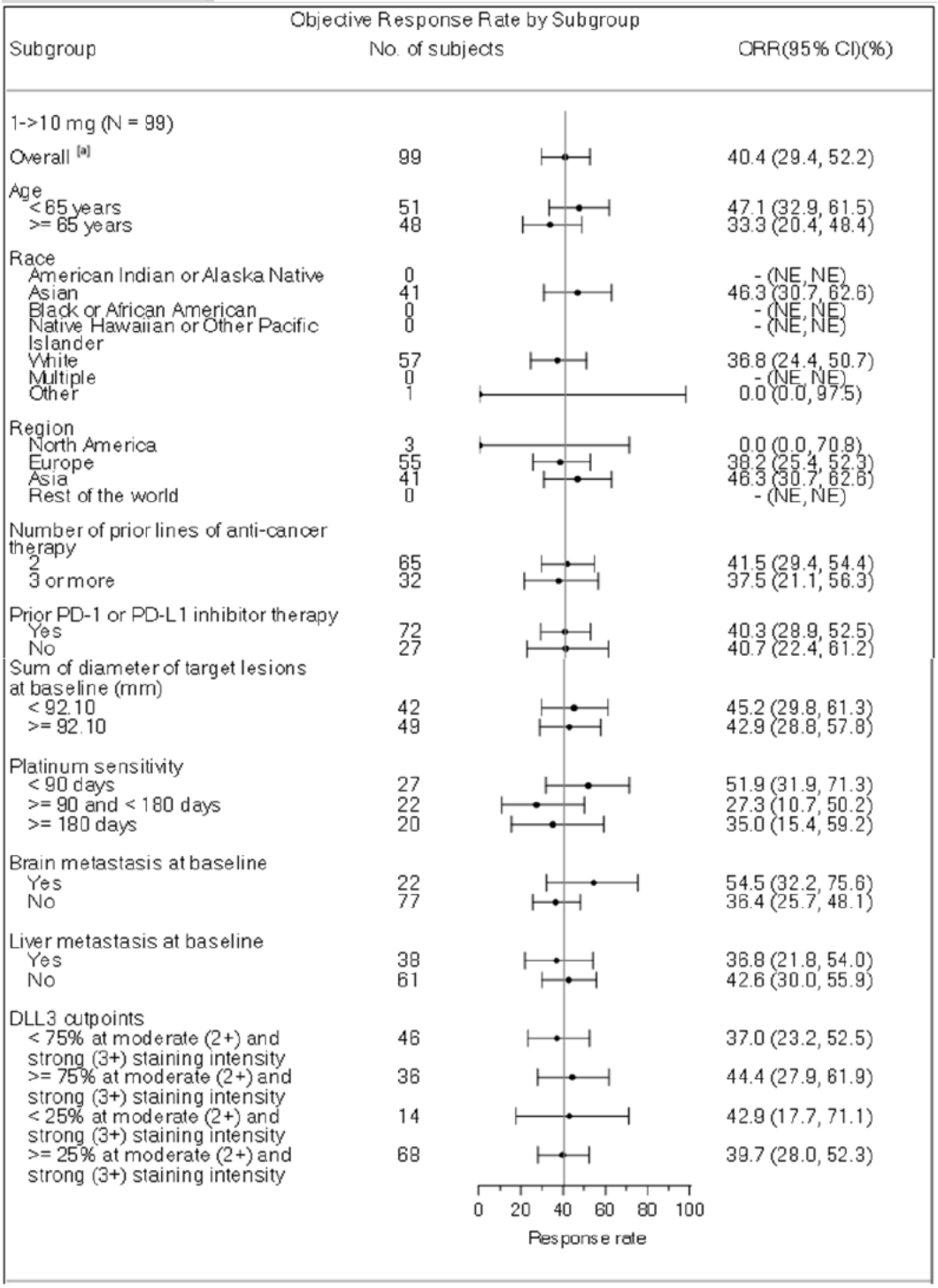
Analyses were conducted for best overall response to evaluate concordance between assessments by BICR (primary endpoint) and the study center investigator (secondary endpoint). Of the 186 subjects, 164 subjects had scans evaluable by BICR and the investigator; of these 164 subjects, 146 subjects (89.0%) were concordant (Table 14-4.2 of Study 20200491).

A post hoc subgroup analysis by sex and ECOG performance status at baseline also showed that efficacy was observed across these subgroups; ORR, DOR, DoDC, PFS, and OS across these subgroups were generally consistent with those from the primary analyses.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. Forest plots of the subgroup analyses for Part 1 and 2 (10 mg only) are presented in Figure 22. Review showed generally consistent ORRs across multiple subgroups including age, sex, race, number of prior lines of anticancer therapy, prior PD-(L)1 therapy, and DLL3 cutpoints. DLL3 cutpoints were previously validated by the Applicant at the 25% and 75% cutoffs at moderate (2+) and strong (3+) staining intensity. Review of efficacy data at these cutoffs did not show any differences in ORR across subgroups. There were also 2 patients who were also DLL3 negative, with 1 patient responding to tarlatamab treatment.

Figure 22. Forest Plot of Subgroup Analyses of Objective Response Rate at 10 mg Tarlatamab Dose as Assessed by BICR (BICR Full Analysis Set for Part 1 and Part 2) (Study 20200491 Primary Analysis).



Data cutoff date: 27 June 2023.

Source: Figure 7 of Module 2.5 in the Applicant's Clinical Overview.

Although based on its mechanism of action a differential effect is not expected for tarlatamab in patients with platinum-sensitive vs platinum-resistant disease, data was also reviewed regarding patient's sensitivity to platinum. Of the 99 patients who received tarlatamab 10 mg, data on platinum sensitivity was available in 69 patients. The ORR was 52% (95% CI: 32%, 71%) in 27 patients with platinum-resistant SCLC (defined as < 90 days after end of first line platinum therapy to date of progression) and 31% (95% CI: 18%, 47%) in 42 patients with platinum-sensitive SCLC (defined as ≥90 days after end of first line platinum therapy to date of progression). The ORR for the 30 patients with data unavailable for platinum sensitivity was 43% (95% CI: 25%, 63%). Although the ORR point estimates differ between these subgroups, the 95% CI overlap, and given the known mechanism of action of tarlatamab as a targeted agent that causes activation of the immune system, FDA considers that a true difference in efficacy based on platinum sensitivity status is unlikely with tarlatamab.

Supportive analysis was performed by patient's sensitivity to platinum using an alternative definition where the patient's progression free interval was defined as time from first line platinum treatment to disease progression or start of second line treatment. Using this alternative definition, the ORR was 45% (95% CI: 29%, 62%) in 38 patients with platinum-sensitive disease and 38% (95% CI: 25%, 52%) in 55 patients with platinum-resistant disease with a 50% ORR in 6 patients with unknown platinum sensitivity. This analysis is encouraging to suggest that there is no difference to tarlatamab response by platinum sensitivity status. Further information regarding this will be available from the confirmatory trial.

For this application the proposed indication from the Applicant (SCLC with disease progression on or after platinum-based chemotherapy) differs from the population enrolled in Study 20200491 (SCLC with disease progression after receiving previous treatment with platinum-based chemotherapy and at least one other line of prior therapy). FDA conducted multiple subgroup analyses based on prior therapies in Parts 1 and 2 of Study 20200491 in patients who received the 10 mg dose. The ORR in patients who received 2 lines of prior therapy was 42% (95% CI: 29%, 54%) in 65 patients, and ORR was 38% (95% CI: 21%, 56%) in 32 patients who received 3 or more lines of prior therapy. Of these patients, 50 received a topoisomerase I inhibitor (topotecan, irinotecan or belotecan) as a prior treatment while 47 did not. The ORR in patients who received a prior topoisomerase I inhibitor was 46% (95 CI: 32%, 61%), while the ORR in patients who did not receive a prior topoisomerase I inhibitor was 41% (95% CI: 27%, 56%). Given that topoisomerase I inhibitors (including topotecan) are considered standard treatments for ES-SCLC with progression after platinum-based chemotherapy and topotecan is the only therapy with traditional approval from FDA in this setting, FDA analyzed the prior treatments received and the response rates in patients who did not receive a topoisomerase-I inhibitor per the table below.

Table 36 Tarlatamab efficacy for second line therapies for patients who did not receive a prior topoisomerase-I inhibitor

Therapy	N (n=47)	ORR
Amrubicin	5	4/5 (80%)
CAV	10	3/10 (30%)
Gemcitabine + Paclitaxel	1	1/1 (100%)
Lurbinectedin	3	0/3 (0%)
Paclitaxel	1	1/1 (100%)
PD-(L)1 +/- experimental drug	4	2/4 (50%)
Platinum +/- PD-(L)1	20	7/20 (35%)
Temozolomide + PARP	3	1/3 (33%)

The grand majority (42/47; 89%) of patients received standard treatment as the following are considered either preferred or other recommended regimens in the US: CAV, gemcitabine plus paclitaxel, lurbinectedin, paclitaxel, anti-PD-(L)1 antibody, temozolomide, and platinum retreatment with or without anti-PD-(L)1 therapy. The ORR is 36% in these 42 patients. Although amrubicin is not approved in the US, clinical trials have shown comparable efficacy between amrubicin and topotecan (von Pawel, 2014). In addition, upon excluding patients with either unknown platinum sensitivity or platinum resistant disease who received platinum +/- PD-L1 rechallenge (n=3 and n=3, respectively) and patients who received amrubicin (n=5), the ORR is 31% in the remaining 36 patients.

From this analysis, the majority of patients received second line treatments that are consistent with standard of care in the United States. Analysis of the ORR in patients who received prior topoisomerase I inhibitor, as well as in patients who did not receive prior topoisomerase I inhibitor (including and not including patients who received other standard of care therapies) were generally consistent with the response rate observed for the overall study population. Furthermore, it is not expected that treatment with additional therapies following platinum-based chemotherapy would increase the likelihood of response to tarlatamab relative to treatment with tarlatamab used as second-line therapy following platinum-based chemotherapy. In light of the observed results and particularly considering the ORR observed with tarlatamab in patients with platinum-resistant SCLC, which far exceeds ORR reported with standard of care therapies, the available data for tarlatamab supports the proposed indication for treatment of SCLC with disease progression on or after platinum-based chemotherapy.

Lastly, FDA notes that subgroup analyses for time-to-event endpoints such as PFS and OS, and PRO endpoints, are difficult to interpret in the absence of an appropriate control arm.

Additional Efficacy Considerations

Updates made to the primary analysis dataset are described in the document submitted on 12 December 2023 (SN 0014) and in the accompanying tables, figures, and listings (Module 5.3.5.2). The updated data do not impact the primary endpoint of ORR by BICR as presented in the BLA. A listing of updated tumor responses assessed by Investigator was provided in Appendix 4 of the Response Document (12 December 2023, SN 0014).

The FDA's Assessment:

FDA generally agrees with the Applicant's position. An updated datacut for DoR was provided as well to provide the median with data and is described in the FDA's assessment of efficacy data in Section 8.1.2.

8.1.7. Integrated Assessment of Effectiveness

Data:

Data are presented above in Section 8.1.1. Efficacy data were not pooled across the phase 1 and 2 studies due to differences in study populations, number of prior cancer treatments, tarlatamab dose, or other aspects of treatment (monotherapy vs combination therapy).

The Applicant's Position:

Results from both Study 20200491 (phase 2) and Study 20160323 (phase 1) demonstrated the clinical activity of tarlatamab in subjects with advanced SCLC, a disease state with high unmet medical need. Both studies showed rapid, durable responses, and consistent median PFS and OS; improvements in PRO assessments were also seen with tarlatamab treatment in the phase 2 study.

Overall, tarlatamab demonstrated a clinically meaningful durable objective response and potential survival benefits of PFS and OS. Median OS and median PFS are considered potential survival benefits and will be further evaluated in the ongoing phase 3 randomized, active-controlled Study 20210004.

The FDA's Assessment:

FDA generally agrees with the Applicant's position that tarlatamab demonstrated clinically meaningful durable objective response. Time-to-event endpoints such as PFS and OS, and PRO endpoints are difficult to interpret in the absence of an appropriate control arm.

FDA considers the observed 40% response rate (95% CI: 31%, 51%) from patients enrolled to Parts 1 and 2 of Study 20200491 who received tarlatamab at the proposed dosing regimen a clinically meaningful improvement over available therapy. The response rates were supported by a median DoR of 9.7 months with 68% of patients with an observed DoR ≥6 months and 40% of patients with an observed DoR ≥12 months.

The observed ORR was generally consistent across most patient subgroups, defined by relevant demographic and disease-related characteristics, including across subgroups of patients with platinum-sensitive and platinum-refractory disease and across subgroups with various DLL3 expression cut-offs. Of the 99 patients who received tarlatamab at the proposed dosing regimen, 69 patients had available data regarding platinum sensitivity status. In this subgroup of patients, the ORR was 52% (95% CI: 32%, 71%) in 27 patients with platinum-resistant SCLC (defined as < 90 days after end of first line platinum therapy to date of progression) and 31% (95% CI: 18%, 47%) in 42 patients with platinum-sensitive SCLC (defined as ≥90 days after end of first line platinum therapy to date of progression). Although the ORR point estimates differ between these subgroups, the 95% CI overlap, and FDA considers that a true difference in efficacy based on platinum sensitivity status is unlikely with tarlatamab.

For this application, the proposed indication, SCLC with disease progression on or after platinum-based chemotherapy, differs from the population enrolled in Study 20200491, SCLC with disease progression after receiving previous treatment with platinum-based chemotherapy and at least one other line of prior therapy. Overall, the ORR and DoR data from the primary efficacy population in Study 20200491, which enrolled a more heavily treated patient population (3rd line or greater), is greater than the ORR and DoR observed with topotecan, the only available therapy with traditional approval from the FDA for patients with SCLC previously treated with first-line chemotherapy (ORR of 24% in platinum sensitive disease and 2-7% in platinum resistant disease). Review of prior therapies in the primary efficacy population from Study 20200491 showed that 52% of patients received a topoisomerase I inhibitor as second-line therapy. Of the remaining patients who did not receive a prior topoisomerase I inhibitor, the grand majority (89%) received other second line therapies considered treatment options per U.S. standard of care. The ORR in the subgroups of patients who received prior topoisomerase I inhibitor; and who did not receive prior topoisomerase I inhibitor (with or without patients who received standard of care therapies), were generally consistent across subgroups and consistent with the ORR observed in the overall study population. Furthermore, it is not expected that treatment with additional therapies following platinum-based chemotherapy would increase the likelihood of response to tarlatamab relative to treatment with tarlatamab used as second-line therapy following platinum-based chemotherapy. In light of the observed results and particularly considering the ORR observed with tarlatamab in patients with platinum-resistant SCLC, which far exceeds ORR reported with standard of care therapies, the available data for tarlatamab supports the proposed indication for treatment of SCLC with disease progression on or after platinum-based chemotherapy.

Data from Part 3 of Study 20200491 and from patients who received the tarlatamab 10 mg dose in Study 20160323 were considered supportive of the primary efficacy results from Study 20200491.

These results provide substantial evidence of effectiveness of tarlatamab for the treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy.

8.2. Review of Safety

Data:

As of the time of this marketing application, the number of subjects who have been exposed to ≥ 1 dose of tarlatamab is provided in Table 37.

Table 37. Applicant – Exposure to Tarlatamab

Study Number	Number of Subjects Who Received Tarlatamab: Any Dose	10 mg Dose	100 mg Dose	Other Investigational Product
Integrated Monotherapy Analysis				
20200491 (all subjects)	220	133	87	-
20160323 (monotherapy cohorts)	197	27	76	-
20200040	(b) (4)			-
Integrated Combination Analysis				
20160323 (cohorts with pembrolizumab)	8	-	-	pembrolizumab
20200469 20200439	(b) (4)			
Other Studies				
20210004		(b) (4)		

- = not applicable
Data from Study 20210004 are blinded. (b) (4)

Sources: Table 1 of Module 2.7.4, SCS

Table 38. Applicant – Exposure to Tarlatamab Based on 90-day Safety Update as of 02 October 2023

Study Number	Number of Subjects Who Received Tarlatamab: Any Dose	10 mg Dose	100 mg Dose	Other Investigational Product
Integrated Monotherapy Analysis				
20200491 (all subjects)	220	133	87	-
20160323 (monotherapy cohorts)	224	54	76	-
20200040	[redacted] (b) (4)			-
Integrated Combination Analysis				
20160323 (cohorts with pembrolizumab)	8	-	-	pembrolizumab
20200469 20200439	[redacted] (b) (4)			
Other Studies				
20210004	[redacted] (b) (4)			

- = not applicable
[a]Data from Study 20210004 are blinded. [redacted] (b) (4) .

Sources: 90 DSU Table 1

The Applicant's Position:

Data from these studies allow for an informed assessment of the safety profile of tarlatamab and an evaluation of the overall benefit-risk in adult subjects with advanced SCLC with disease progression on or after platinum-based chemotherapy. This safety population is also considered appropriate for the detection and characterization of common adverse events and to provide guidance on toxicity management.

The FDA's Assessment:

Safety analyses were conducted on the complete datasets provided by the Applicant for the pooled population which includes Study 20200491 and Study 20160323 based on an October 2, 2023 data cut-off. FDA notes that the primary safety population from Study 20200491 included 99 patients in Parts 1 and 2 of protocol which required hospitalization for 48 hours post tarlatamab infusion for Cycle 1 Day 1 and Cycle 1 Day 8 doses. In Part 3 of the protocol (n=34), patients were hospitalized for 24 hours post tarlatamab infusion for cycle 1 day 1 and day 8 doses. In supportive Study 20160323 (n=54) patients were hospitalized for 48 hours post tarlatamab infusion on Cycle 1 Day 1

and Cycle 1 Day 8 doses.

The Applicant converted safety data from Study 20160323 from CTCAE version 4.0 to CTCAE version 5.0 as well as upgraded CRS grading from Lee et al, 2014 criteria to American Society for Transplantation and Cellular Therapy (ASTCT) 2019 grading scale when all data was available. FDA agrees that the safety data provided allows for an appropriate analysis of adverse events and the characterization of the safety profile of tarlatamab.

8.2.1. Safety Review Approach

Data:

Not applicable

The Applicant's Position:

The primary analysis of safety for the proposed indication is based on the integrated safety analysis of pooled data from subjects with SCLC who were treated with tarlatamab monotherapy at a dose of 10 or 100 mg Q2W in pivotal phase 2 Study 20200491 and FIH phase 1 Study 20160323; this population is the primary focus in this section. Supportive integrated safety data across all tarlatamab monotherapy doses (Studies 20200491, 20160323, and 20200040) and all tarlatamab combination therapy doses (with pembrolizumab in Part C of Study 20160323, AMG 404 in Study 20200439, and atezolizumab or durvalumab $\pm$ carboplatin and etoposide in Study 20200469) are provided in Module 2.7.4, Summary of Clinical Safety (SCS) and in the Integated Summary of Safety (ISS).

Demographics, baseline disease characteristics, exposure, adverse events, and other safety assessments were summarized using the safety analysis set, which included all subjects enrolled who received ≥ 1 dose of tarlatamab in monotherapy cohorts and ≥ 1 dose of any investigational product in combination cohorts.

Throughout the tarlatamab clinical development program, safety was continuously evaluated by Amgen through routine signal detection activities such as review of all serious adverse events across all the clinical studies.

Four adverse events of interest (EOIs) were analyzed for tarlatamab: cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS) and associated neurological events, neurological events (nervous system disorders [system organ class]/psychiatric disorders [system organ class]), and neutropenia. These events were clinically monitored through protocol designated reporting of clinical signs and symptoms, as well as scheduled assessments of laboratory tests.

The FDA's Assessment:

FDA generally agrees with the Applicant's description of the primary and supportive safety sets included in the BLA. FDA's safety review approach for the proposed indication was based on the updated 90-day safety datasets (DCO of October 2, 2023) of pooled data from Study 20200491

and Study 20160323 in 187 patients with extensive stage SCLC who were treated with tarlatamab at a step dose of 1 mg on Cycle Day 1 followed by the proposed dose of 10 mg on Cycle 1 Day 8, Cycle 1 Day 15 and every 2 weeks thereafter. FDA reviewed but did not independently verify data submitted for patients treated with tarlatamab at a dose of 100 mg every 2 weeks.

8.2.2. Review of the Safety Database

Data:

As of the data cutoff date for the pooled safety data, a total of (b) (4) subjects received at least 1 dose of tarlatamab monotherapy across studies (Table 37). This includes 160 subjects who were treated with the proposed tarlatamab dose of 10 mg Q2W, and 163 subjects who were treated with the tarlatamab dose of 100 mg Q2W (Table 4 of Module 2.7.4, SCS).

Integrated Monotherapy Studies (Studies 20200491, 20160323, and 20200040)

Overall, the median exposure for tarlatamab monotherapy across doses was (b) (4) weeks, with a median relative dose intensity of tarlatamab of (b) (4) (Table 2 of Module 2.7.4, SCS. The median (range) number of doses received was (b) (4) (Table 2 of Module 2.7.4, SCS). Overall, (b) (4) had discontinued tarlatamab treatment; the most frequently reported (subject incidence (b) (4) reason for treatment discontinuation was disease progression (b) (4) (Table 4 of Module 2.7.4, SCS).

Integrated Combination Studies (Studies 20160323, 20200469, and 20200439)

The median exposure for subjects treated with tarlatamab combination therapy in Studies 20160323, 20200469, and 20200439 was (b) (4) weeks, respectively (Table 3 of Module 2.7.4, SCS). The median relative dose intensity of tarlatamab was (b) (4) across the studies, similar to the monotherapy studies.

Safety Update as of 02 October 2023

As of the data cutoff date for the pooled safety data, a total of (b) (4) subjects received at least 1 dose of tarlatamab monotherapy across studies. This includes 187 subjects who were treated with the proposed tarlatamab dose of 10 mg Q2W, and 163 subjects who were treated with the tarlatamab dose of 100 mg Q2W.

Integrated Monotherapy Studies (Studies 20200491, 20160323, and 20200040)

Overall, the median exposure for tarlatamab monotherapy across doses and median relative dose intensity was the same as that reported for the initial integrated summary of safety (ISS) analysis at (b) (4) weeks and (b) (4) respectively.

The median (range) number of doses received was (b) (4) Overall, (b) (4) had discontinued tarlatamab treatment; the most frequently reported (subject incidence (b) (4) reason for treatment discontinuation was disease progression (b) (4)

Integrated Combination Studies (Studies 20160323, 20200469, and 20200439)

The median exposure for subjects treated with tarlatamab combination therapy in Study 20160323 remained the same as that reported for the initial ISS analysis, 9.71 weeks. Median exposure in Studies 20200469 and 20200439 increased to (b) (4) weeks, respectively. The median relative dose intensity of tarlatamab was (b) (4) across the studies, similar to the monotherapy studies (90-daySU ISS Table 14-5.1.2).

The Applicant's Position:

As of the data cutoff date for this marketing application, (b) (4) subjects received at least 1 dose of tarlatamab as monotherapy, 160 of whom were subjects with SCLC who received tarlatamab at the intended 10 mg Q2W dose. Compared with the initial ISS analysis, the 90-Day Safety Update includes 27 additional subjects from Study 20160323 treated with 10 mg tarlatamab monotherapy, for a total of (b) (4) subjects who received at least 1 dose of tarlatamab across studies, and 187 subjects treated with tarlatamab 10 mg Q2W.

The FDA's Assessment:

FDA agrees that exposures to tarlatamab in the pooled population of patients from Study 20200491 and Study 20160323 (n=187) with extensive stage SCLC who were treated with tarlatamab at the recommended dose of allowed for an adequate assessment of safety. The median duration of exposure was 108 days (range 1 to 427 days). Among these 187 patients, 31% were exposed for 6 months or longer and 14% were exposed for greater than one year. Please see Section 6 and 19.4 (Clinical Pharmacology and OCP Appendices) for more detail on exposure analyses.

Relevant characteristics of the safety population:

Data:



Table 39. Applicant – Baseline Demographics – Monotherapy – Studies 20200491, 20200040 and Monotherapy Cohorts of Study 20160323 (Integrated Monotherapy Safety Analysis Set)

	Study 20160323 and 20200491		Overall Studies
	1->10 mg (N = 160)	1->100 mg (N = 163)	(b) (4)
Sex - n (%)			
Male	105 (65.6)	106 (65.0)	
Female	55 (34.4)	57 (35.0)	
Race - n (%)			
Asian	46 (28.8)	48 (29.4)	
Black or African American	2 (1.3)	4 (2.5)	
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	
White	109 (68.1)	104 (63.8)	
Ethnicity - n (%)			
Hispanic/Latino	1 (0.6)	3 (1.8)	
Not Hispanic/Latino	108 (67.5)	101 (62.0)	
Other	3 (1.9)	7 (4.3)	
Age (years)			
Mean	64.1	61.6	
SD	8.7	9.1	
Median	65.0	62.0	
Q1, Q3	58.0, 70.0	56.0, 68.0	
Min, Max	35, 82	34, 80	
Age group - n (%)			
18 - <65 years	76 (47.5)	102 (62.6)	
³ 65 - <75 years	64 (40.0)	50 (30.7)	
³ 75 - <85 years	20 (12.5)	11 (6.7)	
³ 85 years	0 (0.0)	0 (0.0)	

N = number of subjects in the safety analysis set; n = number of subjects who received at least 1 dose of tarlatamab; Q3W = every 3 weeks

The safety analysis set is defined as all subjects who receive at least 1 dose of tarlatamab.

1->10 mg includes Study 20160323 cohorts 8 and 32 and Study 20200491 1->10 mg (part 1 randomized arm, part 2, and part 3); 1->100 mg includes Study 20160323 cohorts 10, 30, 11 (tarlatamab + dexamethasone), and 34 (24-hr outpatient) and Study 20200491 1->100 mg (part 1 randomized arm). Overall subjects includes all subjects who received tarlatamab as a monotherapy.

Source: Table 5 of Module 2.7.4, SCS and ISS Table 14-2.1.1

Table 40. Applicant – Key Baseline Characteristics – Studies 20200491, 20200040 and Monotherapy Cohorts of Study 20160323 (Integrated Monotherapy Safety Analysis Set)

	Study 20160323 and 20200491		Overall Studies (b) (4)
	1->10 mg (N = 160)	1->100 mg (N = 163)	
ECOG status at baseline - n (%)			
0	45 (28.1)	50 (30.7)	
1	114 (71.3)	112 (68.7)	
2	1 (0.6)	1 (0.6)	
Number of prior lines of therapy - n (%)			
1	8 (5.0)	23 (14.1)	
2	101 (63.1)	75 (46.0)	
3	28 (17.5)	40 (24.5)	
>3	23 (14.4)	25 (15.3)	
Smoking history - n (%)			
Never	16 (10.0)	10 (6.1)	
Current	26 (16.3)	24 (14.7)	
Former	118 (73.8)	129 (79.1)	
Missing	0 (0.0)	0 (0.0)	
Prior PD-1 or PD-L1 inhibitor therapy - n (%)			
Yes	122 (76.3)	111 (68.1)	
No	38 (23.8)	52 (31.9)	
Prior radiotherapy for current malignancy - n (%)			
Yes	121 (75.6)	130 (79.8)	
Prior brain radiotherapy for current malignancy - n (%)			
Yes	87 (54.4)	91 (55.8)	
Prior surgery for current malignancy - n (%)			
Yes	21 (13.1)	17 (10.4)	
Time from initial cancer diagnosis to enrollment (months)			
Mean (SD)	19.08 (10.82)	22.23 (18.10)	

ECOG = Eastern Cooperative Oncology Group; N = number of subjects in the safety analysis set; n = number of subjects with observed data; PD-1 = programmed death protein 1; PD-L1 = programmed death protein 1 ligand. The safety analysis set is defined as all subjects who receive at least 1 dose of tarlatamab.

1->10 mg includes Study 20160323 cohorts 8 and 32 and Study 20200491 1->10 mg (part 1 randomized arm, part 2, and part 3); 1->100 mg includes Study 20160323 cohorts 10, 30, 11 (tarlatamab + dexamethasone), and 34 (24-hr outpatient) and Study 20200491 1->100 mg (part 1 randomized arm). Overall Subjects includes all subjects who received tarlatamab as a monotherapy. *Source: Table 7 of Module 2.7.4, SCS and ISS Table 14-2.2.1*

The Applicant's Position:

(b) (4)

The FDA's Assessment:

FDA's safety population included patients from Study 20200491 and Study 20160323 (n=187) with extensive stage SCLC who were treated with tarlatamab monotherapy at the recommended dose of 10 mg. Median age was 66 years (range 35 to 82); other demographic information: male (65%), White (70%), Asian, (26%), Hispanic/Latino (2.1%) and Black (2.1%).

Although the safety patient population included a lower proportion of females compared to the US population with SCLC, it is considered generally representative of the overall population of patients with advanced SCLC in the US, except with regards to race/ethnicity. Despite these limitations, the overall data is considered supportive of the proposed indication in the US population. However, a postmarketing commitment (PMC) will be issued for analyses from ongoing or planned clinical trials enrolling a sufficient representation of U.S. racial and ethnic minority patients that is reflective of the US population of patients with SCLC to further characterize the safety and efficacy of tarlatamab in these patients.

Table 41. FDA Analysis of Demographic Characteristics of Safety Population

	Pooled Studies 20200491 and 20160323 N = 187 N (%)
Sex	
M	121 (65)
F	66 (35)
Age	
Mean (SD)	64 (8)
Median (Min - Max)	66 (35 - 82)
18 - 64 years	86 (46)
65 - 74 years	79 (42)
75 - 84 years	22 (12)
Race	
White	130 (70)
Asian	48 (26)

	Pooled Studies 20200491 and 20160323 N = 187 N (%)
Black	4 (2.1)
HISPANIC OR LATINO	4 (2.1)

Source: ADSL (Subject-Level Analysis Dataset) - 2024-01-11.

Adequacy of the safety database:

Data:

A table of all clinical studies which contributed to the safety analysis is provided in Table 25 (see also Table 1 of Module 2.7.4, Summary of Clinical Safety). As of the data cutoff dates for the pooled safety database, a total of (b) (4) subjects were treated with tarlatamab monotherapy across all studies and doses (Table 42; Section 1.2 of Module 2.7.4, Summary of Clinical Safety). This includes 160 subjects who were treated with the intended tarlatamab dose of 10 mg Q2W.

Safety Update as of 02 October 2023

As of the 02 October 2023, a total of (b) (4) subjects were treated with tarlatamab monotherapy across all studies and doses (Table 43). This includes 187 subjects with SCLC treated with tarlatamab monotherapy at the intended tarlatamab dose of 10 mg Q2W across Studies 20200491 and 20160323. Compared with the initial ISS analysis, the 90-day Safety Update Monotherapy Safety Analysis Set includes 27 additional subjects from Study 20160323 treated with 10 mg tarlatamab monotherapy.

The Applicant's Position:

The safety database is considered adequate to assess the safety of tarlatamab in the intended indication.

Table 42. Applicant – Exposure to Tarlatamab Monotherapy – Studies 20200491, 20200040 and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)

	Study 20160323				Study 20160323 and 20200491		Study 20200040	Overall Studies
								(b) (4)
	≤ 3 mg (N = 35)	1->30 mg (N = 8)	eIV Cohorts (N = 32)	Alternative Dosing Cohorts (N = 19)	1->10 mg (N = 160)	1->100 mg (N = 163)		
Number of doses per subject								
n	35	8	32	19	160	163		
Mean	10.4	5.9	10.9	7.8	11.7	11.9		
SD	13.3	4.5	8.7	4.8	9.6	11.7		
Median	4.0	4.5	8.0	7.0	8.0	8.0		
Q1, Q3	2.0, 14.0	2.5, 9.0	4.5, 14.5	4.0, 13.0	5.0, 17.0	3.0, 18.0		
Min, Max	1, 59	2, 13	1, 31	1, 16	1, 47	1, 61		
Cumulative dose (mg)								
n	35	8	32	19	160	163		
Mean	25.979	143.538	1019.234	828.737	104.993	988.610		
SD	91.556	140.440	874.447	740.659	92.014	1174.782		
Median	2.000	106.000	615.000	526.000	71.000	501.000		
Q1, Q3	0.600, 10.500	46.000, 241.000	415.000, 1415.000	426.000, 1126.000	31.500, 161.000	102.000, 1402.000		
Min, Max	0.036, 539.000	1.300, 361.000	59.680, 3100.000	1.000, 2701.000	1.000, 451.000	1.000, 6001.000		

Footnotes are defined on the last page of this table.

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Table 42. Applicant – Exposure to Tarlatamab Monotherapy – Studies 20200491, 20200040 and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)

	Study 20160323				Study 20160323 and 20200491		Study 20200040	Overall Studies
	≤ 3 mg (N = 35)	1->30 mg (N = 8)	eIV Cohorts (N = 32)	Alternative Dosing Cohorts (N = 19)	1->10 mg (N = 160)	1->100 mg (N = 163)	(b) (4)	
Relative dose intensity (%)[a]								
n	35	8	32	19	160	163		
Mean	115.7	87.7	91.5	81.0	89.4	79.1		
SD	104.5	34.9	16.1	31.3	25.6	31.7		
Median	100.0	100.0	100.0	100.0	97.1	95.5		
Q1, Q3	100.0, 100.0	100.0, 100.0	85.7, 100.0	71.5, 100.0	84.4, 100.0	72.1, 100.0		
Min, Max	10.7, 663.3	1.4, 100.0	32.9, 100.0	0.9, 100.0	3.2, 225.5	0.3, 114.1		
Treatment duration (weeks)								
n	35	8	32	19	160	163		
Mean	19.19	8.41	19.31	13.99	20.65	22.28		
SD	27.32	8.75	17.39	12.86	20.04	24.80		
Median	6.14	5.14	14.43	8.14	14.14	13.14		
Q1, Q3	2.14, 24.14	2.43, 14.29	6.14, 27.21	4.29, 19.57	6.14, 32.00	4.00, 33.86		
Min, Max	0.1, 121.1	1.3, 22.3	0.4, 58.4	0.1, 40.0	0.1, 93.4	0.1, 122.0		

Footnotes are defined on the last page of this table.

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Table 42. Applicant – Exposure to Tarlatamab Monotherapy – Studies 20200491, 20200040 and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)

eIV = extended intravenous; N = number of subjects in the safety analysis set; n = number of subjects with observed data; Q3W = every 3 weeks
The safety analysis set is defined as all subjects who receive at least 1 dose of tarlatamab.
£ 3 mg includes cohorts 1-7; 1->30 mg includes cohort 9; eIV Cohorts includes cohorts 26 (30 mg eIV-100 mg), 27 and 31 (100 mg eIV-100 mg); Alternative Dosing Cohorts include 2-step dosing cohort 23 (1->25->100 mg), cohort 37 (1->100->200 mg Q3W 21 day/cycle), and cohort 38 (1->100 mg day 1/day 8 21 day/cycle); 1->10 mg includes Study 20160323 cohorts 8 and 32 and Study 20200491 1->10 mg (Part 1 randomized arm, Part 2, and Part 3); 1->100 mg includes Study 20160323 cohorts 10, 30, 11 (tarlatamab + dexamethasone), and 34 (24-hr outpatient) and Study 20200491 1->100 mg (Part 1 randomized arm); 1->100# mg (b) (4). Overall Subjects includes all subjects who received tarlatamab as a monotherapy.
[a] Relative dose intensity (%) is calculated as (actual cumulative dose / planned cumulative dose) * 100, where: Cumulative actual dose is the total dose of tarlatamab given up to the data cutoff. For subjects who did not take any drug the cumulative actual dose is 0 mg. Cumulative planned dose is the planned dose of tarlatamab accumulated over the actual duration on-study treatment.
Source: ISS Table 14-5.1.1

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Reference ID: 5382024

Table 43. Applicant – Exposure to Tarlatamab Monotherapy – Studies 20200491, 20200040 and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set) 90-Day Safety Update

	Study 20160323				Study 20160323 and 20200491		Study 20200040	Overall Studies
	≤ 3 mg (N = 35)	1->30 mg (N = 8)	eIV Cohorts (N = 32)	Alternative Dosing Cohorts (N = 19)	1->10 mg (N = 187)	1->100 mg (N = 163)	(b) (4)	
Number of doses per subject								
n	35	8	32	19	187	163		
Mean	10.7	5.9	11.8	10.5	12.4	13.1		
SD	14.8	4.5	10.4	9.5	11.2	14.1		
Median	4.0	4.5	8.0	7.0	9.0	8.0		
Q1, Q3	2.0, 14.0	2.5, 9.0	4.5, 16.0	4.0, 15.0	4.0, 17.0	3.0, 19.0		
Min, Max	1, 72	2, 13	1, 43	1, 31	1, 61	1, 74		
Cumulative dose (mg)								
n	35	8	32	19	187	163		
Mean	29.694	143.538	1107.359	1048.737	111.539	1089.518		
SD	113.086	140.440	1045.760	1083.084	105.934	1396.803		
Median	2.000	106.000	615.000	701.000	71.000	501.000		
Q1, Q3	0.600, 10.500	46.000, 241.000	415.000, 1415.000	426.000, 1301.000	31.000, 161.000	102.000, 1402.000		
Min, Max	0.036, 669.000	1.300, 361.000	59.680, 4243.000	1.000, 4301.000	1.000, 551.000	1.000, 7301.000		

Footnotes are are defined on the last page of this table.

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Reference ID: 5382024

Table 43. Applicant – Exposure to Tarlatamab Monotherapy – Studies 20200491, 20200040 and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set) 90-Day Safety Update

							(b) (4)
Relative dose intensity (%)[a]							
n	35	8	32	19	187	163	
Mean	115.9	87.7	91.5	81.5	89.4	78.7	
SD	104.9	34.9	16.2	31.3	23.3	31.9	
Median	100.0	100.0	100.0	100.0	100.0	96.3	
Q1, Q3	100.0, 100.0	100.0, 100.0	85.7, 100.0	71.5, 100.0	85.9, 100.0	72.1, 100.0	
Min, Max	10.7, 663.3	1.4, 100.0	32.2, 100.0	0.9, 100.0	3.2, 225.5	0.3, 114.1	
Treatment duration (weeks)							
n	35	8	32	19	187	163	
Mean	19.93	8.41	21.25	19.47	22.17	24.89	
SD	30.36	8.75	20.89	21.51	23.04	29.83	
Median	6.14	5.14	14.43	8.14	15.43	13.14	
Q1, Q3	2.14, 24.14	2.43, 14.29	6.14, 30.21	4.29, 38.14	4.14, 30.29	4.00, 34.29	
Min, Max	0.1, 147.1	1.3, 22.3	0.4, 84.3	0.1, 67.0	0.1, 121.0	0.1, 149.0	

eIV = extended intravenous; Q3W = every 3 weeks

The safety analysis set is defined as all subjects who receive at least 1 dose of tarlatamab.

≤ 3 mg includes cohorts 1-7; 1->30 mg includes cohort 9; eIV Cohorts includes cohorts 26 (30 mg eIV-100 mg), 27 and 31 (100 mg eIV-100 mg); Alternative Dosing Cohorts include 2-step dosing cohort 23 (1->25->100 mg), cohort 37 (1->100->200 mg Q3W 21 day/cycle), and cohort 38 (1->100 mg day 1/day 8 21 day/cycle); 1->10 mg includes Study 20160323 cohorts 8, 32, and 35 and Study 20200491 1->10 mg (Part 1 randomized arm, Part 2, and Part 3); 1->100 mg includes Study 20160323 cohorts 10, 30, 11 (tarlatamab + dexamethasone), and 34 (24-hr outpatient) and Study 20200491 1->100 mg (Part 1 randomized arm); (b) (4) Overall Subjects includes all subjects who received tarlatamab as a monotherapy.

[a] Relative dose intensity (%) is calculated as (actual cumulative dose / planned cumulative dose) * 100, where: Cumulative actual dose is the total dose of tarlatamab given up to the data cutoff. For subjects who did not take any drug the cumulative actual dose is 0 mg. Cumulative planned dose is the planned dose of tarlatamab accumulated over the actual duration on-study treatment.

Source: 90-daySU ISS Table 14-5.1.1

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The FDA's Assessment:
FDA agrees with the Applicant's assessment of the adequacy of the safety database to support review of the BLA.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:

The study centers were monitored by contract research organizations for Study 20200491 and by Amgen staff and partners in Study 20160323. Monitors were responsible for reviewing adherence to the protocol; compliance with GCP; and the completeness, accuracy, and consistency of the data. Direct access to subject medical and laboratory records was permitted to verify entries on the study-specific eCRFs.

Investigator staff training was provided by Amgen Development during investigator meetings, initiation, and routine monitoring visits. The sponsor organized investigator and clinical research associate meetings before study start and during the study to provide information on the investigational product, the study rationale and design, responsibilities under ICH GCP, and training on the detailed study requirements.

Central laboratories were used in the studies. Where local laboratories were used, their participation in internal and external quality control, quality assurance, and accreditation schemes was evaluated by the study monitors.

The investigators were responsible for all data entered in the eCRFs and documented their review and approval of the data by signing a form verifying the validity and completeness of the data. The investigator was responsible for appropriate retention of essential study documents.

Case report form data were captured (via data entry by study center personnel in an Amgen database system [Amgen RAVE Electronic Data Capture]). Data quality checks were applied using manual and electronic verification methods. An audit trail to support data query resolution and any modification to the data was maintained.

The Applicant's Position:

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

The FDA's Assessment:

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FDA agrees that the information in the application, including safety datasets and individual case narratives, was adequate to support the safety analysis. There were findings noted from the GCP site inspections as described in Section 4.1. The Applicant conducted a 100% SDR/SDV for all clinical sites that participated in Study 20200491 which yielded updated data for efficacy and safety that did not impact FDA's interpretation of the trial results in a meaningful way. The updated 90-day safety datasets with DCO of October 2, 2023, were used for FDA's safety review and labeling.

Categorization of Adverse Event

Data:

Not applicable, please see Applicant's position.

The Applicant's Position:

Standard methodologies were used to categorize adverse events. The analyses used Medical Dictionary for Regulatory Activities (MedDRA) version 26.0 for initial ISS analysis and MedDRA version 26.1 for 90-day update. The severity of each adverse event was graded using National Cancer Institute – Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for Studies 20200491 and 20200469. The severity of each adverse event for Studies 20160323, (b) (4) was converted from CTCAE version 4.0 to 5.0, if applicable. A description of the methodology used for this conversion is provided in the Clinical Events Classification Charter (ISS Module 5.3.5.3). Events of interest were evaluated based on standardized MedDRA queries.

The collection of adverse events in the clinical studies was also appropriate. The protocols defined adverse events and serious adverse events, as well as the reporting procedures. Adverse events were collected after enrollment through the safety follow-up visit. All adverse events considered to be related to investigational product and all serious adverse events regardless of relationship were required to be followed until stabilization or reversibility. Treatment-emergent adverse events were defined as any adverse event with an onset date between the date of first dose and up to and including 42 days after the date of last dose of investigational product or the end of study date, whichever was earlier.

The FDA's Assessment:

FDA agrees with the Applicant's description of AE categorization. The FDA review was completed using MedRA preferred terms (PTs) and CTCAE grade as well as custom grouped terms (GT) when performing independent analyses of AEs.

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The applicant upgraded all adverse events (AEs) excluding cytokine release syndrome (CRS) and laboratory data, from CTCAE version 4.0 to CTCAE version 5.0 if all the necessary data was available. CRS AEs graded using Lee, 2014 criteria were also upgraded to ASTCT 2019 grading scale (Lee, 2019) if all the data was available but was limited to the availability of temperature and vasopressor use as data regarding hypoxia/oxygen intervention were not collected and/or consistently reported.

Routine Clinical Tests

Data:

In Studies 20200491 and 20160323, all protocol-required laboratory assessments, including routine hematology and serum chemistry panels, were to be conducted in accordance with the laboratory manual and the schedule of assessments in the protcols. Laboratory values were graded using the current version of NCI CTCAE and converted if necessary (see above). Vital signs, physical measurements, and electrocardiograms (ECGs) were also assessed during study visits as outlined in the schedule of assessments. Clinically significant abnormal vital signs or findings were to be reported as adverse events.

The Applicant's Position:

The clinical monitoring of subject safety was considered adequate for the expected toxicities associated with tarlatamab treatment. The time points and analyses of clinical tests were defined in the study protocols.

The FDA's Assessment:

FDA agrees that the clinical monitoring of patient safety was adequate. For Studies 20200491 and 20160323, multiple safety assessments were conducted on the days of screening and infusion which included physical examinations, neurological examinations, vital signs, height and weight, performance status according to Karnofsky and laboratory evaluation (hematology, chemistry panels, urinalysis, and pregnancy tests).

For Study 20200491 during Cycle 1 (Parts 1 and 2) vitals were performed every 15 minutes during infusion and during the first 2 hours after end of infusion (EOI), followed by every 30 minutes from 2 to4 hours after EOI, every hour from 4 to8 hours after EOI, 12 hours post-EOI, 20 hours post-EOI, 24 hours post-EOI. After 24 hours post-EOI, vital signs should be assessed per institutional standards. For Cycle 1 (Part 3) vitals were assessed every 30 minutes during infusion, during first 4 hours post-EOI, every hour from 4-8 hours EOI, 12 hours post-EOI, 20 hours post-EOI and 24 hours post-EOI.

ECGs were collected pre and post infusion as part of standard monitoring for QT prolongation. Triplicate ECGs were collected pre-infusion on Cycle 1 Day 1 (C1D1) and post-infusion on C2D1

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and C2D15 for the first approximately 50 patients in Part 1. ECGs were collected pre and post infusion for those patients who did not have triplicated ECGs performed.

8.2.4. Safety Results

Deaths

Data:

Monotherapy Studies

Overall, fatal adverse events were reported for 19 subjects (4.2%) treated with tarlatamab monotherapy; the most frequently reported (> 1 subject) fatal adverse events were aspiration, cardio-respiratory arrest, neuroendocrine carcinoma of the prostate, pneumonia, and respiratory failure (2 subjects [0.4%] each (Table 44). The 2 fatal events of respiratory failure were considered treatment related (ISS Table 14-6.2.15). Both subjects had significant confounders.

In the 10 mg dose group, fatal adverse events were reported for 5 subjects (3.1%) with no preferred term reported for more than 1 subject. In the 100 mg group, fatal adverse events were reported for 6 subjects (3.7%); all events occurred in 1 subject except cardio-respiratory arrest (2 subjects [1.2%]).

Combination Therapy Studies

No fatal adverse events were reported for subjects treated with tarlatamab combination therapy in Studies 20160323 Part C (b) (4)

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

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Table 44. Applicant – Fatal Adverse Events by Preferred Term – Monotherapy – Studies 20200491, 20200040 and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)

	Study 20160323 and 20200491		Overall Studies
Preferred Term	1->10 mg (N = 160) n (%)	1->100 mg (N = 163) n (%)	(b) (4)
Number of subjects reporting treatment-emergent fatal adverse events	5 (3.1)	6 (3.7)	
Aspiration	1 (0.6)	1 (0.6)	
Cardio-respiratory arrest	0 (0.0)	2 (1.2)	
Neuroendocrine carcinoma of prostate	0 (0.0)	0 (0.0)	
Pneumonia	1 (0.6)	0 (0.0)	
Respiratory failure	1 (0.6)	0 (0.0)	
COVID-19	0 (0.0)	1 (0.6)	
Cardiac arrest	0 (0.0)	1 (0.6)	
Coronavirus infection	0 (0.0)	1 (0.6)	
Metastases to central nervous system	0 (0.0)	0 (0.0)	
Pancreatic carcinoma metastatic	0 (0.0)	0 (0.0)	
Prostate cancer	0 (0.0)	0 (0.0)	
Prostate cancer metastatic	0 (0.0)	0 (0.0)	
Pulmonary embolism	1 (0.6)	0 (0.0)	
Respiratory acidosis	1 (0.6)	0 (0.0)	

MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in the safety analysis set; n = number of subjects with observed data
1->10 mg includes Study 20160323 cohorts 8 and 32 and Study 20200491 1->10 mg (Part 1 randomized arm, Part 2, and Part 3); 1->100 mg includes Study 20160323 cohorts 10, 30, 11 (tarlatamab + dexamethasone), and 34 (24-hr outpatient) and Study 20200491 1->100 mg (Part 1 randomized arm); Overall Subjects includes all subjects who received tarlatamab as a monotherapy.
Coded using MedDRA version 26.1.
Events of small cell lung cancer/disease progression are excluded.
Source: ISS Table 14-6.2.13

Safety Update as of 02 October 2023

Monotherapy Studies

Analysis of adverse events for the Monotherapy Safety Analysis Set were generally consistent between the initial ISS analysis and 90-day Safety Update. Overall, as of 02 October 2023, fatal adverse events were reported for 24 subjects (5.0%) treated with tarlatamab monotherapy (Table 45). (b) (4)

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(b) (4)

For the 10 mg target dose, fatal adverse events were reported for 2 additional subjects since the initial ISS analysis, for a total of 7 subjects (3.7%). As of 02 October 2023, fatal adverse events were reported in > 1 subject for the preferred term of pneumonia (2 subjects). This is in contrast to the initial ISS analysis, where no preferred term was reported for > 1 subject.

For the 100 mg target dose, fatal adverse events were reported for 1 additional subject since the initial ISS analysis, for a total of 7 subjects (4.3%). Consistent with the initial ISS analysis, the only fatal adverse events by preferred term reported for > 1 subject was cardio-respiratory arrest (2 subjects).

Subject-level details for the additional subjects with fatal adverse events are provided in Section 2.1.3.1 90-Day Safety Update.

Combination Therapy Studies

No fatal adverse events were reported for subjects treated with tarlatamab combination therapy in Study 20160323 Part C as of the data cutoff date for this report. (b) (4)

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Reference ID: 5382024

Table 45. Applicant – Fatal Adverse Events by Preferred Term – Monotherapy – Studies 20200491, 20200040 and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set) 90-Day Safety Update

	Study 20160323 and 20200491		Overall Studies
Preferred Term	1->10 mg (N = 187) n (%)	1->100 mg (N = 163) n (%)	(b) (4)
Number of subjects reporting treatment-emergent fatal adverse events	7 (3.7)	7 (4.3)	
Neuroendocrine carcinoma of prostate	0 (0.0)	0 (0.0)	
Pneumonia	2 (1.1)	0 (0.0)	
Aspiration	1 (0.5)	1 (0.6)	
Cardio-respiratory arrest	0 (0.0)	2 (1.2)	
Neuroendocrine cancer of the prostate metastatic	0 (0.0)	0 (0.0)	
Respiratory failure	1 (0.5)	0 (0.0)	
COVID-19	0 (0.0)	1 (0.6)	
Cardiac arrest	0 (0.0)	1 (0.6)	
Coronavirus infection	0 (0.0)	1 (0.6)	
Metastases to central nervous system	0 (0.0)	0 (0.0)	
Myocardial infarction	1 (0.5)	0 (0.0)	
Prostate cancer	0 (0.0)	0 (0.0)	
Prostate cancer metastatic	0 (0.0)	0 (0.0)	
Pulmonary embolism	1 (0.5)	0 (0.0)	
Respiratory acidosis	1 (0.5)	0 (0.0)	
Septic shock	0 (0.0)	1 (0.6)	

The safety analysis set is defined as all subjects who receive at least 1 dose of tarlatamab.
N = Number of subjects in analysis set. n = Number of subjects with observed data. eIV = Extended IV. hr = Hour. Q3W = Every 3 weeks.
1->10 mg includes study 20160323 cohorts 8, 32 and 35, and study 20200491 1->10 mg (part 1 randomized arm, part 2, and part 3); 1->100 mg includes study 20160323 cohorts 10, 30, 11 (tarlatamab + dexamethasone), and 34 (24-hr outpatient) and study 20200491 1->100 mg (part 1 randomized arm); Overall Subjects includes all subjects who received tarlatamab as a monotherapy.
Coded using MedDRA version 26.1.
Events of small cell lung cancer/disease progression are excluded.
Source: 90 DSU ISS Table 14-6.2.13

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Reference ID: 5382024

The Applicant's Position:

Review of fatal adverse events across the tarlatamab clinical development program as of the data cutoff dates did not identify any meaningful trends suggesting a causal association between tarlatamab use and fatalities.

The FDA's Assessment:

FDA confirmed the information above and reviewed all narratives for on-treatment deaths in the pooled safety population. There were 22 fatal events which were attributed to disease progression. Narratives were provided for 10 patients who had fatal adverse events not due to disease progression who were treated with tarlatamab at the recommended dose of 10 mg; 5 of these events occurred more than 30 days after discontinuing study therapy (all n=1, pneumonia, necrotizing pneumonia, dyspnea, hepatic failure and myocardial infarction).

The narratives for the five patients with on-treatment deaths not due to disease progression that were within 30 days of discontinuation of study treatment are reviewed in further detail below.

Table 46 FDA Analysis of Treatment-Emergent Deaths in Study 20200491 and Study 20160323

Patient ID	Brief Narrative (Bolded AE is the condition to which the investigator attributed the patient's death)	FDA's Assessment of Causality
(b) (6)	This was a 64 year old male with a history of chronic obstructive pulmonary disease (COPD) who developed Grade 3 CRS on Cycle 1 day 1 (after their 1 mg step dose) and was also diagnosed with pneumonitis at a similar time. The patient had marked respiratory deterioration 2 to 3 days after their last dose of tarlatamab (C1D1), requiring high flow oxygen. The patient died 6 days after their last dose of the study treatment, due to **Grade 5 respiratory failure.**	Given the history of COPD, decreased baseline pulmonary reserve, radiation pneumonitis, pulmonary embolism and the required use of supplemental oxygen this event is consistent with respiratory failure, possibly due to pneumonitis.
(b) (6)	This was a 74 year old male who developed Grade 5 lung infection on Day 21 of treatment. The patient's last dose of treatment was C1D15. Adverse events that	No additional details were available and in the absence of additional information we defer to the

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Patient ID	Brief Narrative (Bolded AE is the condition to which the investigator attributed the patient's death)	FDA's Assessment of Causality
	occurred within a +/- 7-day window of the onset of the SAE included flank pain (Grade 1), and nausea (Grade 1). Concomitant medications taken at the onset of the pneumonia and up to 3 days prior to event onset included: benzydamine hydrochloride, calcium carbonate;colecalciferol, cough and cold preparations, dexamethasone, erdosteine, ferrous sulfate, glimepiride, levofloxacin, magnesium oxide, megestrol acetate, metformin hydrochloride, metoclopramide hydrochloride, naloxone hydrochloride;oxycodone hydrochloride, oxycodone hydrochloride, paracetamol, sodium bicarbonate, sodium chloride, and teneligliptin hydrobromide. The patient died on Day 21 from **Grade 5 lung infection.**	Applicant's attribution of death due to an adverse event of lung infection due to pneumonia.
(b) (6)	The patient was a 53 year old female developed Grade 2 pyrexia and chills starting on Day 1 which resolved, Grade 1 cytokine release syndrome on Day 2 which resolved and recurred on Day 10. The patient subsequently developed Grade 3 fatigue and malaise on Day 7 which resolved but was considered a serious adverse event for which the patient was hospitalized. The patient had high CRP level (53.5 mg/L) on Day 17. Concomitant medications taken at the onset of the pulmonary embolism and up to 3 days prior to event onset included alprazolam, budesonide, calcium carbonate, colecalciferol, dexamethasone, formoterol, magnesium aspartate, paracetamol, phosphorus, potassium gluconate, propranolol hydrochloride, protein, sodium chloride, and tinzaparin. The patient died	The history and hospitalization are consistent with Grade 5 pulmonary embolism.

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.

Patient ID	Brief Narrative (Bolded AE is the condition to which the investigator attributed the patient's death)	FDA's Assessment of Causality
	from **Grade 5 pulmonary embolism** on Day 20 and 5 days after the last treatment dose.	
(b) (6)	The patient was a 70-year-old male received his last dose of treatment on Day 16 and on Day 17 the patient developed Grade 5 respiratory acidosis which was considered a serious adverse event. The patient had a high bicarbonate level of 30 mmol/L and high chloride level (106 mmol/L) on laboratory assessment. Adverse events that occurred within a +/- 7-day window of the onset of the SAE included Grade 2 dyspnea. Concomitant medications taken at the onset of the respiratory acidosis and up to 3 days prior to event onset included dexamethasone, and sodium chloride. The patient died on Day 17 from **Grade 5 respiratory acidosis.**	The history and hospitalization are consistent with Grade 5 respiratory acidosis.
(b) (6)	This patient was a 68-year-old male who died on Day 2 of treatment from Grade 5 broncoaspiration. Adverse events that also occurred within the onset of the SAE included Grade 3 asthenia, Grade 2 balance disorder, Grade 2 cytokine release syndrome, and Grade 1 hyperuricaemia. Concomitant medications taken at the onset of the aspiration and up to 3 days prior to event onset included dexamethasone, enalapril, intravenous solutions, levothyroxine, midazolam, morphine, simvastatin, tinzaparin, and urea. The patient died on Day 2 after receiving treatment from **Grade 5 bronchoaspiration.**	The history and hospitalization are consistent with Grade 5 bronchoaspiration.

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Reference ID: 5382024

Serious Adverse Events

Data:
The incidence of serious adverse events in the monotherapy studies that occurred in ≥ 1% of subjects at the doses of 10 and 100 mg are shown in Table 47.

The incidence of serious adverse events was generally lower across the combination therapy studies (25.0% to 64.3%) compared with monotherapy (59.3%); the most frequently reported serious adverse event with combination therapy was CRS (ISS Tables 14-6.2.5 and 14-6.2.6).

In Study 20200491 alone, serious adverse events were reported for 134 subjects (60.9%) overall (58 subjects [58.6%] in the 10 mg target dose group in Part 1 and Part 2, 61 subjects [70.1%] in the 100 mg target dose group, and 15 subjects [44.1%] in the Part 3 modified safety monitoring 10 mg target dose group) (Table 48).

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Reference ID: 5382024

Table 47. Applicant – Serious Adverse Events by Preferred Term (Occurring in at Least 1% of Subjects Overall) – Monotherapy – Studies 20200491, 20200040 and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)

	Studies 20160323 and 20200491		Overall Studies
			(b) (4)
Preferred Term	1->10 mg (N = 160) n (%)	1->100 mg (N = 163) n (%)	
Number of subjects reporting treatment-emergent serious adverse events	87 (54.4)	103 (63.2)	
Cytokine release syndrome	37 (23.1)	56 (34.4)	
Pyrexia	7 (4.4)	8 (4.9)	
Pneumonia	5 (3.1)	6 (3.7)	
Immune effector cell-associated neurotoxicity syndrome	4 (2.5)	10 (6.1)	
Hyponatraemia	4 (2.5)	7 (4.3)	
Fatigue	3 (1.9)	2 (1.2)	
Confusional state	0 (0.0)	4 (2.5)	
Dyspnoea	1 (0.6)	1 (0.6)	
COVID-19	1 (0.6)	5 (3.1)	
Encephalopathy	0 (0.0)	6 (3.7)	
Device related infection	3 (1.9)	2 (1.2)	
Neutropenia	1 (0.6)	3 (1.8)	
Pneumonia aspiration	2 (1.3)	1 (0.6)	
Superior vena cava syndrome	3 (1.9)	2 (1.2)	

Notes: The safety analysis set is defined as all subjects who receive at least 1 dose of tarlatamab.
1->10 mg includes Study 20160323 cohorts 8 and 32 and Study 20200491 1->10 mg (Part 1 randomized group, Part 2, and Part 3).
1->100 mg includes Study 20160323 cohorts 10, 30, 11 (tarlatamab + dexamethasone), and 34 (24-hr outpatient) and Study 20200491 1->100 mg (Part 1 randomized group).
Overall subjects includes all subjects who received tarlatamab as a monotherapy at any dose: £ 3 mg (N = 35), 30 mg (N = 8), extended intravenous (N = 32), and alternative dosing cohorts (N = 19) in Study 20160323; 10 mg in Studies 20200491 (N = 133) and 20160323 (N = 27); and 100 mg in Studies 20200491 (N = 87), 20160323 (N = 76), (b) (4)
Adverse events were coded using Medical Dictionary for Regulatory Activities version 26.0.
Events of small cell lung cancer/disease progression are excluded.
Source: ISS Table 14-6.2.5

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Reference ID: 5382024

Table 48. Applicant – Subject Incidence of Serious Treatment-emergent Adverse Events by System Organ Class and Preferred Term for > 1% of Subjects Overall (Safety Analysis Set) (Study 20200491 Primary Analysis)

System Organ Class Preferred Term	1->10 mg (N = 99) n (%)	1->100 mg (N = 87) n (%)	1->10 mg Modified Safety Monitoring (N = 34) n (%)	Overall (N = 220) n (%)
Number of subjects with serious treatment-emergent adverse events	58 (58.6)	61 (70.1)	15 (44.1)	134 (60.9)
Blood and lymphatic system disorders	3 (3.0)	3 (3.4)	1 (2.9)	7 (3.2)
Neutropenia	1 (1.0)	2 (2.3)	0 (0.0)	3 (1.4)
General disorders and administration site conditions	8 (8.1)	6 (6.9)	1 (2.9)	15 (6.8)
Pyrexia	6 (6.1)	5 (5.7)	0 (0.0)	11 (5.0)
Fatigue	1 (1.0)	1 (1.1)	1 (2.9)	3 (1.4)
Immune system disorders	26 (26.3)	31 (35.6)	5 (14.7)	62 (28.2)
Cytokine release syndrome	26 (26.3)	31 (35.6)	5 (14.7)	62 (28.2)
Infections and infestations	14 (14.1)	17 (19.5)	2 (5.9)	33 (15.0)
Pneumonia	4 (4.0)	5 (5.7)	0 (0.0)	9 (4.1)
COVID-19	1 (1.0)	5 (5.7)	0 (0.0)	6 (2.7)
Device related infection	3 (3.0)	2 (2.3)	0 (0.0)	5 (2.3)
Respiratory tract infection	3 (3.0)	0 (0.0)	1 (2.9)	4 (1.8)
Pneumonia aspiration	1 (1.0)	1 (1.1)	1 (2.9)	3 (1.4)
Metabolism and nutrition disorders	6 (6.1)	4 (4.6)	1 (2.9)	11 (5.0)
Hyponatraemia	4 (4.0)	3 (3.4)	0 (0.0)	7 (3.2)
Nervous system disorders	8 (8.1)	14 (16.1)	4 (11.8)	26 (11.8)
Immune effector cell-associated neurotoxicity syndrome	2 (2.0)	8 (9.2)	2 (5.9)	12 (5.5)
Respiratory, thoracic and mediastinal disorders	6 (6.1)	5 (5.7)	4 (11.8)	15 (6.8)
Pneumonitis	0 (0.0)	2 (2.3)	1 (2.9)	3 (1.4)
Vascular disorders	1 (1.0)	2 (2.3)	1 (2.9)	4 (1.8)
Superior vena cava syndrome	1 (1.0)	2 (2.3)	1 (2.9)	4 (1.8)

-> = step dose to target dose (eg, 1 -> 10 mg = 1 mg step dose to 10 mg target dose)
The safety analysis set includes all subjects who received at least 1 dose of tarlatamab.
Adverse events were coded using Medical Dictionary for Regulatory Activities version 26.0.
Events of small cell lung cancer/disease progression are excluded.
Data snapshot date: 01 March 2024; data cutoff date: 27 June 2023
Source: Table 14-6.2.6 of Study 20200491

Safety Update as of 02 October 2023

The incidence of serious adverse events in the monotherapy studies that occurred in ≥ 1% of subjects at the doses of 10 and 100 mg are shown in Table 49.

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Overall, as of 02 October 2023, serious adverse events were reported for 289 subjects (59.7%) treated with tarlatamab monotherapy. Consistent with the initial ISS analysis, the most frequently reported (≥ 3% of subjects) serious adverse events by preferred term included CRS (26.9%), pneumonia (4.1%), and pyrexia (3.9%).

For the 10 mg target dose, serious adverse events were reported for 104 subjects (55.6%) as of 02 October 2023. Consistent with the initial ISS analysis, the most frequently reported (≥ 3% of subjects) serious adverse events by preferred term included CRS (23.5%), pneumonia (3.7%), pyrexia (3.7%); in contrast, hyponatremia was also reported in ≥ 3% of subjects (3.2%).

For the 100 mg target dose, serious adverse events were reported for 103 subjects (63.2%) as of 02 October 2023. Consistent with the initial ISS analysis, the most frequently reported (≥ 3% of subjects) serious adverse events by preferred term were CRS (34.4%), ICANS (6.1%), pyrexia (4.9%); hyponatremia (4.3%); pneumonia and encephalopathy (3.7% each); and COVID-19 (3.1%).

In the combination therapy studies, the subject incidence of serious adverse events ranged from 43.6% to 56.5% across studies, compared to 59.5% treated with tarlatamab monotherapy. The most frequently reported serious adverse event was CRS (90 DSU ISS Table 14-6.2.6).

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Reference ID: 5382024

Table 49. Applicant – Serious Adverse Events by Preferred Term (Occurring in at Least 1% of Subjects Overall) – Monotherapy – Studies 20200491, 20200040 and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)
90-Day Safety Update

	Study 20160323 and 20200491		Overall Studies
Preferred Term	1->10 mg (N = 187) n (%)	1->100 mg (N = 163) n (%)	(b) (4)
Number of subjects reporting treatment-emergent serious adverse events	104 (55.6)	103 (63.2)	
Cytokine release syndrome	44 (23.5)	56 (34.4)	
Pneumonia	7 (3.7)	6 (3.7)	
Pyrexia	7 (3.7)	8 (4.9)	
Hyponatraemia	6 (3.2)	7 (4.3)	
Immune effector cell-associated neurotoxicity syndrome	4 (2.1)	10 (6.1)	
Fatigue	3 (1.6)	2 (1.2)	
Confusional state	0 (0.0)	4 (2.5)	
Encephalopathy	1 (0.5)	6 (3.7)	
COVID-19	1 (0.5)	5 (3.1)	
Dyspnoea	1 (0.5)	1 (0.6)	
Neutropenia	1 (0.5)	4 (2.5)	
Pneumonia aspiration	2 (1.1)	2 (1.2)	
Superior vena cava syndrome	4 (2.1)	2 (1.2)	
Delirium	1 (0.5)	3 (1.8)	
Device related infection	3 (1.6)	2 (1.2)	

N = Number of subjects in analysis set. n = Number of subjects with observed data. eIV = Extended IV. hr = Hour. Q3W = Every 3 weeks.
1->10 mg includes study 20160323 cohorts 8, 32 and 35, and study 20200491 1->10 mg (part 1 randomized arm, part 2, and part 3); 1->100 mg includes study 20160323 cohorts 10, 30, 11 (tarlatamab + dexamethasone), and 34 (24-hr outpatient) and study 20200491 1->100 mg (part 1 randomized arm); Overall Subjects includes all subjects who received tarlatamab as a monotherapy.
Coded using MedDRA version 26.1.
Events of small cell lung cancer/disease progression are excluded.
Source: 90-daySU ISS Table 14-6.2.5

The Applicant's Position:

Overall, serious adverse events were reported for (b) (4) subjects (b) (4) treated with tarlatamab monotherapy; the most common (≥ 3% of subjects) serious adverse events were CRS (b) (4) pyrexia (b) (4) pneumonia (b) (4), hyponatremia (b) (4), and ICANS (b) (4) The incidences of the most common serious adverse events were generally comparable between the dose groups except for CRS, ICANS, and encephalopathy, which occurred more frequently with 100 mg than

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10 mg (Table 47). The incidence and most frequently occurring serious adverse events with the 90-day safety update were similar to those seen at the initial ISS analysis.

The FDA's Assessment:

FDA performed an independent analysis of the incidence of SAEs in the pooled safety population of patients who received tarlatamab at the recommended dose of 10 mg in Studies 20200491 and 20160323. Refer to Table 50 for FDA's analysis of SAEs in the pooled safety population. SAEs occurred in 108 patients (58%). The most frequently reported SAEs (≥ 3% of patients) were cytokine release syndrome (24%), pneumonia (6%), pyrexia (3.7%), and hyponatremia 3.7%.

Table 50. FDA Analysis of Serious Adverse Events ≥3%

	Pooled Studies 20200491 and 20160323 N = 187 N (%)
Patients with SAEs	108 (58)
Cytokine Release Syndrome	44 (24)
Pneumonia	11 (6)
Pyrexia	7 (3.7)
Hyponatremia	7 (3.7)

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

The subject incidence of adverse events leading to discontinuation of tarlatamab that occurred in ≥ 2 subjects in the Monotherapy Safety Analysis Set is provided in Table 51.

Adverse events leading to discontinuation of tarlatamab were reported for 32 subjects (7.0%) treated with tarlatamab monotherapy. Overall, the most frequently reported (≥ 2 subjects) adverse events leading to discontinuation of tarlatamab by preferred term were CRS and pneumonia (0.7% each); and COVID-19 pneumonia, dysphagia, encephalopathy, ICANS, and decreased neutrophil count (0.4% each). By dose, adverse events leading to discontinuation of

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tarlatamab were reported for 11 subjects (6.9%) and 13 subjects (8.0%) treated with 10 mg and 100 mg, respectively.

Results for adverse events leading to treatment interruption or discontinuation in the combination studies were generally comparable to those seen with monotherapy. See Section 2.1.5.1.2 and 2.1.5.2.2 of Module 2.7.4, SCS.

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Table 51. Applicant – Adverse Events Leading to Discontinuation of Tarlatamab by Preferred Term (Occurring in at Least 2 Subjects Overall) – Monotherapy – Studies 20200491, 20200040 and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)

	Study 20160323 and 20200491		Overall Studies (b) (4)
Preferred Term	1->10 mg (N = 160) n (%)	1->100 mg (N = 163) n (%)	
Number of subjects reporting treatment-emergent adverse events leading to discontinuation of tarlatamab	11 (6.9)	13 (8.0)	
Cytokine release syndrome	1 (0.6)	1 (0.6)	
Pneumonia	0 (0.0)	1 (0.6)	
COVID-19 pneumonia	1 (0.6)	1 (0.6)	
Dysphagia	0 (0.0)	2 (1.2)	
Encephalopathy	0 (0.0)	2 (1.2)	
Immune effector cell-associated neurotoxicity syndrome	0 (0.0)	2 (1.2)	
Neutrophil count decreased	0 (0.0)	2 (1.2)	

MedDRA = Medical Dictionary for Regulatory Activities
1->10 mg includes Study 20160323 cohorts 8 and 32 and Study 20200491 1->10 mg (Part 1 randomized arm, Part 2, and Part 3); 1->100 mg includes Study 20160323 cohorts 10, 30, 11 (tarlatamab + dexamethasone), and 34 (24-hr outpatient) and Study 20200491 1->100 mg (Part 1 randomized arm); Overall Subjects includes all subjects who received tarlatamab as a monotherapy.
Coded using MedDRA version 26.1.
Events of small cell lung cancer/disease progression are excluded.
Source: ISS Table 14-6.2.21

Safety Update as of 02 October 2023

The subject incidence of adverse events leading to discontinuation of tarlatamab that occurred in ≥ 2 subjects in the Monotherapy Safety Analysis Set is provided in Table 52.

Overall, as of the 02 October 2023 data cut off date, adverse events leading to discontinuation of tarlatamab were reported for (b) (4) subjects (b) (4) treated with tarlatamab monotherapy, including 13 subjects (7.0%) treated with 10 mg tarlatamab and 13 subjects (8.0%) treated with 100 mg tarlatamab. Consistent with the initial ISS analysis, overall, the most frequently reported (≥ 2 subjects) adverse events leading to discontinuation of tarlatamab by preferred term included CRS (0.8%); pneumonia (0.6%); COVID-19 pneumonia, decreased neutrophil count, dysphagia, encephalopathy, and ICANS (0.4% each); in contrast, tumor lysis syndrome (0.4%) was also reported for ≥ 2 subjects. For the 10 mg target dose, the most frequently reported (≥ 2 subjects) adverse events leading to discontinuation of tarlatamab by preferred term were CRS and tumor lysis syndrome (1.1% each) compared with CRS and COVID-19

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pneumonia (0.6% each) reported for the initial ISS analysis. For the 100 mg target dose, the most frequently reported (≥ 2 subjects) adverse events leading to discontinuation of tarlatamab by preferred term remained consistent with the initial ISS analysis and included decreased neutrophil count, dysphagia, encephalopathy, and ICANS (1.2% each).

(b) (4)

Table 52. Applicant – Adverse Events Leading to Discontinuation of Tarlatamab by Preferred Term (Occurring in at Least 2 Subjects Overall) – Monotherapy – Studies 20200491, 20200040 and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)
90-Day Safety Update

	Study 20160323 and 20200491		Overall Studies (b) (4)
Preferred Term	1->10 mg (N = 187) n (%)	1->100 mg (N = 163) n (%)	
Number of subjects reporting treatment-emergent adverse events leading to discontinuation of tarlatamab	13 (7.0)	13 (8.0)	
Cytokine release syndrome	2 (1.1)	1 (0.6)	
Pneumonia	0 (0.0)	1 (0.6)	
COVID-19 pneumonia	1 (0.5)	1 (0.6)	
Dysphagia	0 (0.0)	2 (1.2)	
Encephalopathy	0 (0.0)	2 (1.2)	
Immune effector cell-associated neurotoxicity syndrome	0 (0.0)	2 (1.2)	
Neutrophil count decreased	0 (0.0)	2 (1.2)	
Tumour lysis syndrome	2 (1.1)	0 (0.0)	

eIV = extended intravenous; MedDRA = Medical Dictionary for Regulatory Activities; Q3W = every 3 weeks
The safety analysis set is defined as all subjects who receive at least 1 dose of tarlatamab.
1->10 mg includes Study 20160323 cohorts 8 and 32 and Study 20200491 1->10 mg (Part 1 randomized arm, Part 2, and Part 3); 1->100 mg includes Study 20160323 cohorts 10, 30, 11 (tarlatamab + dexamethasone), and 34 (24-hr outpatient) and Study 20200491 1->100 mg (Part 1 randomized arm); (b) (4) Overall Subjects includes all subjects who received tarlatamab as a monotherapy.
Coded using MedDRA version 26.1.
Events of small cell lung cancer/disease progression are excluded.
Source: 90-daySU ISS Table 14-6.2.21

The Applicant's Position:

The incidence of adverse events leading to discontinuation of tarlatamab was (b) (4) subjects treated with tarlatamab monotherapy). The 2 most common adverse events leading to

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treatment discontinuation were CRS and pneumonia [(b) (4)] each); all others occurred in 1 or 2 subjects each (ISS Table 14-6.2.21). The incidence and most frequently occurring events leading to discontinuation of tarlatamab with the 90-day safety update were similar to those seen at the initial ISS analysis.

The FDA's Assessment:

In FDA's analysis of the pooled safety population, adverse events leading to treatment discontinuation occurred in 13 patients (7%). Adverse reactions which resulted in permanent discontinuation of IMDELLTRA in >1% of patients included cytokine release syndrome (1.1 %) and tumor lysis syndrome (1.1%).

Dose Interruption/Reduction Due to Adverse Effects

Data:

Adverse events leading to dose reduction or interruption of tarlatamab were reported for 157 subjects (34.4) treated with tarlatamab monotherapy, with the following preferred terms reported for ≥ 2% of subjects: CRS (6.1%), COVID-19 (3.9%), neutropenia (2.8%), fatigue (2.6%), and pyrexia (2.0%) (ISS Table 14-6.2.17).

The incidence of adverse events leading to dose reduction or interruption of tarlatamab was lower in the monotherapy 10 mg group (49 subjects [30.6%]) than in the 100 mg group (71 subjects [43.6%]). The most frequently reported (³ 5% in either treatment group) adverse events leading to dose reduction or interruption of tarlatamab occurred at a lower incidence in the 10 mg group compared with the 100 mg group: CRS (3.8% vs 9.2%), COVID-19 (3.8% vs 6.1%), and neutropenia (0.6% vs 5.5%).

Safety Update as of 02 October 2023

Overall, adverse events leading to dose reduction or interruption of tarlatamab were reported for [(b) (4)] treated with tarlatamab monotherapy, including 57 subjects (30.5%) with SCLC treated with 10 mg tarlatamab and 71 subjects (43.6%) with SCLC treated with 100 mg tarlatamab. Consistent with the initial ISS analysis, overall, the most frequently reported (≥ 2% of subjects) adverse events leading to dose reduction or interruption of tarlatamab were CRS (5.8%), COVID-19 (3.9%), neutropenia (2.9%), and fatigue (2.7%).

The Applicant's Position:

The incidence of adverse events leading to dose reduction or interruption of tarlatamab was lower in the monotherapy 10 mg group (30.6%) than in the 100 mg group (43.6%). The most frequently reported adverse events leading to dose reduction or interruption of tarlatamab

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(CRS, COVID-19, and neutropenia) occurred at a lower incidence in the 10 mg group compared with the 100 mg group). The incidence and most frequently occurring events leading to dose reduction or interruption of tarlatamab with the 90-day safety update were similar to those seen at the initial ISS analysis.

The FDA's Assessment:

In FDA's analysis of the pooled safety population, adverse events leading to dose interruptions occurred in 55 patients (27%). The most frequently reported adverse events leading to dose interruptions in ≥2% of patients included fatigue (3.2%), cytokine release syndrome (2.7%) and respiratory tract infection (2.1%). All events were coded as dose reduced but based on the narratives, all were dose interruptions (dose reductions were not permitted).

Significant Adverse Events

Data:

In the monotherapy studies, grade ≥ 3 adverse events were reported with similar frequency overall (b) (4)) and in the 10 and 100 mg dose groups (63.1% and 64.4%, respectively) (Table 53). Overall, the most frequently reported (> 5% of subjects) grade ≥ 3 adverse events were anemia (7.4%), fatigue (6.3%), hyponatremia (6.1%), and decreased lymphocyte count (5.3%) (Table 13 of Module 2.7.4, SCS and ISS Table 14-6.2.9). Some of the grade ≥ 3 adverse events were reported at a lower frequency in the 10 mg group than in the 100 mg group, including neutropenia (3.1% vs 6.7%), CRS (1.3% vs 6.1%), and white blood cell count decreased (0.6% vs 4.3%). Lymphopenia occurred at a higher frequency in the 10 mg group (7.5%) than in the 100 mg group (3.1%). The types of grade ≥ 3 adverse events reported with combination therapy were generally similar to those reported for the monotherapy population (Section 2.1.2.2 of Module 2.7.4, Summary of Clinical Safety).

Safety Update as of 02 October 2023

The types of grade ≥ 3 adverse events for the Monotherapy Safety Analysis Set were generally consistent between the initial ISS analysis and 90-day Safety Update. Consistent with the initial ISS analysis, overall, the most frequently reported (≥ 5% of subjects) grade ≥ 3 adverse events by preferred term for subjects treated with tarlatamab monotherapy included anemia (7.2%), fatigue (6.4%), hyponatremia (6.6%), and decreased lymphocyte count (5.6%) (90DSU ISS Table 14-6.2.9). In contrast to the initial ISS analysis, lymphopenia (5.2%) was also reported for ≥ 5% of subjects.

For the 10 mg target dose, consistent with the initial ISS analysis, the most frequently reported

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(≥ 5% of subjects) grade ≥ 3 adverse events by preferred term for subjects treated with tarlatamab monotherapy were lymphopenia (8.0%); decreased lymphocyte count, anemia, and hyponatremia (6.4% each); and fatigue (5.9%).

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For the 100 mg target dose, consistent with the initial ISS analysis, the most frequently reported (≥ 5% of subjects) grade ≥ 3 adverse events by preferred term for subjects treated with tarlatamab monotherapy were neutropenia, anemia, fatigue, and hyponatremia (6.7% each); and CRS (6.1%).

The Applicant's Position:

The types of grade ≥ 3 adverse events reported for subjects with SCLC treated with tarlatamab at the 10 mg dose were generally similar to those reported for subjects treated at the 100 mg dose, although the incidences of certain grade ≥ 3 events (hyponatremia, neutropenia, and CRS) were higher in the 100 mg group than in the 10 mg group. The incidence of grade ≥ 3 adverse events with the 90-day safety update was similar to that seen in the initial ISS analysis.

The FDA's Assessment:

FDA's analysis of significant adverse events in the pooled population included CRS, neurologic toxicity including ICANS, and cytopenias, which are further described in section 8.2.5 of this review. Other significant adverse events included infections, hepatotoxicity and hypersensitivity which are included in the Warnings and Precaution section of the label.

Infections in the pooled safety population, including opportunistic infections, occurred in 41% of patients who received tarlatamab. Grade 3 or 4 infections occurred in 13% of patients. The most frequent infections were COVID-19 (9%, majority during the COVID-19 pandemic), urinary tract infection (10%), pneumonia (9%), respiratory tract infection (3.2%), and candida infection (3.2%).

Hepatotoxicity in the pooled safety population included elevated ALT occurring in 42% of patients with Grade 3 or 4 ALT elevation occurring in 2.1% of tarlatamab-treated patients. Elevated AST occurred in 44% of patients, with Grade 3 or 4 AST elevation occurring in 3.2%. Elevated bilirubin occurred in 15% of patients, with Grade 3 or 4 total bilirubin elevations occurring in 1.6% of patients.

Hypersensitivity was also added to the Warnings and Precautions section of the USPI as a potential risk. Clinical signs and symptoms of hypersensitivity may include, but are not limited to, rash and bronchospasm. There were 4 patients identified with hypersensitivity adverse events in the review of overall safety data (3 patients in the 100 mg dose group and 1 patient in the 10 mg dose group). The first patient received 10 mg on Cycle 4 Day 1 and 8 days later developed Grade 3 bronchospasm attributed to a mucous plug. The event resolved and no action was taken with tarlatamab. The second patient received 100 mg on Cycle 2 Day 15 and was subsequently hospitalized for maculopapular rash and treated with prednisolone, zeroveen, and betamethasone valerate. The rash resolved and no action was taken with

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tarlatamab. The third patient received his last dose of 100 mg on Cycle 1 Day 15 and 8 days later experienced symptoms such as cough, hemoptysis, tachycardia, desaturation at 65% and tachypnea at 35 respirations per minute. Despite oxygenation, the patient's general condition deteriorated rapidly. A life-threatening event of respiratory distress was diagnosed, and at the time of the event the patient died from progressive disease. The last patient experienced dyspnea, bronchospasm, and low oxygen saturation approximately 35 minutes after receiving Cycle 1 Day 8 dose of 100 mg, which was the last dose of tarlatamab. Symptoms resolved within 1 hour of receiving antihistamines and steroids.

Treatment-emergent Adverse Events and Adverse Reactions

Data:

Across the monotherapy studies, adverse events were reported for (b) (4) including 94.3% with at least 1 treatment-related adverse event. Grade ≥ 3 and serious adverse events were reported for 63.0% and 59.3% of subjects, respectively. Fatal adverse events were reported for 19 subjects (4.2%), which were treatment related for 2 subjects (0.4%).
Few subjects (7.0%) discontinued tarlatamab due to adverse events.

Results for the 10 and 100 mg dose were generally comparable to those for the overall monotherapy population and are shown in Table 53.

Results for combination therapy studies were generally similar to those for monotherapy and can be found in Table 10 of Module 2.7.4, SCS.

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Table 53. Applicant – Summary of Adverse Events – Monotherapy – Studies 20200491, 20200040 and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)

	Studies 20160323 and 20200491		Overall Studies (b) (4)
	1->10 mg (N = 160) n (%)	1->100 mg (N = 163) n (%)	
All treatment-emergent adverse events	159 (99.4)	163 (100.0)	
Grade ³ 2	145 (90.6)	157 (96.3)	
Grade ³ 3	101 (63.1)	105 (64.4)	
Grade ³ 4	28 (17.5)	24 (14.7)	
Serious adverse events	87 (54.4)	103 (63.2)	
Leading to dose interruption and/or reduction of tarlatamab	49 (30.6)	71 (43.6)	
Leading to discontinuation of tarlatamab	11 (6.9)	13 (8.0)	
Serious	7 (4.4)	11 (6.7)	
Nonserious	4 (2.5)	5 (3.1)	
Fatal adverse events	5 (3.1)	6 (3.7)	
Treatment-related treatment-emergent adverse events	149 (93.1)	156 (95.7)	
Grade ³ 2	115 (71.9)	131 (80.4)	
Grade ³ 3	50 (31.3)	65 (39.9)	
Grade ³ 4	11 (6.9)	9 (5.5)	
Serious adverse events	52 (32.5)	81 (49.7)	
Leading to dose interruption and/or reduction of tarlatamab	24 (15.0)	46 (28.2)	
Leading to discontinuation of tarlatamab	5 (3.1)	10 (6.1)	
Serious	3 (1.9)	8 (4.9)	
Nonserious	2 (1.3)	5 (3.1)	
Fatal adverse events	1 (0.6)	0 (0.0)	

1->10 mg includes Study 20160323 cohorts 8 and 32 and Study 20200491 1->10 mg (Part 1 randomized group, Part 2, and Part 3).
1->100 mg includes Study 20160323 cohorts 10, 30, 11 (tarlatamab + dexamethasone), and 34 (24-hr outpatient) and Study 20200491 1->100 mg (Part 1 randomized group).
Overall subjects includes all subjects who received tarlatamab as a monotherapy at any dose: £ 3 mg (N = 35), 30 mg (N = 8), extended intravenous (N = 32), and alternative dosing cohorts (N = 19) in Study 20160323; 10 mg in Studies 20200491 (N = 133) and 20160323 (N = 27); and 100 mg in Studies 20200491 (N = 87), 20160323 (N = 76), (b) (4)
Event with missing relationship is considered to be treatment related.
Events of small cell lung cancer/disease progression are excluded.
Source: ISS Table 14-6.1.1

Adverse drug reactions were determined to be those events that were reported in ³ 15% of subjects with SCLC who were treated with tarlatamab monotherapy at a dose of 10 mg Q2W

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from Parts 1, 2, and 3 of Study 20200491. A medical review focused on common, grade ≥ 3, and serious adverse events was conducted. Frequently occurring adverse events were assessed, considering expected incidence in patients with underlying diseases to establish an initial threshold. Additional factors, including temporal association, biological plausibility, and medical judgment, were considered to confirm the final adverse drug reactions.

The resulting list of adverse drug reactions for tarlatamab are summarized in the table below.

Table 54. Applicant – Adverse Reactions (≥ 15%) in Subjects with SCLC Who Received Tarlatamab 10 mg in Study 20200491[a]

Adverse Reaction	Tarlatamab 10 mg in Study 20200491 (N = 133)	
	Any Grade[b] (%)	Grade 3 or 4 (%)
Blood and lymphatic system disorders		
Anemia	28.6	7.5
Gastrointestinal disorders		
Constipation	29.3	0.8
Nausea	16.5	1.5
General disorders and administration site conditions		
Pyrexia	36.8	0.0
Asthenia	24.8	5.3
Fatigue	24.1	5.3
Immune system disorders		
Cytokine release syndrome[c]	52.6	0.8
Metabolism and nutrition disorders		
Decreased appetite	33.8	2.3
Hyponatremia	17.3	6.0
Nervous system disorders		
Dysgeusia	30.1	0.0
Respiratory, thoracic and mediastinal disorders		
Dyspnea	15.8	1.5

[a] Adverse reactions occurring at a frequency of < 15% were neutropenia, neutrophil count decreased, immune effector cell-associated neurotoxicity syndrome, neurotoxicity, tremor, confused state, delirium encephalopathy, seizure and ataxia.
[b] Grading defined by NCI CTCAE version 5.0
[c] Based on American Society for Transplantation and Cellular Therapy (ASTCT) (2019)

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Safety Update as of 02 October 2023

Analysis of treatment-emergent adverse events for the Monotherapy Safety Analysis Set were generally consistent between the initial ISS analysis and 90-day Safety Update. Across the monotherapy studies, adverse events were reported for (b) (4) including 94.4% with at least 1 treatment-related adverse event. Grade ≥ 3 and serious adverse events were reported for 63.4% and 59.7% of subjects, respectively. Fatal adverse events were reported for 24 subjects (5.0%), which were treatment related for 2 subjects (0.4%). A total of 7.2% of subjects discontinued tarlatamab due to adverse events (Table 55).

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Reference ID: 5382024

Table 55. Applicant – Summary of Adverse Events – Monotherapy – Studies 20200491, 20200040 and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)
90-Day Safety Update

	Study 20160323 and 20200491		Overall Studies (b) (4)
	1->10 mg (N = 187) n (%)	1->100 mg (N = 163) n (%)	
All treatment-emergent adverse events	186 (99.5)	163 (100.0)	
Grade ≥ 2	170 (90.9)	159 (97.5)	
Grade ≥ 3	118 (63.1)	107 (65.6)	
Grade ≥ 4	36 (19.3)	26 (16.0)	
Serious adverse events	104 (55.6)	103 (63.2)	
Leading to dose interruption and/or reduction of tarlatamab	57 (30.5)	71 (43.6)	
Leading to discontinuation of tarlatamab	13 (7.0)	13 (8.0)	
Serious	9 (4.8)	11 (6.7)	
Non-serious	4 (2.1)	6 (3.7)	
Fatal adverse events	7 (3.7)	7 (4.3)	
Treatment-related treatment-emergent adverse events	175 (93.6)	156 (95.7)	
Grade ≥ 2	137 (73.3)	133 (81.6)	
Grade ≥ 3	63 (33.7)	67 (41.1)	
Grade ≥ 4	14 (7.5)	9 (5.5)	
Serious adverse events	62 (33.2)	81 (49.7)	
Leading to dose interruption and/or reduction of tarlatamab	27 (14.4)	46 (28.2)	
Leading to discontinuation of tarlatamab	6 (3.2)	10 (6.1)	
Serious	4 (2.1)	8 (4.9)	
Non-serious	2 (1.1)	6 (3.7)	
Fatal adverse events	1 (0.5)	0 (0.0)	

ASTCT = American Society for Transplantation and Cellular Therapy; CTCAE = Common Terminology Criteria for Adverse Events CRS = cytokine release syndrome; eIV = extended intravenous; ICANS = immune effector cell-associated neurotoxicity syndrome; Q3W = every 3 weeks
The safety analysis set is defined as all subjects who receive at least 1 dose of tarlatamab.
1->10 mg includes Study 20160323 cohorts 8 and 32 and Study 20200491 1->10 mg (Part 1 randomized arm, Part 2, and Part 3); 1->100 mg includes Study 20160323 cohorts 10, 30, 11 (tarlatamab + dexamethasone), and 34 (24-hr outpatient) and Study 20200491 1->100 mg (Part 1 randomized arm); Overall Subjects includes all subjects who received tarlatamab as a monotherapy.
Study 20200491: CRS and ICANS events graded using ASTCT 2019. All other events graded using CTCAE v5.0.
Studies 20160323 (b) (4) If relevant information was available, CRS events converted from Lee et al, 2014 to ASTCT 2019. Similarly, all other events converted from CTCAE v4.0 to v5.0.
Event with missing relationship is considered treatment related.
Events of small cell lung cancer/disease progression are excluded.
Source: 90-daySU ISS Table 14-6.1.1

The Applicant's Position:

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In the monotherapy studies, the subject incidence of adverse events, grade 3 and higher adverse events, and adverse events leading to discontinuation of tarlatamab were comparable between the 10 and 100 mg doses. The incidences of serious adverse events and adverse events leading to dose interruption or reduction were slightly lower for subjects treated with 10 mg compared with subjects treated with 100 mg (Table 53).

Adverse events that have been determined by the Sponsor to be associated with tarlatamab, based on the totality of the data, are considered to be adverse drug reactions. The identified adverse drug reactions are anemia, neutropenia, constipation, nausea, pyrexia, asthenia, fatigue, CRS, neutrophil count decreased, decreased appetite, hyponatremia, dysgeusia, ICANS, neurotoxicity, tremor, confusional state, delirium, and dyspnea.

The FDA's Assessment:

FDA's analysis of treatment emergent adverse events in the pooled safety population is provided in Table 13.

The most common (>20%) adverse reactions were cytokine release syndrome (55%), fatigue (51%), dysgeusia (36%), pyrexia (36%), decreased appetite (34%), constipation (30%), musculoskeletal pain (30 %), anemia (27%) and nausea (22%).

A total of 393 previously unreported adverse events were identified in 111 patients following 100% SDR/SDV of adverse events in Study 20200491. As a result of the revised 90-day update safety analysis, twenty-eight additional treatment-emergent adverse events were identified in 20 patients treated with tarlatamab at the 10 mg dose. Out of 28 adverse events, 14 Grade 3 adverse events were reported for 10 patients (7.5%). This included lymphopenia (n=4), general health deterioration (n=2), activated partial thromboplastin time prolonged, acute kidney injury, anemia, back pain, cholestasis, decreased appetite, hyperglycemia, and hyponatremia (n=1 in 1 patient each). Two serious adverse events of anemia (one Grade 3 and one Grade 2) were reported for 1 patient treated with tarlatamab monotherapy at the recommended dose of 10 mg.

The overall incidence of any grade CRS increased from 101 patients (54%) to 103 patients (55%) in the 10 mg dose group with no changes in ≥Grade 3 CRS events. The 2 new CRS events in the 10 mg dose group were both Grade 1 and nonserious events. There were no changes in ≥ Grade 2 CRS events, serious CRS events, or CRS events leading to discontinuation of tarlatamab. There were 2 new cases of ICANS, both were Grade 1 events. Overall, there were no changes in ≥Grade 2 ICANS events, serious ICANS, or ICANS events leading to discontinuation of tarlatamab. In addition, there were 6 new cases of neurologic toxicities, peripheral sensory neuropathy, leukoencephalopathy, insomnia (n=2 each), muscular weakness, leukoencephalopathy and dysgeusia (n=1 each), which were all low grade (grade 1 or 2).

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Overall, there was no change in ≥Grade 3 neurological events, serious events, or events leading to discontinuation of tarlatamab.

Table 13. Adverse Reactions (≥ 15%) in Patients with ES-SCLC Who Received IMDELLTRA in Study DeLLphi-300 and Study DeLLphi-301

Adverse Reaction	IMDELLTRA[a] (N = 187)	
	Any Grade (%)	Grade 3 or 4 (%)
Immune system disorders		
Cytokine release syndrome[b]	55	1.6
General disorders and administration site conditions		
Fatigue[c]	51	10
Pyrexia	36	0
Nervous system disorders		
Dysgeusia	36	0
Metabolism and nutrition disorders		
Decreased appetite	34	2.7
Nausea	22	1.6
Gastrointestinal disorders		
Constipation	30	0.5
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[d]	30	1.1
Blood and Lymphatic System Disorders		
Anemia	27	6
Respiratory, thoracic and mediastinal disorders		
Dyspnea[e]	17	2.1
Cough	17	0

[a] Graded using CTCAE version 4.0 and version 5.0.
[b] Based on American Society for Transplantation and Cellular Therapy (ASTCT) 2019.
[c] Includes fatigue and asthenia.
[d] Includes myalgia, arthralgia, back pain, pain in extremity, neck pain, musculoskeletal chest pain, non-cardiac chest pain and bone pain.
[e] Includes dyspnea and exertional dyspnea.

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Laboratory Findings

Data:

In general, clinical laboratory evaluations (eg, serum chemistry, hematology) demonstrated no clinically significant effect of tarlatamab (Section 3 of Module 2.7.4).

The laboratory parameters with a ≥ 3 grade change from baseline reported for ≥ 5% of subjects treated with tarlatamab monotherapy were decrease in lymphocytes (24.3%) and decrease in sodium (12.7%). A lower incidence of grade ≥ 3 decreases from baseline in sodium was observed for subjects with SCLC treated with tarlatamab monotherapy at 10 mg compared with 100 mg (8.8% vs 16.0%) (Section 3 of Module 2.7.4, SCS). Adverse events associated with neutropenia are discussed in Section 8.2.5.3. Neutropenia.

The incidences of liver function test abnormalities were low across all studies. Increases in AST and ALT were mainly grade 1 and grade 2 and occurred in the setting of CRS (see Section 8.2.5.1. Cytokine Release Syndrome). There were no cases of drug-induced liver injury.

Safety Update as of 02 October 2023

Overall, the subject incidence and preferred terms of adverse events related to laboratory abnormalities and changes from baseline in laboratory parameters in subjects treated with tarlatamab monotherapy were consistent with the initial ISS analysis. Laboratory parameters with ≥ 3 grades change from baseline reported for ≥ 5% of subjects treated with monotherapy were decrease in lymphocytes from grade 0 to 3 (19.0%) and decrease in sodium from grade 0 to 3 (11.8%), consistent with the initial ISS analysis. No new cases that met the Hy's Law criteria were reported since the initial ISS analysis.

The Applicant's Position:
There were no notable trends in laboratory evaluations, and the results were consistent with the known safety profile of tarlatamab (Section 3 of Module 2.7.4 Summary of Clinical Safety).

The FDA's Assessment:

FDA's analysis of selected laboratory abnormalities that worsened from baseline in the pooled safety population are provided in Table 39 below.

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Reference ID: 5382024

Table 56 FDA Analysis of Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients with ES - SCLC in Study DeLLphi-300 and Study DeLLphi-301

Laboratory Abnormality	IMDELLTRA[a]	
	All Grades (%)	Grade 3 or 4 (%)
Hematology		
Decreased lymphocytes	84	57
Decreased hemoglobin	58	5
Decreased white blood cells	44	3.8
Decreased platelets	33	3.2
Decreased neutrophils[b]	12	6
Chemistry		
Decreased sodium	68	16
Decreased potassium	50	5
Increased aspartate amino transferase	44	3.2
Increased alanine aminotransferase	42	2.1
Decreased magnesium	33	1.6
Increased creatinine	29	0.5
Increased sodium	26	0.0
Increased alkaline phosphate	22	0.0

[a] The denominator used to calculate the rate varied from 41 to 187 based on the number of patients with a baseline value and at least one post-treatment value.
[b] All Grade lab abnormalities occurring at a frequency less than 20% included decreased neutrophils.

Vital Signs

Data:

The assessments of vital signs and electrocardiograms for the integrated safety analysis set are provided in Section 4 of Module 2.7.4, Summary of Clinical Safety.

No clinically relevant changes were observed in body weight, pulse rate, blood pressure, or body temperature.

The Applicant's Position:

No clinically relevant changes were observed in body weight, pulse rate, blood pressure, or body temperature.

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The FDA's Assessment:
FDA agrees with the Applicant's analysis of vital signs.

Electrocardiograms (ECGs)

Data:
Electrocardiogram (ECG) results are for Study 20200491 and 20160323. Overall, elevated postbaseline corrected QT intervals (Fridericia) (QTcFs) were reported infrequently in subjects treated with tarlatamab monotherapy, with maximum postbaseline QTcF intervals > 480 to 500 msec or > 500 msec reported for 2 subjects (0.4%) each. No subject with SCLC treated with tarlatamab monotherapy at 10 mg had postbaseline QTcF intervals > 480 to 500 msec or > 500 msec. No subjects with SCLC treated with tarlatamab monotherapy at 10 mg or 100 mg had postbaseline QTcF intervals > 500 msec.

Few subjects treated with tarlatamab monotherapy had changes from baseline in QTcF interval > 30 to 60 msec (7.4%) or > 60 msec (0.9%) with similar incidences between the 10 mg and 100 mg groups (Section 4.2 of Module 2.7.4, SCS).

The Applicant's Position:

Overall, the incidence of changes in ECGs was low and no notable ECG abnormalities potentially associated with tarlatamab were observed.

The FDA's Assessment:

FDA agrees with the Applicant's description of the incidence and severity of QT prolongation. No clinically significant QT prolongation was observed in the clinical and non-clinical QT assessment. The data presented do not suggest a mechanism for QT prolongation by tarlatamab.

Immunogenicity

Data:
To support this marketing application, immunogenicity was determined by measuring antitarlatamab antibody formation using a validated electro-chemiluminescence-based bridging immunoassay in 5 clinical studies (20160323, 20200491, (b) (4)
For the pivotal phase 2 Study 20200491, samples confirmed to be positive for binding antibodies were subsequently tested in a validated cell-based bioassay to determine the neutralizing activity against tarlatamab. Detailed description of these assays and impact analyses is presented in the Integrated Summary of Immunogenicity (Module 5.3.5.3).

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At the proposed dosing regimen of 10 mg Q2W, treatment-emergent antitarlatamab incidence was 12% (3 of 25 subjects) for the FIH Study 20160323 and 3.2% (4 of 124 subjects) for the pivotal phase 2 Study 20200491, for a pooled total of 7 of 149 subjects (4.7%) across these studies (ISS Table 14-10.1.1). In the pivotal phase 2 Study 20200491, which employed the neutralizing assay, none of the subjects receiving the 10 mg target dose developed neutralizing antibodies. Potential impact of antitarlatamab antibodies on the PK, clinical efficacy, and clinical safety of tarlatamab was assessed with the following results:

- Based on the population PK model, individuals with positive ADA binding status at any time during the study were estimated to have approximately 21% higher clearance, which translated to an approximately 24% decrease in serum trough concentrations on average (see Sections 6.3.1 and 19.4.1).
- The efficacy results (including ORR, DCR, and DOR) were comparable for antitarlatamab binding antibody positive subjects compared with those who were antitarlatamab antibody negative (see Section 6.3.1).
- There was no impact of antitarlatamab antibody development on safety based on assessment of adverse events (see Section 3.3 of Module 2.7.4, SCS).

Safety Update as of 02 October 2023

Consistent with the initial ISS analysis, the overall incidence of antitarlatamab antibody development was low. Overall, 44 subjects (9.4%) treated with tarlatamab monotherapy were antitarlatamab antibody positive (23 pre-existing antitarlatamab antibody positive and 21 treatment-induced antitarlatamab antibody positive) out of (b) (4) subjects with an on-study result across Studies 20160323, 20200491, and 20200040 (90-daySU ISS Table 14-10.1.1). These included (b) (4) subjects treated with 10 mg tarlatamab (b) (4) pre-existing antitarlatamab antibody positive and (b) (4) treatment induced antitarlatamab antibody positive) out of (b) (4) subjects with an on-study result and (b) (4) subjects treated with 100 mg tarlatamab (b) (4) pre-existing antitarlatamab antibody positive and 5 treatment induced antitarlatamab antibody positive) out of 163 subjects with an on-study result from Studies 20160323 and 20200491.

The Applicant's Position:

The incidence of antitarlatamab antibody development is low. At the proposed clinical regimen of 10 mg Q2W, 7/149 (4.7%) of tarlatamab-treated subjects developed treatment-emergent antitarlatamab antibodies. The majority of these subjects had low magnitude antibody response and none of the subjects who were ADA positive developed neutralizing antibodies. The development of antitarlatamab antibodies did not have a clinically relevant impact on tarlatamab efficacy or safety.

The FDA's Assessment:

FDA agrees with the Applicant's assessment that the incidence of ADA was low. In Study

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20200491 in the 1mg step up/10mg dosage cohort, 3.2% (4/124) of patients tested positive for ADA and none of the patients developed Nab. Due to the low occurrence of ADA, the impact of ADA on PK, safety, and effectiveness is inconclusive.

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1. Cytokine Release Syndrome

Data:

Monotherapy Studies

Using the AMQ narrow search, CRS adverse events of any grade were reported for 270 subjects (59.1%) across all doses (ISS Table 14-6.1.7), with 265 subjects having resolved events and 6 subjects with ongoing events as of the data cutoff date (ISS Table 14-6.7.5). Serious CRS events were reported for 122 subjects (26.7%), and 3 subjects (0.7%) had a CRS event that led to tarlatamab treatment discontinuation.

In subjects receiving tarlatamab 10 mg monotherapy in the 2 clinical studies, using the AMQ narrow search, CRS occurred in 53.8% of subjects, including (worst) grade 1 in 31.0%, grade 2 in 21.4%, and grade 4 in 0.8% of subjects. No subject had a grade 3 or grade 5 event of CRS. Serious events of CRS were reported in 23.1% of subjects. There were no fatal CRS events.

After the first dose of tarlatamab (cycle 1 day 1), 41.3% of subjects experienced any grade CRS, with 28.8% of subjects experiencing any grade CRS after the second dose (ISS Table 14-6.2.404). The majority of CRS events occurred after the first 2 doses, with 8.8% of subjects experiencing CRS following the third dose or later. Following the day 1 infusion, 15.6% of subjects experienced ≥ grade 2 CRS. Following the day 8 infusion, 4.4% of subjects experienced ≥ grade 2 CRS. Clinical signs and symptoms of CRS included pyrexia, hypotension, fatigue, tachycardia, headache, chills, nausea, and vomiting. The majority of these events did not lead to tarlatamab discontinuation.

Subjects with SCLC treated with tarlatamab monotherapy at 100 mg had higher rates of grade ≥ 3 CRS events (6.1%) compared with subjects treated with 10 mg (1.3%) (ISS Table 14-6.1.7). Otherwise, the overall frequency and severity of CRS events (ie, grade 2 and above, serious CRS, and CRS events leading to discontinuation of tarlatamab) were generally similar among subjects treated with tarlatamab monotherapy at 10 and 100 mg. Hence, the median time to onset and duration of CRS are provided below for the overall pooled monotherapy studies with results for

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10 and 100 mg provided in Section 2.1.5.3.1.1 of Module 2.7.4, SCS.

The median time to first onset of CRS (AMQ, narrow search) from the first dose of tarlatamab was 19.8 hours for any grade CRS, 29.0 hours for grade ≥ 2 CRS, and 56.1 hours for grade ≥ 3 CRS. The median time to first onset of CRS (AMQ, narrow search) from the last prior dose of tarlatamab was 12.6 hours for any grade CRS, 15.4 hours for grade ≥ 2 CRS, and 32.0 hours for grade ≥ 3 CRS (ISS Table 14-6.7.1 and ISS Table 14-6.7.3).

The median duration of resolved CRS adverse events (AMQ, narrow search) was 3 days for any grade CRS, 4 days for grade ≥ 2 CRS, and 4 days for grade ≥ 3 CRS, as of the data cutoff date. The Kaplan-Meier median (95% CI) time to resolution was 4 (3, 4) days for any grade CRS, 4 (3, 4) days for grade ≥ 2 CRS, and 4 (3, 5) days for grade ≥ 3 CRS (ISS Table 14-6.7.5).

Study 20200491

To provide the clinically most meaningful safety analysis, the following CRS analysis focuses on CRS events in Study 20200491 reported for subjects treated with tarlatamab 10 mg with a 1 mg step dose in cycle 1 where the data collected were more detailed for CRS. When meaningful, data are also provided for subjects in the 100 mg group initiated by step dosing in cycle 1, since the step dose of 1 mg is common to both treatment groups and will be used with the dose of 10 mg.

In Study 20200491, the incidence of CRS adverse events for subjects treated with tarlatamab monotherapy at 10 mg and 100 mg was 40.6% and 28.7% on cycle 1 day 1; 29.3% and 49.4% on cycle 1 day 8; 7.5% and 6.9% on cycle 1 day 15. The incidence of CRS events was lower in cycle 2 and beyond, ranging from 0 to 1.5% in the 10 mg group and 0 to 4.6% in the 100 mg group (Table 14-6.5.401 of Study 20200491).

On cycle 1 day 1, after the 1 mg infusion, 31 of 220 subjects (14.1%) had a grade ≥ 2 CRS event that generally required interventions of low flow oxygen and IV hydration (Table 14-6.13.402 of Study 20200491). On cycle 1 day 1, grade ≥ 2 CRS events that required interventions including low and high flow oxygen or IV hydration occurred before 24 hours in 16 of 220 subjects (7.3%), and after 24 hours in 4 of 220 subjects (1.8%). The median time to first onset of grade ≥ 2 CRS (AMQ, narrow search) was 25.9 hours from the first dose of tarlatamab (Table 14-6.10.2 of Study 20200491).

On cycle 1 day 8, in the 10 mg group, there were 4 of 133 subjects (3%) that had grade ≥ 2 CRS events that generally required interventions of low flow oxygen and IV hydration. No grade ≥ 3 CRS events were reported (Table 14-6.5.401 of Study 20200491). High flow oxygen (≥ 6 L/min) was not used in events after the cycle 1 day 8 dose (Figure 14-6.1.401 of Study 20200491). No grade ≥ 2 CRS events that required interventions including low flow oxygen and IV hydration

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occurred before 24 hours (Table 14.6.13.401 of Study 20200491). One subject in the 10 mg cohort had grade 2 CRS that required IV hydration and a single vasopressor at 69.8 hours after the cycle 1 day 8 dose. The median time to grade 1 CRS was 8.2 hours, and the median time from grade 1 to grade 2 was 20.2 hours from the first dose of tarlatamab (Table 14-6.6.401 of Study 20200491). The median (Q1, Q3) time to first onset of grade ≥ 2 CRS (AMQ, narrow search) was 15.2 (9.0, 31.2) hours from the last prior dose of tarlatamab (Table 14-6.10.5 of Study 20200491).

The most common treatments administered for any grade CRS were low flow oxygen (for hypoxia), IV fluids (for hypotension), and tocilizumab. Additional less common treatments included high flow oxygen (for hypoxia), and vasopressors (for hypotension) (Table 14-6.13.501 of Study 20200491).

Combination Therapy Studies

Across the combination studies, the incidence of CRS using the AMQ narrow search was 29 of 54 subjects (53.7%), and the most frequently reported preferred term was CRS. Serious CRS events were reported for 11 subjects (20.3%) and grade ≥ 3 events occurred in 1 subject (1.8%). No events were fatal. See Section 2.1.5.3.2.1 of Module 2.7.4 (SCS) for additional information.

Safety Update as of 02 October 2023

Monotherapy Studies

Of the (b) (4) subjects overall in the Monotherapy Safety Analysis Set, (b) (4) had CRS adverse events of any grade using the AMQ broad search. Consistent with the initial ISS analysis, the most frequently reported (≥ 20% of subjects) preferred terms included CRS (60.7%), pyrexia (39.0%), fatigue (29.3%), nausea (25.4%), and asthenia (21.5%).

Using the AMQ narrow search, CRS adverse events of any grade were reported for 294 subjects (60.7%), with 286 subjects having resolved events and 9 subjects with ongoing events as of the data cutoff date (90-daySU ISS Table 14-6.7.6); CRS was the only preferred term reported. As reported in the initial ISS analysis, a grade 4 CRS event was reported for 1 subject (0.2%) treated with 10 mg tarlatamab monotherapy. Consistent with the initial ISS analysis, no CRS events were fatal (90-daySU ISS Table 14-6.1.9).

The median (Q1, Q3) time to first onset of CRS (AMQ narrow search) from the first dose of tarlatamab was 18.9 (8.8, 175.3) hours for any grade CRS, 26.0 (9.3, 188.5) hours for grade ≥ 2 CRS, and 55.3 (22.8, 196.6) hours for grade ≥ 3 CRS (90-daySU ISS Table 14-6.7.1).

The median (Q1, Q3) duration of resolved CRS (AMQ narrow search) adverse events was 3 (2, 5) days for any grade CRS, 4 (2, 6) days for grade ≥ 2 CRS, and 4 (3, 5) days for grade ≥ 3 CRS (90-daySU ISS Table 14-6.7.6). The Kaplan-Meier median (95% CI) time to resolution was 3 (3, 4)

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days for any grade CRS, 4 (3, 4) days for grade ≥ 2 CRS, and 4 (3, 5) days for grade ≥ 3 CRS (90-daySU ISS Table 14-6.7.6).

Consistent with the initial ISS analysis, subjects treated with tarlatamab 100 mg had higher rates of serious and grade ≥3 CRS events compared with subjects treated with tarlatamab 10 mg. Otherwise, the clinical presentation of the CRS events was generally similar among subjects treated with 10 mg and 100 mg.

Combination Therapy Studies

Across the combination studies, the incidence of CRS using the AMQ narrow search was 52 of 109 subjects (47.7%), and the most frequently reported preferred term was CRS. Serious CRS events were reported for 21 subjects (19.3%) and grade ≥ 3 events occurred in 1 subject (0.9%). No events were fatal. See Section 2.1.5.3.1.2 of 90-Day Safety Update for additional information.

The Applicant's Position:

Most cases of CRS were grade 1 and grade 2 events that could be conservatively managed. Grade 3 and grade 4 CRS adverse events were rare. Most cases did not require measures such as tocilizumab, oxygen, or vasopressors. In general, events of CRS did not recur after subsequent doses of tarlatamab. In cases where it did progress, it took many hours to evolve from grade 1 to grade 2 to grade 3, where intervention would be required; the median time to first onset of CRS (AMQ, narrow search) from the first dose of tarlatamab was 26.0 and 55.3 hours for grade $\geq$ 2 and grade $\geq$ 3 CRS, and from the last prior dose of tarlatamab was 15.1 and 30.6 hours, respectively. There were few grade 2 and higher events or hospital-based interventions used from cycle 1 day 15 and beyond.

The FDA's Assessment:

FDA agrees that most instances of CRS were Grade 1 or 2 and that most patients experienced CRS following tarlatamab administration of initial step up dose of 1 mg IV on Cycle 1 Day 1. Patients received premedication with dexamethasone 8 mg IV administered 1 hour prior to infusion on Days 1 and 8 of Cycle 1 only and post IV hydration with 1 liter of normal saline over 4-5 hours.

In the pooled safety population (n = 187), CRS occurred in 55% of patients, including 34% Grade 1, 19% Grade 2, 1.1% Grade 3 and 0.5% Grade 4 of tarlatamab-treated patients. Tocilizumab was used in 9% of patients and there were no fatal Grade 5 events. Recurrent CRS occurred in 24% of tarlatamab-treated patients (18% Grade 1, 6% Grade 2).

Most events (43%) of CRS occurred after the first dose with 29% of patients experiencing any grade CRS after the second dose and 9% of patients experiencing CRS following the third dose or later. Following the Day 1, Day 8, Day 15 infusions, 16%, 4.3%, and 2.1% of patients

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experienced ≥ Grade 2 CRS, respectively. The median time to onset of all grade CRS from most recent dose of tarlatamab was 13.5 hours (range: 1 to 268 hours). The median time to onset of ≥ Grade 2 CRS from most recent dose of tarlatamab was 14.6 hours (range: 2 to 566 hours).

FDA did not agree with the Applicant's initial proposal in the USPI to monitor patients for (b) (4) hours after first infusion and to remain within 1 hour of an appropriate healthcare setting for (b) (4) hours after each tarlatamab infusion on Cycle 1 Day 1 and Cycle 1 Day 8. In Part 3 of the pivotal study (modified monitoring cohort), patients were hospitalized for 24 hours post tarlatamab infusion for Cycle 1 day 1 and Cycle 1 Day 8 doses. Based on the data provided, FDA agreed that monitoring of patients from the start of tarlatamab infusion for 22-24 hours on Cycle 1 Day 1 and Cycle 1 Day 8 in an appropriate healthcare setting would be appropriate to mitigate risk. FDA also recommend patients remain within 1 hour of an appropriate healthcare setting for a total of 48 hours from the start of the infusion with tarlatamab following Cycle 1 Day 1 and Cycle 1 Day 8, accompanied by a caregiver.

FDA also carefully considered the need for Risk Evaluation and Mitigation Strategies (REMS) given the major identified safety finding of CRS and have determined that a REMS is not needed. Based on our review, we have determined that the toxicity profile of the tarlatamab can be adequately conveyed through labeling (including a Boxed Warning for serious or life-threatening CRS and neurologic toxicity, including ICANS). In addition, enhanced pharmacovigilance and a Dear Healthcare Provider letter are non-REMS adjuncts recommended to help convey these risks. Refer to Section 12 for rationale for not requiring a REMS.

8.2.5.2. Immune Effector Cell-associated Neurotoxicity Syndrome

Data:
In the monotherapy studies, a total of 72 (b) (4) had ICANS and associated neurological events (AMQ broad search) with a lower incidence in the 10 mg group (15 subjects [9.4%]) than in the 100 mg group (35 subjects [21.5%]). Serious ICANS events occurred in 27 subjects (5.9%) overall with a lower incidence with 10 mg (4 subjects [2.5%]) than with 100 mg (18 subjects [11.0%]). Fourteen subjects (3.1%) had grade ≥ 3 ICANS events (none in the 10 mg group), of whom 2 subjects (0.4%) had grade ≥ 4 events, and there were no fatal events (ISS Table 14-6.1.7).

ICANS events led to dose interruption in 11 subjects (2.4%), mainly from the 100 mg group (9 [5.5%] vs 1 [0.6%] from the 10 mg group) (ISS Table 14-6.1.7). ICANS events led to treatment discontinuation in 6 subjects (1.3%), mainly from the 100 mg group (4 subjects [2.5%] vs 1 [0.6%] from 10 mg).

In the 10 mg dose group (N = 160), 15 subjects (9.4%) experienced ICANS and associated neurological events. Preferred terms in these subjects included ICANS (7 subjects), assessed as

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related to tarlatamab in 4 subjects (2.5%); muscular weakness (7 subjects), aphasia (1 subject), depressed level of consciousness (1 subject), and leukoencephalopathy (1 subject). Four subjects (2.5%) had serious events, all ICANS by preferred term. The median time from the last dose of tarlatamab to the first onset of ICANS was 3 days (range: 1 to 15 days). The median time to resolution of ICANS was 33 days (range 1 to 93 days).

In the 100 mg dose group (N = 163), 35 subjects (21.5%) had ICANS events, with serious events reported in 18 subjects (11.0%). The preferred terms for the serious events were: ICANS (10 [6.1%]) and encephalopathy (6 [3.7%]), all assessed as related to tarlatamab. The remaining preferred terms were low incidence, mostly nonserious and not related to tarlatamab (ISS Table 14-6.2.67).



Safety Update as of 02 October 2023

Since the initial ISS analysis, 2 additional subjects had ICANS and associated neurological events based on the AMQ broad search; 74 of the (b) (4) subjects overall in the Monotherapy Safety Analysis Set had ICANS and associated neurological events, which were considered related to tarlatamab in 56 subjects (11.6%). As reported in the initial ISS analysis, 2 subjects (0.4%) had grade ≥ 4 events. Serious ICANS and associated neurological events were reported for 29 subjects (6.0%), and 6 subjects (1.2%) had events leading to tarlatamab discontinuation; no ICANS and associated neurological events were fatal (Table 16 and 90-daySU ISS Table 14 6.1.9). Consistent with the initial ISS analysis, the most frequently reported (≥ 2% of subjects) preferred terms were muscular weakness (5.0%), ICANS (4.3%), and encephalopathy (2.5%).

Among subjects receiving 10 mg tarlatamab, since the initial ISS analysis, a serious event of encephalopathy was reported in 1 subject (0.5%) which was considered to be related to tarlatamab by the investigator. The subject was known to have brain metastases; details are provided in Section 2.1.5.3.2.1 of 90-Day Safety Update.



The Applicant's Position:

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ICANS is an important identified risk for tarlatamab. In the tarlatamab monotherapy studies (n = 457), ICANS and associated neurological adverse events using the ICANS AMQ broad search strategy were observed in 72 subjects (15.8%). At the 10 mg tarlatamab dose (n = 160), ICANS events were observed in 15 subjects (9.4%). Across the tarlatamab monotherapy studies, most ICANS events were mild to moderate. No fatal events have been reported. Most of the events were self-limiting without the need for treatment discontinuation or dose reduction.

The FDA's Assessment:

Based on FDA analysis in the pooled safety population, neurologic toxicity including ICANS occurred in 47% of patients who received tarlatamab, including 10% Grade 3; there were no Grade 4 events. The most frequent neurologic toxicities were headache (14%), peripheral neuropathy (7%), dizziness (7%), insomnia (6%), muscular weakness (3.7%), delirium (2.1%), syncope (1.6%) and neurotoxicity (1.1%).

ICANS occurred in 9% of patients and recurrent ICANS occurred in 1.6% of patients. Most patients experienced ICANS following cycle 2 day 1 (24%). Following Day 1, Day 8, and Day 15 infusions, 0.5%, 0.5% and 3.7% of patients experienced ≥ Grade 2 ICANS, respectively. The median time to onset of ICANS from the first dose of tarlatamab was 29.5 days (range: 1 to 154 days). The median time to resolution of ICANS was 33 days (range: 1 to 93 days).

FDA did not agree with the Applicant's initial proposal in the USPI to monitor patients for (b) (4) hours after first infusion and to remain within 1 hour of an appropriate healthcare setting for (b) (4) hours after each tarlatamab infusion on Cycle 1 Day 1 and Cycle 1 Day 8. In Part 3 of the pivotal study (modified monitoring cohort), patients were hospitalized for 24 hours post tarlatamab infusion for Cycle 1 day 1 and Cycle 1 Day 8 doses. Based on the data provided, FDA agreed that monitoring of patients from the start of tarlatamab infusion for 22-24 hours on Cycle 1 Day 1 and Cycle 1 Day 8 in an appropriate healthcare setting would be appropriate to mitigate risk. FDA also recommend patients remain within 1 hour of an appropriate healthcare setting for a total of 48 hours from the start of the infusion with tarlatamab following Cycle 1 Day 1 and Cycle 1 Day 8, accompanied by a caregiver.

FDA carefully considered the need for Risk Evaluation and Mitigation Strategies (REMS) given the major identified safety findings of neurologic toxicity including ICANS and have determined that a REMS is not needed. Based on our review, we have determined that the toxicity profile of the tarlatamab can be adequately conveyed through labeling (including a Boxed Warning for serious or life-threatening CRS and neurologic toxicity, including ICANS). In addition, enhanced pharmacovigilance and a Dear Healthcare Provider letter are non-REMS adjuncts recommended to help convey these risks. Refer to Section 12 for rationale for not requiring a REMS.

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Table 57 FDA Analysis of CRS and neurologic toxicity, including ICANS

	Pooled Studies 20200491 and 20160323 [a] N = 187		
	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Patients with TEAEs	186 (99)	75 (40)	22 (12)
Cytokine Release Syndrome	103 (55)	2 (1.1)	1 (0.5)
ICANS[b]	16 (9)	1 (0.5)	0 (0.0)
Neurologic Toxicities			
Musculoskeletal Pain	56 (30)	2(1.1)	0 (0.0)
Headache	27 (14)	0 (0.0)	0 (0.0)
Peripheral Neuropathy[c]	14 (7)	0 (0.0)	0 (0.0)
Dizziness[d]	14 (7)	0 (0.0)	0 (0.0)
Insomnia	12 (6.4)	1 (0.5)	0 (0.0)
Syncope	2 (1.1)	2 (1.1)	0 (0.0)
Delirium	4 (2.1)	1 (0.5)	0 (0.0)
Neurotoxicity	2 (1.1)	0 (0.0)	0 (0.0)

Source: FDA Primary Analysis Adverse Events Analysis Dataset (adae.xpt)
[a]NCI CTCAE version 4 and version 5
[b] Includes muscular weakness, encephalopathy, immune effector cell-associated neurotoxicity syndrome, depressed level of consciousness, leukoencephalopathy, aphasia.
[c]Includes peripheral sensory neuropathy, peripheral neuropathy, paraesthesia, dysaesthesia, hypoaesthesia.
[d]Includes dizziness and vertigo.

8.2.5.3. Neutropenia

Data:

Across the monotherapy studies (b) (4) subjects (b) (4) had adverse events of neutropenia based on the AMQ broad search (ISS Table 14-6.1.7). Using this search, the most frequently reported (≥ 5% of subjects) preferred terms were neutropenia (7.9%), decreased neutrophil count (6.1%), and decreased white blood cell count (5.3%) (ISS Table 14-6.2.65). Using the narrow search, 63 subjects (13.8%) had adverse events of neutropenia, 37 subjects (8.1%) had grade ≥ 3 events, and 12 subjects (2.6%) had grade ≥ 4 events. Serious neutropenia events were reported for 9 subjects (2.0%), and 2 subjects (0.4%) had neutropenia events leading to tarlatamab discontinuation. No neutropenia adverse events were fatal. Results for the 10 and 100 mg dose groups were similar for neutropenia, with the exception of a higher incidence of grade ≥ 3 events with 100 mg (11.7%) than with 10 mg (6.3%).

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Based on pooled safety data from Studies 20200491 and 20160323, in the 10 mg dose group, 27 of 160 subjects (16.9%) had adverse events of neutropenia based on the AMQ broad search (ISS Table 14-6.1.7) with neutropenia (8.8%) and decreased neutrophil count (5.0%) reported in ≥ 5% of subjects (ISS Table 14-6.2.25). Based on the AMQ narrow search, 23 subjects (14.4%) had any event of neutropenia, 10 subjects (6.3%) had grade ≥ 3 events, and 4 subjects (2.5%) had grade ≥ 4 events; serious neutropenia events were reported for 2 subjects (1.3%) and are described in Section 2.1.5.3.4.1 of Module 2.7.4, SCS. No neutropenia events were fatal. Neutropenia leading to dose interruption occurred in 0.6% of subjects with none leading to treatment discontinuation. The events were mainly nonserious and resolved spontaneously or with the use of granulocyte colony stimulating factor (G-CSF).

The median time from the first dose of tarlatamab to the first onset of any grade and grade ≥ 2 neutropenia events was 43 and 45 days, respectively (ISS Table 14-6.7.1). The median time from the last prior dose of tarlatamab to the first onset of any grade and grade ≥ 2 neutropenia events was 8 and 13 days, respectively. The median duration of resolved grade ≥ 2 neutropenia adverse events was 8 days, with 17 subjects having resolved events and 2 subjects with ongoing events as of the data cutoff date. The Kaplan-Meier median (95% CI) time to resolution was 8 (6, 14) days (ISS Table 14-6.7.5). Overall, in the 10 mg cohort, 3 (1.9%) subjects received G-CSF treatment for the neutropenia events.

In the 100 mg dose group, 30 of 163 subjects (18.4%) had adverse events of neutropenia based on the AMQ broad search (ISS Table 14-6.1.7) with decreased neutrophil count (8.6%), neutropenia (8.0%), and decreased white blood cell count (8.0%), reported in ≥ 5% of subjects (ISS Table 14-6.2.25). Based on the AMQ narrow search, 27 subjects (16.6%) had adverse events of neutropenia, 19 subjects (11.7%) had grade ≥ 3 events, and 6 subjects (3.7%) had grade ≥ 4 events; serious neutropenia events were reported for 4 subjects (2.5%); 2 subjects (1.2%) had events that led to discontinuation of tarlatamab; and no neutropenia events were fatal. The median time from the first dose of tarlatamab to the first onset of any grade and grade ≥ 2 neutropenia events, from last prior dose of tarlatamab to onset of events, median duration of resolved events, and median time to resolution were similar to those seen with 10 mg (ISS Table 14-6.7.5). Overall, in the 100 mg cohorts, 7 subjects (4.4%) were treated with G-CSF for their neutropenia events.

Safety Update as of 02 October 2023

Of the (b) (4) subjects overall in the Monotherapy Safety Analysis Set, (b) (4) subjects (b) (4) had adverse events of neutropenia based on the AMQ broad search (90-daySU ISS Table 14-6.1.9). Using this search, consistent with the initial ISS analysis, the most frequently reported preferred terms were neutropenia (8.5%), decreased neutrophil count (6.4%), and decreased white blood cell count (4.8%). Using the narrow search, 70 subjects (14.5%) had adverse events of

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neutropenia. A total of 61 (12.6%) had grade ≥ 2 neutropenia events and 39 subjects (8.1%) had grade ≥ 3 events. Serious neutropenia events were reported for 11 subjects (2.3%) and 2 subjects (0.4%) had neutropenia adverse events leading to tarlatamab discontinuation. No neutropenia adverse events were fatal.

Neutropenia results in both the 10 mg and 100 mg target dose groups of tarlatamab remained consistent with the initial ISS analysis, with similar frequency, severity and types of neutropenia events (Section 2.1.5.3.4 90-Day Safety Update). In subjects treated with tarlatamab monotherapy at 10 mg, 32 of 187 subjects (17.1%) had adverse events of neutropenia based on the AMQ broad search. Based on the AMQ narrow search, 28 subjects (15.0%) had adverse events of neutropenia. In subjects treated with tarlatamab monotherapy at 100 mg, 31 of 163 subjects (19.0%) had adverse events of neutropenia based on the AMQ broad search; based on the AMQ narrow search, 29 subjects (17.8%) had adverse events of neutropenia. The proportion of subjects requiring treatment with G-CSF was similar to the initial ISS analysis (2.1% and 4.4% for 10 and 100 mg, respectively).

As of 02 October 2023, a serious adverse event of neutrophil count decreased was reported for 1 (1.3%) additional subject enrolled in Study 20200491 (10 mg). Details are provided in Section 2.1.5.3.4.1 of 90-Day Safety Update.

The Applicant's Position:
Based on the available safety data from clinical studies, neutropenia is a risk of tarlatamab. Neutropenia observed with tarlatamab is generally mild and not associated with febrile neutropenia. The majority of neutropenia events were non-serious and resolved spontaneously with or without the use of G-CSF. The data do not suggest that tarlatamab causes immunosuppression and therefore the safety profile is not anticipated to be different in this patient population.

The FDA's Assessment:

FDA's analysis of treatment emergent adverse events of interest the pooled safety population included cytopenias which includes neutropenia, thrombocytopenia and anemia. Refer to Table 56 for laboratory findings including cytopenia.

In the pooled safety population, decreased neutrophils occurred in 12% of patients, including Grade 3 or 4 in 6% of patients. The median time to onset for Grade 3 or 4 neutropenia was 29.5 days (range: 2 to 213). Decreased platelets occurred in 33% including Grade 3 or 4 in 3.2% of patients. The median time to onset for Grade 3 or 4 decreased platelets was 50 days (range: 3 to 420). Decreased hemoglobin occurred in 58% including 5% Grade 3 or 4. Febrile neutropenia occurred in 0.5% of patients treated with IMDELLTRA.

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

Data:

Patient-reported outcomes are discussed in FDA agrees with the Applicant's position. Efficacy Results – *Secondary or exploratory COA (PRO) endpoints*.

The Applicant's Position:

Patient-reported outcomes are discussed in FDA agrees with the Applicant's position. Efficacy Results – *Secondary or exploratory COA (PRO) endpoints*.

The FDA's Assessment:

FDA reviewed the summary of the PRO data. Refer to FDA's assessment of PRO endpoints in Section 8.1.2 under Efficacy Results – Secondary or exploratory COA (PRO) endpoints.

8.2.7. Safety Analyses by Demographic Subgroups

Data:

Summaries of adverse events and treatment-related adverse events; subject incidence of adverse events and treatment-related adverse events by preferred term; and subject incidence of adverse events and treatment-related adverse events by system organ class were analyzed by intrinsic and extrinsic factor subgroups of race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other), ethnicity (Hispanic/Latino, Not Hispanic/Latino – only for subjects reporting 'White' race), age ($<$ 65 years versus $\geq$ 65 years and $<$ 75 years versus $\geq$ 75 years), sex, ECOG status (ECOG status 0, 1, 2), and region (Asia, Europe, North America, rest of world).

Overall summaries of adverse events by subgroup are provided in Section 5.1 and Section 5.2 of Module 2.7.4, SCS. In the integrated monotherapy analysis set, no notable safety trends were observed across the subgroups examined. No meaningful differences were observed in the types of adverse events or treatment-related adverse events reported in the subgroups examined; however, small sample sizes in some subgroups limit the ability to draw meaningful conclusions.

The Applicant's Position:

Overall, subgroup analyses demonstrated a pattern of events consistent with that reported for the overall study population.

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The FDA's Assessment:

The tables below provide an overview of adverse events by sex, age, and race category in the pooled safety population. The rate of Aes and SAEs were relatively similar across all categories including in patients with ECOG of 0 (n=56) and ECOG of 1 (n=129). In patients with ECOG 0 the incidences of Aes and SAEs were 100% and 48%. In patients with ECOG 1 the incidences of Aes were 99% and 58% respectively.

Table 58. Analysis of Adverse Events by Sex

Study 20160323 and 20200491 (N=187)		
	Male (N1=121) N (%)	**Female (N2=66) N (%)**
All treatment-emergent adverse events	121 (100.0)	65 (99)
Serious adverse events	63 (52)	41 (62)
Leading to dose interruption and/or reduction of tarlatamab	36 (30)	21 (32)
Leading to discontinuation of tarlatamab	7 (6)	6 (9)

Table 59. Analysis of Adverse Events by Age Group

Study 20160323 and 20200491 (N=187)		
	Age < 65 (N1 = 86) n (%)	**Age ≥ 65 (N2 = 101) n (%)**
All treatment-emergent adverse events	86 (100)	100 (99)
Serious adverse events	47 (55)	57 (56)
Leading to dose interruption	26 (30)	31 (31)

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Study 20160323 and 20200491 (N=187)		
and/or reduction of tarlatamab		
Leading to discontinuation of tarlatamab	4 (5)	9 (9)

Table 60. Analysis of Adverse Events by Race

Study 20160323 and 20200491 (N=187)				
	Hispanic/Latino (N=4) n (%)	Not Hispanic/Latino (N=126) n (%)	Asian (N=48) n (%)	White (N=130) N (%)
All treatment-emergent adverse events	3 (75)	126 (100)	48 (100)	129 (99)
Serious adverse events	0 (0)	70 (56)	28 (58)	70 (54)
Leading to dose interruption and/or reduction of tarlatamab	1 (25)	39 (31)	12 (25)	53 (51)
Leading to discontinuation of tarlatamab	0 (0)	11 (9)	2 (4.2)	8 (8)

8.2.8. Specific Safety Studies/Clinical Trials

Data:

Not applicable as no studies were conducted to evaluate a specific safety concern.

The Applicant's Position:

Not applicable

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The FDA's Assessment:
Not applicable.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development
Data:

Not applicable

The Applicant's Position:

See Pharmacology/Toxicology review.

The FDA's Assessment:

FDA agrees with the Applicant's assessment and has no further comments. Refer to Section 5.5.3 for Pharmacology Toxicology review or carcinogenicity.

Human Reproduction and Pregnancy
Data:

No clinical studies of tarlatamab have been conducted in pregnant or breastfeeding women. No breastfeeding cases were reported with exposure to tarlatamab.

There are no clinical studies to evaluate the effect of tarlatamab on fertility.

The Applicant's Position:

There are no available data from the use of tarlatamab in pregnant women. Based on its mechanism of action, tarlatamab may cause fetal harm when administered to a pregnant woman.

It is unknown whether tarlatamab is secreted in human milk. Because many medicinal products, including antibodies, can be secreted in human milk, a risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue tarlatamab treatment taking into account the benefit of breast-feeding for the child and the benefit of tarlatamab treatment for the woman.

There are no clinical studies to evaluate the effect of tarlatamab on fertility.

The FDA's Assessment:

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FDA agrees with the Applicant's statement. There were no patients who were discontinued from trial due to pregnancy, and birth control measures during treatment and ongoing pregnancy screening were enforced to ensure that no fetus was exposed to study drug. Therefore, no information on the use of tarlatamab during pregnancy or lactation. Refer to Section 5.5.4 for Pharmacology Toxicology review of reproductive and developmental toxicology.

Pediatrics and Assessment of Effects on Growth

Data:

Not Applicable

The Applicant's Position:

Safety and effectiveness of tarlatamab in pediatric patients have not been established. Tarlatamab is on the non-relevant molecular target list and given that tarlatamab has an orphan drug designation, Amgen is exempt from submitting a pediatric study plan under PREA statutory requirement.

The FDA's Assessment:

FDA agrees with the Applicant's statement and has no further comments.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data:

There is no clinical experience with overdose with tarlatamab. Doses up to 100 mg Q2W and 200 mg Q3W have been administered in clinical trials. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required.

The Applicant's Position:

See above

The FDA's Assessment:

FDA agrees with the Applicant's statement and has no further comments.

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8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Data:
Not applicable

The Applicant's Position:

Not applicable. Tarlatamab is not currently registered or approved in the US or in any other part of the world.

The FDA's Assessment:

FDA agrees with the Applicant's statement and has no further comments.

Expectations on Safety in the Postmarket Setting
Data:

Not applicable

The Applicant's Position:

Toxicities are adequately represented in the tarlatamab safety database for this submission. Routine pharmacovigilance will continue to be conducted to monitor and continue to update the safety profile of tarlatamab. The ongoing and planned clinical studies will contribute additional safety information to further elucidate the safety profile of tarlatamab.

The FDA's Assessment:

FDA agrees with the description of the safety database provided by the Applicant and refers to product labeling and FDA's analysis for specific incidences of adverse events.

The Applicant also agreed to conduct an integrated safety analysis of data from patients with extensive stage small cell lung cancer to further characterize the long-term incidence, severity, and outcome of the known serious risks of cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome and neurologic toxicity. This postmarketing requirement is intended to provide additional safety information to support the safety of the product. Please refer to Section 13 for postmarketing requirements.

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8.2.11. Integrated Assessment of Safety

Data:

The key risks with tarlatamab treatment are as follows:

Cytokine release syndrome

- Cytokine release syndrome events were reported in approximately half of the subjects who received the 10 mg dose of tarlatamab across monotherapy studies. Most of the CRS events were nonserious and mild or moderate. No fatal CRS events have been reported. In general, CRS is manageable and reversible (interventions may include oxygen supplementation, IV fluids, vasopressors, and/or anti-interleukin [IL]-6 therapy). In some instances, tarlatamab treatment interruption or discontinuation may be required for reversibility.

Immune effector cell-associated neurotoxicity syndrome (ICANS)

- Across monotherapy studies, ICANS and associated neurotoxicity events have been reported in $<$ 10% of subjects who received the 10 mg dose of tarlatamab. Most of the events were mild or moderate. No fatal events have been reported. Most of the events were self-limiting without the need for treatment discontinuation or dose reduction.

These risks can be successfully managed by monitoring patients for signs and symptoms of CRS and ICANS following tarlatamab infusion, with temporary interruption or discontinuation depending on the severity of the event.

Tarlatamab was generally well tolerated, with a low rate of adverse events leading to treatment discontinuation in pivotal Study 20200491 and FIH Study 20160323 (6.9% in the 10 mg dose group).

Routine risk minimization activities (ie, risk communications through prescribing information or product packaging) are considered adequate to address the safety concerns associated with the use of tarlatamab.

The Applicant's Position:

Tarlatamab is generally well tolerated, and risks associated with tarlatamab use can be adequately managed through communication in product labeling, routine pharmacovigilance activities, and routine risk minimization activities. Tarlatamab demonstrated an acceptable safety profile in adult subjects with previously treated advanced SCLC.

The FDA's Assessment:

FDA agrees that the safety data presented in the BLA are derived from the pooled safety population from Study 20200491 and Study 20160323 in 187 patients with extensive stage SCLC

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who were treated with tarlatamab at a step dose of 1 mg on Cycle Day 1 followed by the proposed dose of 10 mg on Cycle 1 Day 8, Cycle 1 Day 15, and every 2 weeks thereafter. FDA agrees that the CRS and neurotoxicity including ICANS can be managed through communication in labeling (including a black box warning). In addition, enhanced pharmacovigilance and a Dear Healthcare Provider letter are non-REMS adjuncts recommended to help convey these risks. Other significant adverse events included infections, hepatotoxicity and hypersensitivity which are included in the Warnings and Precaution section of the label. The observed toxicity profile of tarlatamab is considered acceptable in the context of a life-threatening disease.

Analysis of safety was based on the 90-day updated safety datasets using DCO of October 2, 2023. Missing adverse events from Study 20200491 were assessed and did not change the overall safety profile of tarlatamab. Refer to Section 8.2.4 (Treatment-emergent Adverse Events and Adverse Reactions) for further information on unreported adverse events.

FDA carefully considered the need for Risk Evaluation and Mitigation Strategies (REMS) given the major identified safety findings of CRS and neurologic toxicity including ICANS and have determined that a REMS is not needed; please refer to Section 12 for details. Based on our review, we have determined that the toxicity profile of tarlatamab can be adequately conveyed through labeling. In addition, enhanced pharmacovigilance and a Dear Healthcare Provider letter are non-REMS adjuncts recommended to help convey these risks.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

There were no major statistical issues with this application. In the primary efficacy population (n=99), the confirmed ORR per BICR was 40% (95% CI: 31%, 51%), which was considered clinically meaningful, and the tumor responses generally appeared durable with a median DOR of 9.7 (95% CI: 6.9, NE) months and a median follow-up time of 15.1 months. The analyses of time-to-event endpoints such as PFS and OS are difficult to interpret in the absence of an appropriate comparator.

8.4. Conclusions and Recommendations

The FDA's Assessment:

The review team recommends accelerated approval of tarlatamab under the provisions of 21 CFR 314.510 Subpart H for the treatment of adult patients with ES-SCLC who have progressed on or after platinum-containing chemotherapy.

The recommendation is based on the favorable benefit-risk assessment for tarlatamab

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observed from Parts 1 and 2 of Study 20200491 (DeLLphi-301) and from Part 3 of Study 20200491 and Study 20160323 in ES-SCLC, a serious and life-threatening condition.

The primary efficacy population consisted of 99 patients enrolled in from Parts 1 and 2 of Study 20200491 who received tarlatamab at the proposed dose. Of the 99 patients, 73 patients (74%) had received prior anti-PD-(L)1 therapy; of these 73 patients, 58 (59%) received anti-PD-(L)1 therapy in combination with platinum-based chemotherapy in the first line setting. The confirmed ORR by BICR was 40% (95% CI: 31%, 51%), with a median DoR of 9.7 months (range 2.7 to 20.7+ months). Of the patients with responses, 68% of patients had an observed DoR ≥6 months and 40% of patients had an observed DoR ≥12 months. The observed ORR and DoR were clinically meaningful, and responses were observed across subgroups of patients with platinum-sensitive and platinum-refractory disease and across subgroups with various tumor DLL3 expression cut-offs. Although the ORR point estimates differ between platinum sensitivity subgroups (31% in 42 patients with platinum sensitive SCLC and 52% in 27 patients with platinum resistant SCLC), the 95% confidence intervals overlap, and FDA considers that a true difference in efficacy with tarlatamab based on platinum sensitivity status is unlikely.

In context of approved therapies in the U.S. for the proposed indication, the ORR and DoR data from the primary efficacy population in Study 20200491, which enrolled a more heavily treated patient population (3rd line or greater) is greater than the ORR and DoR observed with topotecan, the only available therapy with traditional approval from the FDA for patients with SCLC previously treated with first-line chemotherapy (ORR of 24% in platinum sensitive disease and 2-7% in platinum resistant disease). Review of prior therapies in the primary efficacy population from Study 20200491 showed that 52% of patients received a topoisomerase I inhibitor as second line therapy. Of the remaining patients, the grand majority (89%) received second line therapies considered treatment options per U.S. standard of care. The ORR in the subgroups of patients who received prior topoisomerase I inhibitor, and who did not receive prior topoisomerase I inhibitor (with or without patients who received standard of care therapies), were generally consistent across subgroups and consistent with the ORR observed in the overall study population. Furthermore, it is not expected that treatment with additional therapies following platinum-based chemotherapy would increase the likelihood of response to tarlatamab relative to treatment with tarlatamab used as second-line therapy following platinum-based chemotherapy. In light of the observed results and particularly considering the ORR observed with tarlatamab in patients with platinum-resistant SCLC, which far exceeds ORR reported with standard of care therapies, the available data for tarlatamab supports the proposed indication for treatment of SCLC with disease progression on or after platinum-based chemotherapy.

Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial, conducted as a PMR. The Applicant proposes to verify the clinical benefit of tarlatamab in the treatment of patients with SCLC who have disease

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progression on or after prior platinum-containing therapy, based on the results of an ongoing randomized controlled trial, DeLLphi-304 (Study 20210004), comparing tarlatamab to investigator's choice standard of care therapy with a primary endpoint of overall survival (OS).

X	X
Primary Statistical Reviewer Mengdie Yuan	Statistical Team Leader Anup Amatya
X	X
Primary Clinical Reviewer Yufan Liu Jeannette Nashed	Clinical Team Leader Amy Barone

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9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

FDA did not refer this application to an advisory committee or seek input from other external consultants because this application did not raise significant public health questions regarding the role of tarlatamab for the proposed indication.

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10 Pediatrics

The Applicant's Position:

Tarlatamab was not studied in pediatric subjects. Given that the molecular target of tarlatamab was moved to the nonrelevant molecular target list leading to waiver, FDA Reauthorization Act of 2017 requirements no longer apply, and given tarlatamab's orphan drug designation, Amgen is exempt from the requirements of the Pediatric Research Equity Act. Subsequently, Amgen was informed by the FDA that the initial Pediatric Study Plan had been administratively closed.

The FDA's Assessment:

FDA agrees with the Applicant's position.

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11 Labeling Recommendations

Data:
This is an original application; please see annotated label in Module 1 for proposed labeling.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
Full Prescribing Information		FDA added a boxed warning for cytokine release syndrome (CRS) and neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS) due to the serious and life-threatening adverse reactions observed.
1 INDICATIONS AND USAGE		FDA revised (b) (4) to "extensive stage" for consistency with small cell lung cancer staging terminology.
2 DOSAGE AND ADMINISTRATION 2.1 Important Dosing Information		FDA added this new subsection to put important information at the beginning of the DOSAGE AND ADMINISTRATION section. FDA added clear description of "step-up" dosing required to reduce the risk of CRS.
2.2 Recommended Dosage and Administration		FDA added clarifying text and details to the dosage table to prevent misunderstanding and medication errors.
2.3 Recommended Concomitant Medications for IMDELLTRA Administration for Cycle 1		FDA added new subsection and clarifying text and a table for recommended concomitant medications.
2.4 Restarting IMDELLTRA After Dosage Delay		FDA added new subsection and information and dosing information for restarting after a dosage delay to prevent confusion regarding the step-up dosage.
2.5 IMDELLTRA Dosage Modifications and Adverse Reaction Management		FDA revised the Applicant's proposal by separating dosage modification information for CRS and ICANs and other adverse reactions. Extensive revisions were added to the dosage modification tables. FDA added dosage modifications for the

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		management of cyptoenias, infections, and hepatotoxicity adverse reactions.
2.6 Preparation		FDA provided extensive revisions to the preparation instructions based on the results of the Human Factors study that showed a high potential for confusion and medical errors. FDA removed (b) (4) to ensure that information is presented clearly.
5 WARNINGS AND PRECAUTIONS 5.1 Cytokine Release Syndrome		Text revised for consistency with other oncology labeling.
5.2 Immune Effector Cell-Associated Neurotoxicity (ICANs)		FDA revised this section to include neurotoxicity, in addition to ICANs due to the incidence of neurotoxicity during treatment with IMDELLTRA.
5.3 Cytopenias		FDA included a new warning, due to the incidence of neutropenia, thrombocytopenia and anemia during treatment with IMDELLTRA.
5.4 Infections		FDA included a new warning due to the incidence of infections during treatment with IMDELLTRA.
5.5 Hepatotoxicity		FDA included a new warning due to the incidence of increase transaminases and increased bilirubin during treatment with IMDELLTRA.
5.6 Hypersensitivity		The Applicant added this new warning during the review due to the incidence of rash and bronchospasm observed during treatment with IMDELLTRA.
5.7 Embryo-Fetal Toxicity		FDA included this new warning based on the mechanism of action of IMDELLTRA posing a risk to a fetus.
6.1 Clinical Trials Experience		FDA pooled the safety data from Study DeLLphi-300 and Study DeLLphi-301 to provide the largest safety pool possible to best represent the adverse reactions (ARs) observed during treatment with IMDELLTRA.

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		FDA notes footnote "a" on Table 13, corresponds to the Grading of adverse reactions: [a] Graded using CTCAE Version 4.0 and Version 5.0. • FDA reviewed the differences between CTCAE versions 4 and 5. The only difference between the 2 versions is for the grading of cytokine release syndrome (CRS). Footnote "b" corresponds to cytokine release syndrome[b]: • b Based on American Society for Transplantation and Cellular Therapy (ASTCT) 2019. Because CTCAE V4 and V5 only differ in the grading of CRS, and CRS was graded using ASTCT criteria, pooling of these 2 studies was possible.
(b) (4)		FDA removed (b) (4)
8 USE IN SPECIFIC POPULATIONS		FDA revised the proposed text for consistency with other oncology labels and PLLR guidance.
12 CLINICAL PHARMACOLOGY 12.1 Mechanism of Action		FDA revised the proposed text to remove (b) (4) description of targets.
12.2 Pharmacodynamics		FDA revised the proposed text for consistency with other oncology labels and pharmacology guidance.
12.3 Pharmacokinetics		FDA included a table to display the pharmacokinetic parameters of tarlatamab-dlle to be expected during step-up dosing.
12.6 Immunogenicity		FDA revised the Applicant's proposal for consistency with immunogenicity guidance.
14 CLINICAL STUDIES 14.1 Small Cell Lung Cancer		FDA revised the Applicant's proposed text and moved demographic information from table to text. (b) (4) was removed, duration of response was maintained. Response for platinum-sensitive

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		patients was added.
17 PATIENT COUNSELING INFORMATION		Additional details were added to CRS and neurotoxicity and ICANs. New subsections were added: cytopenias, infections, hepatotoxicity, hypersensitivity, embryo-fetal toxicity and lactation.

The Applicant's Position:
The draft US prescribing information is provided with this submission.

The FDA's Assessment:
The proposed labeling submitted by the Applicant required extensive revision by FDA. The format, language, and content of the proposed labeling was evaluated and revised for consistency with 21 Code of Federal Regulations (CFR), labeling guidances and current labeling practices of the Office of Oncologic Diseases. The table above summarizes key labeling changes. Please see reviews by OPDP, DMPP, DMEPA for Medication Guide.

Note: The middle column of this table is for the Applicant to provide commentary. This assessment aid was submitted with a blank labeling table.

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12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

The Division of Oncology 2 (DO2) worked closely with the Division of Risk Management (DRM) and were aligned in the conclusion that a risk evaluation and mitigation strategy (REMS) was not necessary to mitigate the risks of cytokine release syndrome (CRS) and neurologic toxicity including immune-effector cell associated neurotoxicity syndrome (ICANS) associated with tarlatamab-dlle. The Applicant did not propose a REMS; however, the serious risks associated with tarlatamab warranted further review. Similar to other BiTE (bispecific T-cell engager) molecules, tarlatamab is associated with CRS and neurotoxicity including ICANS..

Background

Imdelltra (tarlatamab-dlle), a new molecular entity submitted by Amgen Inc., is a bispecific delta-like ligand 3 (DLL3)-directed CD3 T-cell engager proposed for the treatment of adult patients with extensive stage small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy. Tarlatamab is administered as an intravenous (IV) infusion over one hour. The first full dose is administered following a step-up dose to reduce the incidence and severity of CRS. After the step-up dose, tarlatamab is administered every 2 weeks until disease progression or unacceptable toxicity.

Table 61 Recommended Dosage and Schedule of Imdelltra (tarlatamab) – Proposed Labeling

Dosing Schedule	Day	Dose of IMDELLTRA	Administration Instructions	Required Monitoring
Step-up Dosing Schedule Cycle 1	Day 1[a]	Step-up dose[a] 1 mg	Administer IMDELLTRA as a 1-hour intravenous infusion in an appropriate healthcare setting.	Monitor patients from the start of the infusion for 22 to 24 hours on Cycle 1 Day 1 and Cycle 1 Day 8 in an appropriate healthcare setting. Recommend that patients remain within 1 hour of an appropriate healthcare setting for a total of 48 hours from start of the infusion with IMDELLTRA, accompanied by a caregiver.
	Day 8[a]	10 mg[a]		
	Day 15	10 mg		Observe patients for 6-8 hours post IMDELLTRA infusion.[b]
Cycle 2	Day 1 and 15	10 mg		Observe patients for 6-8 hours post IMDELLTRA infusion.[b]

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Cycles 3 and 4	Day 1 and 15	10mg		Observe patients for 3-4 hours post IMDELLTRA infusion.[b]
Cycle 5 and subsequent infusions	Day 1 and 15	10mg		Observe patients for 2 hours post IMDELLTRA infusion.[b]

[a] Administer recommended concomitant medications before and after Cycle 1 IMDELLTRA infusions as described in Table 3 of the label.
[b] Extended monitoring in a healthcare setting is not required unless patient experiences Grade ≥ 2 CRS, ICANS or neurological toxicity during prior treatments.
Note: (b) (4)

Table 62 Risk Mitigation Comparison and Incidence of CRS and ICANS among BiTE Molecules

	Imdelltra (tarlatamab-dlle)	Columvi (glofitimab-gxbm)	Epkinly (epcoritamab-bysp)	Lunsumio (mosunatuzumab-axgb)	Kimmtrak (tebentafusp-tebn)
App #	BLA 761344	BLA 761309	BLA 761324	BLA 761263	BLA 761228
Mechanism	BiTE - DLL3	BiTE CD20	BiTE CD20	BiTE CD20	BiTE gp100 peptide-HLA
Indication	Extensive Stage Small Cell Lung Cancer	RR DLBCL	RR DLBCL	RR follicular lymphoma	Unresectable or metastatic uveal melanoma
Admin	IV infusion	IV infusion	Subcutaneous	IV infusion	IV infusion
Risk	CRS and ICANS	CRS and ICANS	CRS and ICANS	CRS and ICANS	CRS
CRS	55%	70%	51%	39%	89%
Grade 1	34%	52%	37%	28%	12%
Grade 2	19%	14%	17%	15%	≥ Grade 2 - 77%
Grade 3	1.1%	2.8%	2.5%	2%	0.8%
Grade 4	0.5%	1.4%	0%	0.5%	0%
ICANS	9%	5%	6%	1%	0%
Risk Mitigation	Proposed Labeling:	Labeling:	Labeling: BW - CRS & ICANS	Labeling:	Labeling: BW - CRS

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	BW – CRS and NT incl. ICANS	BW - CRS W&P - ICANS		BW - CRS W&P - NT incl. ICANS

RR: relapsed/refractory
DLBCL: Diffuse large B cell lymphoma
NT: neurotoxicity
BW: Boxed Warning
W&P: Warnings and Precautions

Cytokine Release Syndrome
In the pooled safety population (n = 187), CRS occurred in 55% of patients, including 34% Grade 1, 19% Grade 2, 1.1% Grade 3 and 0.5% Grade 4 of tarlatamab-treated patients. Recurrent CRS occurred in 24% of tarlatamab-treated patients (18% Grade 1, 6% Grade 2).

Most events (43%) of CRS occurred after the first dose with 29% of patients experiencing any grade CRS after the second dose and 9% of patients experiencing CRS following the third dose or later. Following the Day 1, Day 8, Day 15 infusions, 16%, 4.3%, and 2.1% of patients experienced ≥ Grade 2 CRS, respectively. The median time to onset of all grade CRS from most recent dose of IMDELLTRA was 13.5 hours (range: 1 to 268 hours). The median time to onset of ≥ Grade 2 CRS from most recent dose of IMDELLTRA was 14.6 hours (range: 2 to 566 hours).

Neurologic Toxicity including ICANS
In the pooled safety population (n=187), neurologic toxicity including ICANS, occurred in 47% of patients who received tarlatamab, including 10% Grade 3. The most frequent neurologic toxicities were headache (14%), peripheral neuropathy (7%), dizziness (7%), insomnia (6%), muscular weakness (3.7%), delirium (2.1%), syncope (1.6%) and neurotoxicity (1.1%).

ICANS occurred in 9% of IMDELLTRA-treated patients. Recurrent ICANS occurred in 1.6% of patients. Most patients experienced ICANS following cycle 2 day 1 (24%). Following Day 1, Day 8, and Day 15 infusions, 0.5%, 0.5% and 3.7% of patients experienced ≥ Grade 2 ICANS, respectively. The median time to onset of ICANS from the first dose of IMDELLTRA was 29.5 days (range: 1 to 154 days). ICANS can occur several weeks following administration of IMDELLTRA. The median time to resolution of ICANS was 33 days (range: 1 to 93 days).

Rationale for not recommending a REMS

- If approved, labeling will be sufficient to mitigate the risks of CRS and neurotoxicity including ICANS by including:
  - A Boxed Warning for CRS and neurotoxicity including ICANS
  - Important Dosing Information (section 2.1 of the proposed label)

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  - IMDELLTRA should only be administered by a qualified healthcare professional with appropriate medical support to manage severe reactions such as CRS and neurologic toxicity including immune effector cell-associated neurotoxicity syndrome (ICANS) (similar to other approved products).
  - Due to the risk of CRS and neurologic toxicity, including ICANS, patients should be monitored from the start of the IMDELLTRA infusion for 22 to 24 hours on Cycle 1 Day 1 and Cycle 1 Day 8 in an appropriate healthcare setting
- Recommendations for monitoring in labeling that mirror the clinical trial protocol (refer to Table 1)
- Guidelines for Grading and Management of both CRS and ICANS (aligned with other approved drug products)

- The Applicant did not provide study investigators with any specific education and training for managing CRS and neurotoxicity including ICANS outside of the standard clinical protocol training (an information request was sent requesting all training materials be submitted to the FDA).
- The rates of CRS and neurotoxicity including ICANS are of low grade and similar to other BiTE drug products approved without a REMS.
  - No fatal Grade 5 events
  - CRS incidence = 55%
  - Neurotoxicity incidence = 38%
  - ICANS incidence = 9%
  - Tocilizumab use = 9%
- Stakeholder/Oncologists Input
  - At a March 8, 2024, conference, the Associate Supervisory Director for DO2 spoke with academic oncologists specializing in the treatment of lung cancer regarding whether community oncologists would be expected to have familiarity with these serious risks. Anecdotally, the oncologists responded that community oncologists are likely to be familiar with these risks as they do not only treat patients with solid tumors, but they also treat patients with hematologic malignancies whose drug therapies are more likely to have the adverse effects of CRS and neurotoxicity including ICANS.

- CAR-T REMS Changes

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- On March 14, 2024, the Breyanzi (lisocabtagene maraleucel) REMS was modified to remove training requirements to minimize the burden on the healthcare delivery system of complying with the REMS. This modification is one product in the class modification of REMS for BCMA- or CD 19-directed genetically modified autologous T-cell immunotherapies. Part of the rationale for this class-wide modification includes the availability of non-REMS training materials developed by professional societies. These materials support greater awareness and education for the CAR T cell product class, including the recognition and management of toxicities. This highlights the burgeoning availability of literature, outside of a REMS, for the management of CRS and neurologic toxicity, including ICANS, for CAR T products and beyond.
  - This objective was removed from the Breyanzi REMS goal: Ensuring that those who prescribe, dispense, or administer BREYANZI are aware of how to manage the risks of CRS and neurologic toxicities.
  - The following REMS materials were removed: REMS Training Program and associated Knowledge Assessment.

DRM and DO2 agree, if tarlatamab is approved, a REMS is not necessary. The REMS Oversight Committee (ROC) was informed that the review team concluded a REMS is not necessary to ensure the benefits of tarlatamab outweighs its risks for the treatment of ES-SCLC. The ROC agreed with the review team's rationale.

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13 Postmarketing Requirements and Commitment

The FDA's Assessment:
The following Post-Marketing Requirements and Commitments were issued and agreed upon with the Applicant.

Postmarketing Requirements:

1. Conduct a multicenter randomized clinical trial intended to verify and describe the clinical benefit of tarlatamab in patients with extensive stage small cell lung cancer (ES-SCLC) who have had disease progression on or after platinum-based chemotherapy.

   Final Protocol Submission: 12/2022 (Completed)
   Trial Completion: April 2026
   Final Report Submission: August 2026

   PMR Rationale
   Currently, ORR supported by DoR from the 20200491 single-arm trial is the primary basis for accelerated approval. The current available treatment (topotecan) was approved over 15 years ago in a platinum-sensitive SCLC population only. Time-to-event endpoints such as overall survival (OS) and progression-free survival (PFS) cannot be adequately interpreted in single-arm clinical trials due to confounding effects of heterogeneity of the patient population. Long term efficacy outcomes including OS from a randomized controlled clinical trial are needed to confirm clinical benefit of tarlatamab.

2. Conduct an integrated safety analysis of data from patients with extensive stage small cell lung cancer to further characterize the long-term incidence, severity, and outcome of the known serious risks of cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome and neurologic toxicity. Include a comprehensive analysis from all available data sources including but not limited to patient-level and pooled analyses of ongoing and completed clinical trials. These data could also be obtained from the confirmatory study titled "A Randomized, Open-label, Phase 3 Study of Tarlatamab Compared With Standard of Care in Subjects With Relapsed Small Cell Lung Cancer After Platinum-based First-line Chemotherapy (DeLLphi-304)".

   Draft Analysis Plan: January 2024
   Final Analysis Plan: April 2025
   Final Report Submission: August 2025

   PMR Rationale

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Tarlatamab is a half-life extended (HLE) bispecific T cell engager (BiTE®) that targets both delta-like ligand 3 (DLL3) on target cells and CD3 on T cells. Adverse events of special interest for tarlatamab include cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome and neurologic toxicity.

The safety is primarily supported by pooled data from patients in Studies 20200491 and 20160323 with extensive stage small cell lung cancer (SCLC) who received tarlatamab monotherapy at 10 mg. Patients received step up dose of 1 mg on Cycle 1 Day 1, followed by target dose of 10 mg on Cycle 1 Day 8 and Cycle 1 Day 15 and every 2 weeks thereafter. Among 160 patients with extensive stage SCLC treated with the intended marketing dose of tarlatamab 10 mg in Studies 20200491 and 20160323, the incidences of Grade 3-4 adverse events were 64% and fatal adverse events were 2.4%. Serious adverse reactions occurred in 54% and adverse reactions led to dose interruptions occurred in 27% and discontinuation in 8%. The most common reasons for treatment delay (≥3%) were fatigue and cytokine release syndrome. The safety data with tarlatamab is reflective of a median duration of exposure 14.4 weeks (range: 0.1 to 93.4) with 17% exposed for 6 months longer and 14% exposed for greater than 1 year. Further data is needed to identify and characterize safety with longer use of tarlatamab given the intended administration until progressive disease or unacceptable toxicity. The goal of this PMR is to provide additional safety data to further characterize the adverse reactions of interest with longer-term use of tarlatamab, including, but not limited to, cytokine release syndrome, immune effector-cell associated neurotoxicity syndrome and neurologic toxicity.

Postmarketing Commitment

3. Conduct an integrated analysis from ongoing, completed, or planned clinical trials and other potential data sources as appropriate enrolling a sufficient representation of United States (U.S.) racial and ethnic minority patients that is reflective of the U.S. population of patients with SCLC, to further characterize the efficacy, safety and pharmacokinetics of tarlatamab in these patients. In the analysis, include a sufficient number of patients enrolled in the U.S., and a sufficient number of racial and ethnic minorities reflective of the incidence of SCLC in each subpopulation to allow for interpretation of the results. The analyses should support comparative efficacy and safety outcome analyses between the aforementioned populations and White patients.

   Draft Analysis Plan: January 2025
   Final Analysis Plan: April 2025
   Final Report Submission: April 2027

   PMC Rationale

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Study 20200491 was conducted globally and only 3% of the efficacy population in this application was enrolled in the U.S. In addition, racial and ethnic minorities reflective of the U.S. population of patients with SCLC, particularly Black/African American and Hispanic/Latino patients, were significantly underrepresented in the efficacy and safety population that supported this application, with no Black/African American patients and only one Hispanic/Latino patient enrolled. Therefore, it is important to evaluate data further characterizing the efficacy and safety of tarlatamab for the treatment of SCLC in study populations whose demographics are more representative of the population of U.S. patients for the proposed indication.

FDA PMC/PMR Checklist for Trial Diversity and U.S. Population Representativeness

The following were evaluated and considered as part of FDA's review:		Is a PMC/PMR needed?
□	The patients enrolled in the clinical trial are representative of the racial, ethnic, and age diversity of the U.S. population for the proposed indication.	_X_ Yes __ No
□	Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g. race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	__X_ Yes _ No
□	Other considerations (e.g.: PK/PD), if applicable:	_X_Yes __ No

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14 Division Director (DHOT) (NME ONLY)

X

Haleh Saber

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15 Division Director (OCP)

X

Nam Atiqur Rahman

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16 Division Director (OB)

X

Shenghui Tang

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17 Division Director (Clinical)

X

Erin Larkins, MD
Associate Division Director

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18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

Paul Kluetz, MD

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19 Appendices

19.1. References

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19.2. Financial Disclosure

The Applicant's Position:
The Application provided financial disclosure in Form 3455 for all clinical investigators involved in Study 20200491. No concerns were raised regarding the overall integrity of the data.

Covered Clinical Study (Name and/or Number):* 20200491

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 689		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 2 (payment amount did not reach the threshold indicated) Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in study: _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) N/A		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation

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		from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

The FDA's Assessment:

FDA reviewed the financial disclosures for all study investigators. Of the 689 investigators participating in Study 20200491 (as stated above by the Applicant), 679 investigators (99%) did not have significant financial disclosures to report; 2 investigators (0.3%) reported significant financial disclosures, while the Applicant did not have complete financial disclosure information on 8 investigators (1.2%).

Regarding the two investigators from the same site who reported significant financial disclosures, both indicated disclosable interest according to 21 CFR 54.2(f) (significant payments of other sorts means payments made by the Applicant of a covered study to the investigator or the institution to support activities of the investigator that have a monetary value of more than $25,000, exclusive of the costs of conducting the clinical study or other clinical studies, (e.g., a grant to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation or honoraria) during the time the clinical investigator is carrying out the study and for 1 year following the completion of the study). However, the payment amount did not reach the threshold indicated. (b) (6) was enrolled in (b) (6) of the study and this patient received the (b) (6) mg dose of tarlatamab.

Of the 543 investigators participating in Study 20160323, 540 investigators (99%) did not have significant financial disclosures to report; no investigators reported significant financial disclosures, while the Applicant did not have complete financial disclosure information on 3 investigators (0.6%).

Based on the above, it is the opinion of the FDA clinical review team that the submitted financial disclosures as well as the absence of disclosures in a small number of investigators in Study 20200491 are very unlikely to have impacted the study in a meaningful way.

19.3. Nonclinical Pharmacology/Toxicology

Data:
All data are presented in Section 5, Nonclinical Pharmacology/Toxicology.

The Applicant's Position:

Not applicable

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The FDA's Assessment:
[FDA will complete this section.]

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Pharmacokinetic

Summaries of PK parameters following other dosing regimens of tarlatamab in study 20160323 are presented in the Table 62. The peak and trough serum concentrations for the 1/10 mg and 1/100 mg are summarized in Table 63.
Excluding dosage cohorts with only 1 evaluable patient (ranges from 0.003 to 0.1 mg), the dose-normalized AUC_{tau} and C_{max} are generally consistent across the dosage groups, which suggests that tarlatamab exposure appears to be approximately dose proportional across the clinically relevant dosage range of 1 mg to 100 mg Q2W in study 20160323 (Table 62). Applicant did not report exposure for 200 mg Q2W due to limited data.

Table 63. Summary of Tarlatamab PK geometric mean (CV%) following IV administration of Tarlatamab in Cycle 2 (Study 20160323)

Dose (mg)	N	Cmax (µg/mL)	AUC_{tau} (µg·day/mL)	C_{trough} (µg/mL)	AUC_{tau}/ Dose (µg·day/mL)	Cmax/Dose (µg/mL/mg)
0.003	1	0.00083	0.061	0.000099	18.3	0.23
0.01	1	0.0040	0.45	0.00075	38	0.32
0.03	1	0.019	1.7	0.0017	48	0.60
0.1	1	N/A	N/A	N/A	N/A	N/A
0.3	5	0.056 (63%)	8.9 (34%)	0.010 (30%)	35.2 (33%)	0.39 (26%)
1	7	0.23 (36%)	23.8 (66%)	0.014 (72%)	39.7 (63%)	0.24 (83%)
1/3	5	0.98 (17%)	106 (27%)	0.11 (30%)	35.2 (31%)	0.35 (29%)
1/10	19	2.80 (38%)	242 (41%)	0.29 (48%)	29.8 (48%)	0.27 (41%)
1/30	4	9.3 (38%)	879 (45%)	0.68 (46%)	28.1 (49%)	0.27 (21%)
1/100	40	25.1 (41%)	2830 (46%)	4.1 (54%)	34.0 (46%)	0.27 (42%)

a. Individual values are listed when there are less than 3 evaluable measurements.

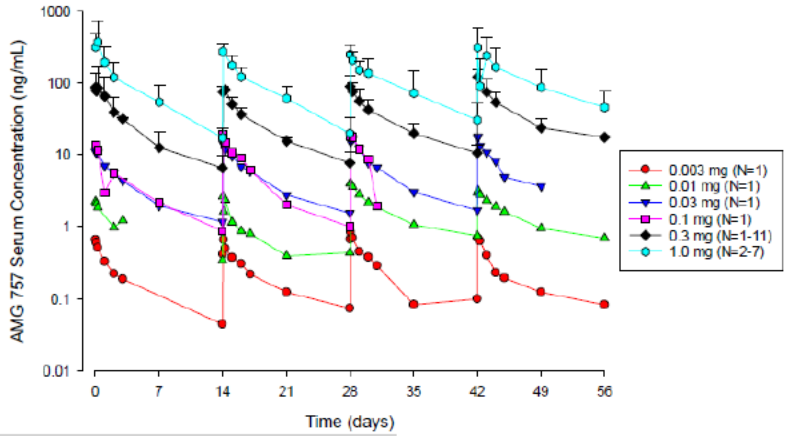
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b. CV is not presented where N<3.

Source: Study 20160323 CSR

Figure 23. Mean (SD) serum tarlatamab concentration-time profiles following administration of tarlatamab using Q2W IV Regimen in Cycle 1 and Cycle 2 in Study 20160323.



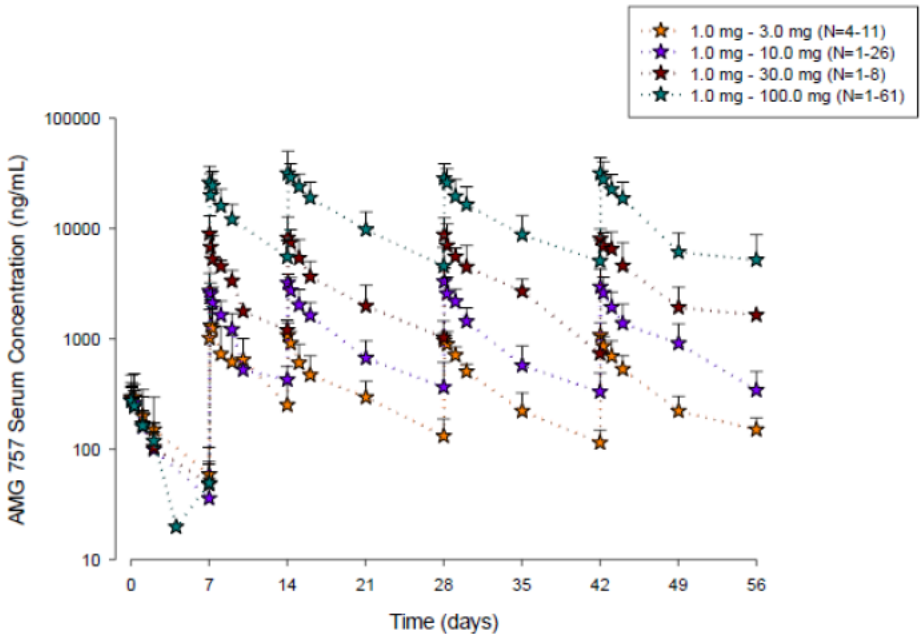
IV: intravenous; Q2W every 2 weeks

Source: Figure 11.1 of Study 20160323 CSR

Figure 24. Mean (SD) serum tarlatamab concentration-time profiles following administration of tarlatamab - 1 mg IV (Day 1) and 3 to 100 mg IV (Days 8 and 15 and Q2W Thereafter) in Cycle 1 and Cycle 2 (Study 20160323)

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IV: intravenous; Q2W: every 2 weeks
Source: Figure 11.2 of Study 20160323 CSR

Table 64. Summary of geometric mean (CV%) tarlatamab peak and trough serum concentration following IV administration of 10 mg or 100mg Q2W regimen with step-up 1mg in Study 20200491.

	Cycle 2 Day 15		Cycle 3 Day 1		Cycle 4 Day 1	
Geometric Mean (%CV) [N]	C_{trough} (µg/mL)	Cmax (µg/mL)	C_{trough} (µg/mL)	Cmax (µg/mL)	C_{trough} (µg/mL)	Cmax (µg/mL)
10 mg	0.47 (43%) [N=87]	4.2 (38%) [N = 84]	0.45(51%) [N=75]	4.3(37%) [N =74]	0.54(47%) [N=64]	4.4 (36%) [N= 62]
100 mg	6.2(50%) [N=44]	41.7 (33%) [N=44]	5.2(70%) [N=42]	46.0(50%) [N=39]	6.7 (53%) [N= 41]	44.8(29%) [N=39]

Source: Study 20200491 CSR

19.4.2. **Pharmacodynamic**

Cytokine

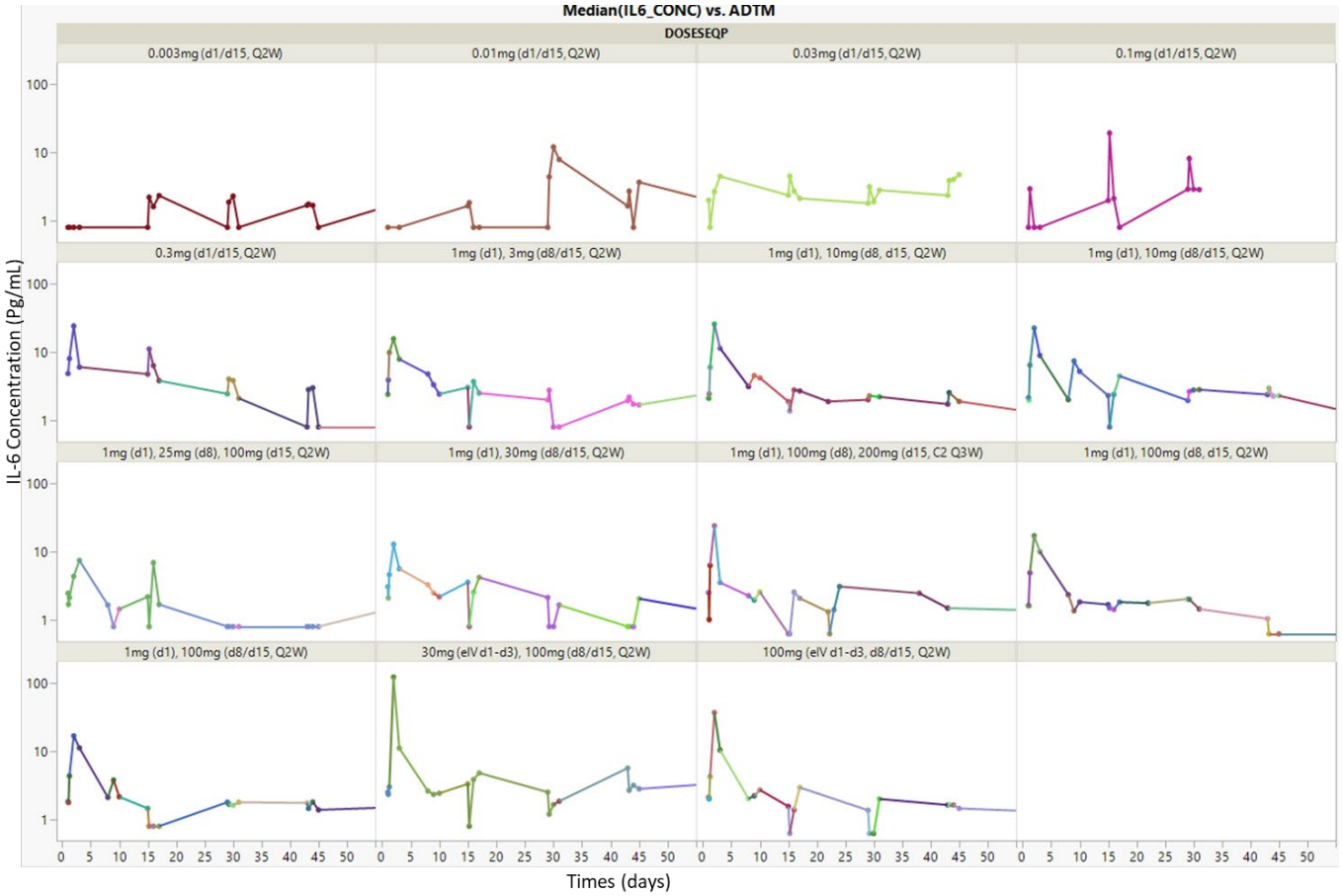
Blood samples for cytokine analysis were collected on pre- and post-dose C1D1, C1D8, and C1D15. Cytokine elevation is observed following 1/10 mg of patients without tocilizumab use in

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study 20160323. Excluding the single patient data, transient elevation of circulating cytokines was observed at dosages starting at 0.3 mg Q2W (Figure 26, Figure 27, Figure 28, Figure 29, and Figure 30). TNF-alpha did not increase significantly from baseline in studies 20160323 or 20200491. Of note, in cytokine profiles were similar in 1/10 mg and 1/100 mg.

Figure 25. FDA –Median IL-6 cytokine concentration-time profiles following tarlatamab by dosages in Study 20160323 dose escalation.

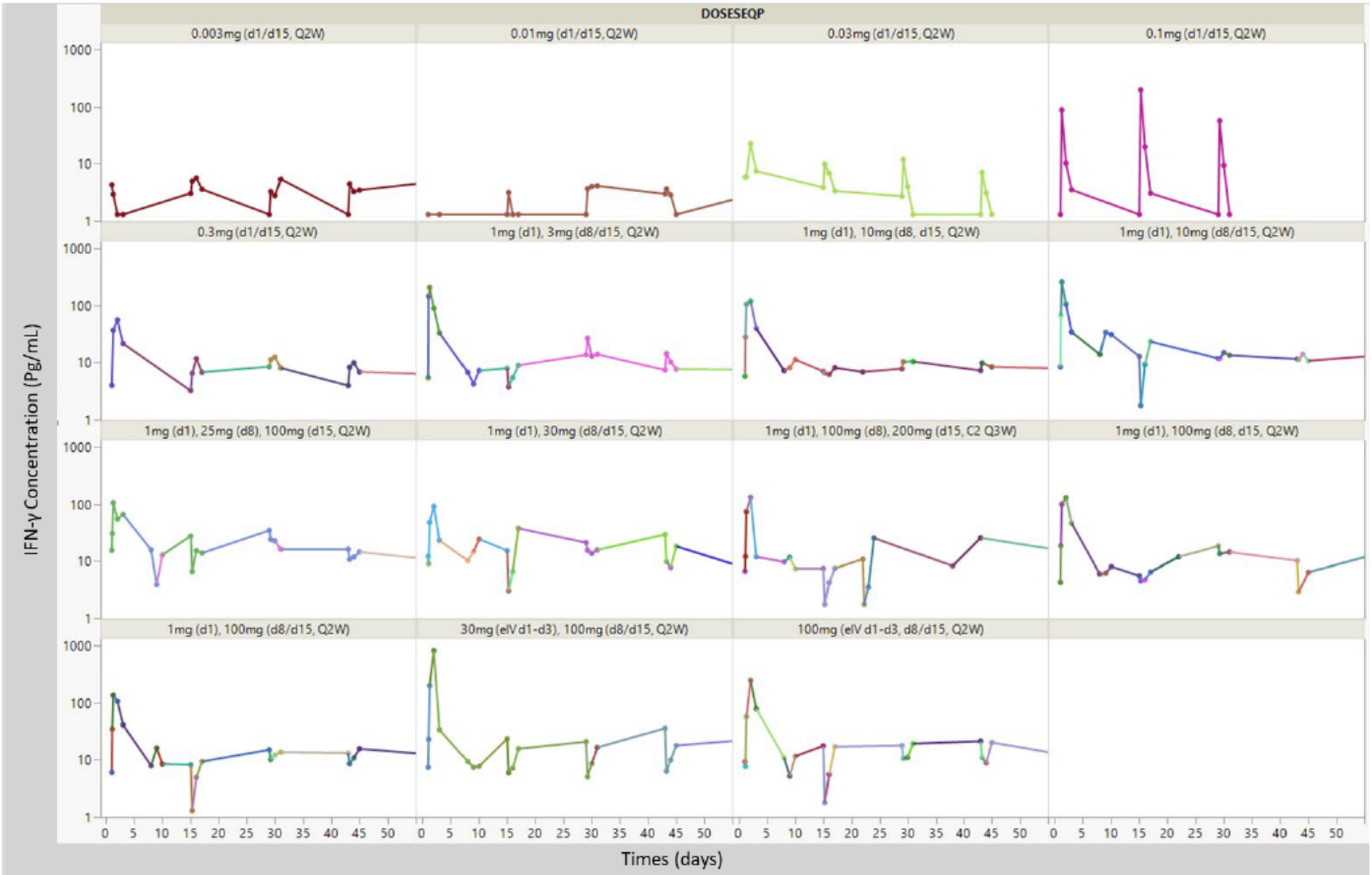


Each color code presents a patient; Each panel represent a dosage cohort; Lines represent arithmetic median value. IL-6 represents interleukin 6; eIV: extended intravenous infused over a 72-hour duration; D: treatment day; Q2W: every 2 weeks.
Source: Reviewer's analysis created from dataset of IR.

Figure 26. Median interferon-gamma (IFN-γ) cytokine concentration-time profiles following tarlatamab by dosages in study 20160323 dose escalation.

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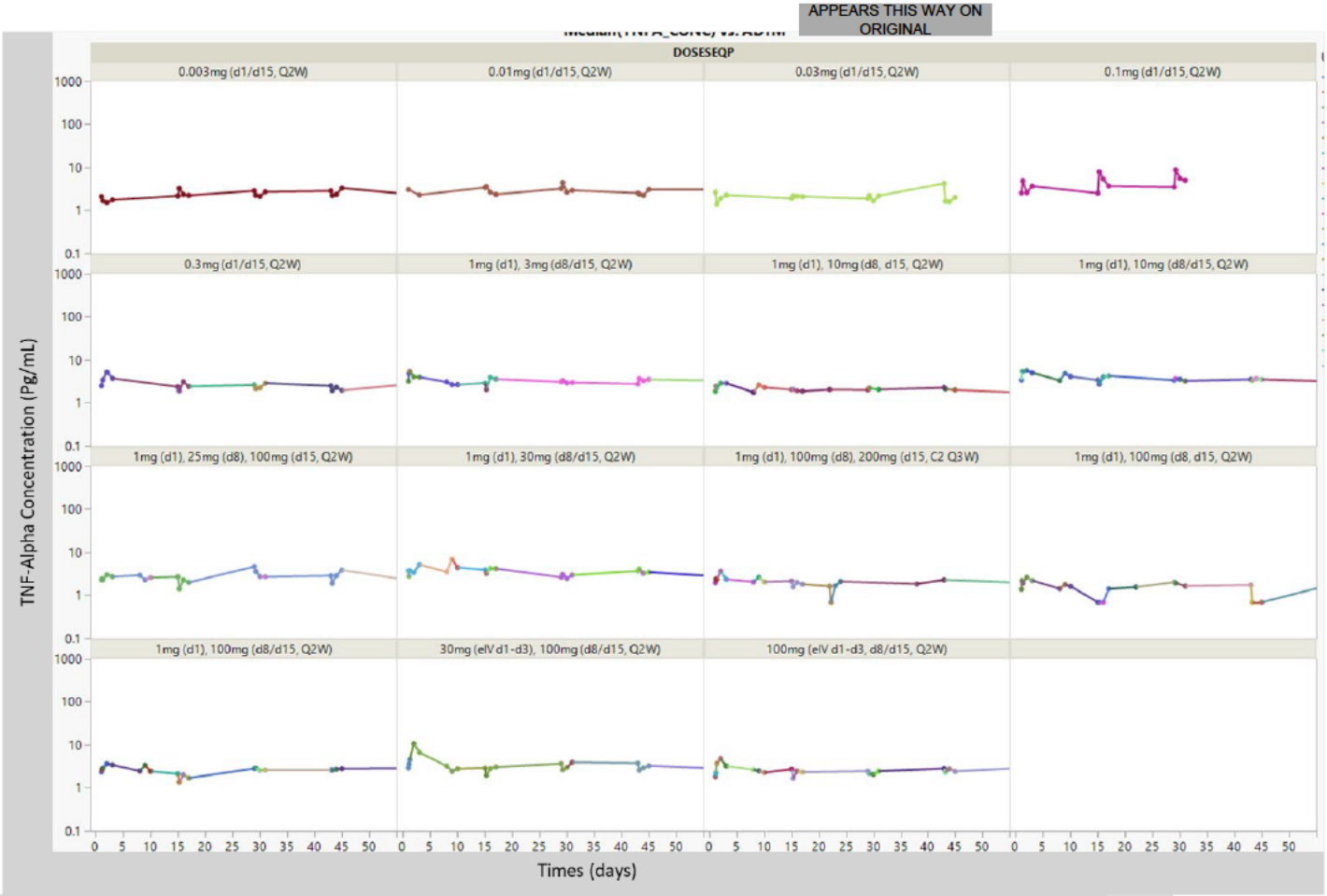


Each color code presents a patient; Each panel represent a dosage cohort; Lines represent arithmetic median value; eIV: extended intravenous infused over a 72-hour duration; D: treatment day; Q2W: every 2 weeks.
Source: Reviewer's analysis created from dataset of IR.

Figure 27. FDA –Median TNF-Alpha cytokine concentration-time profiles following tarlatamab by dosages in study 20160323 dose escalation.

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Each color code presents a patient; Each panel represent a dosage cohort; Lines represent arithmetic median value; eIV: extended intravenous infused over a 72-hour duration; D: treatment day; Q2W: every 2 weeks.
Source: Reviewer's analysis created from dataset of IR.

Figure 28. FDA –Median IL-2 cytokine concentration-time profiles following tarlatamab by dosages in study 20160323 dose escalation.

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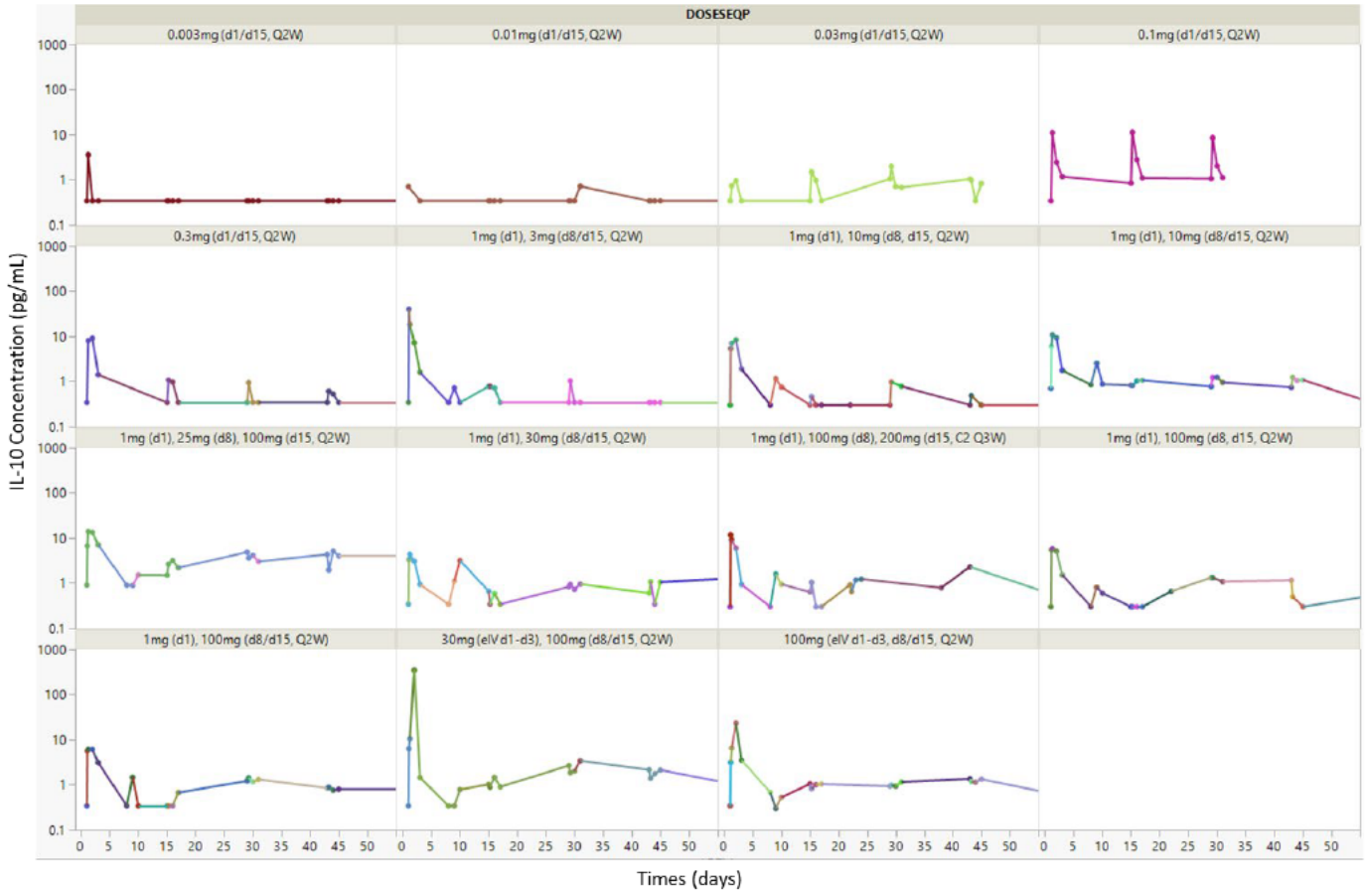


Each color code presents a patient; Each panel represent a dosage cohort; Lines represent arithmetic median value; eIV: extended intravenous infused over a 72-hour duration; D: treatment day; Q2W: every 2 weeks.
Source: Reviewer's analysis created from dataset of IR.

Figure 29. FDA –Median IL-10 cytokine concentration-time profiles following tarlatamab by dosages in study 20160323 dose escalation.

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Each color code presents a patient; Each panel represent a dosage cohort; Lines represent arithmetic median value; eIV: extended intravenous infused over a 72-hour duration; D: treatment day; Q2W: every 2 weeks.
Source: Reviewer's analysis created from dataset of IR.

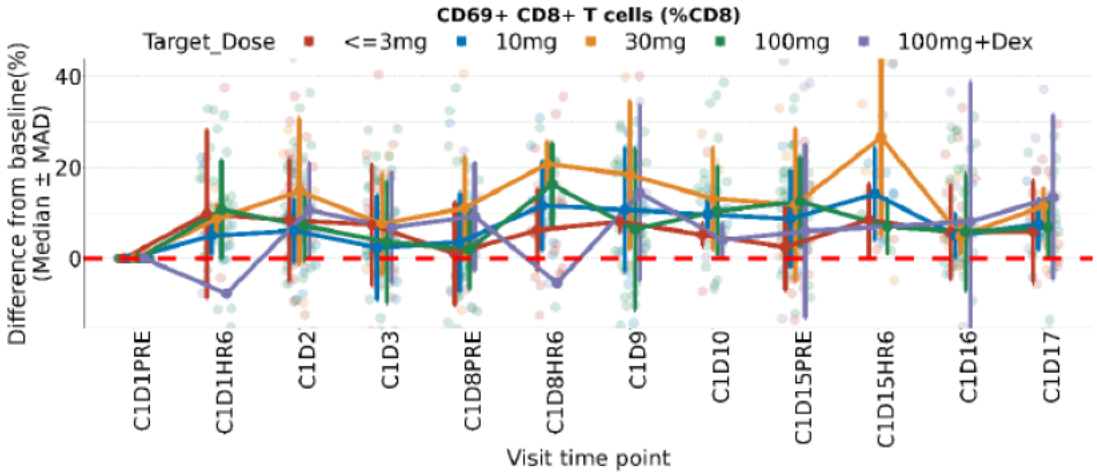
T Cell Distribution

T-cell redistributions after first dose of tarlatamab infusion were characterized by in study 20160323 and 20200491(Figure 31 and Figure 32). In Study 20160323, following initial infusion, peripheral CD8+CD69+ T-cell increased transiently 7.4% to 12.2% from baseline within 24 hours after infusion. Based on Study 20160323's result, there is no clear dose dependent effect in the T cell activation.

In study 20200491, both 1/10 and 1/100 mg increased the activation of CD8+CD69+T-cells, with 1/100 mg demonstrating a higher mean increase from baseline (27.8 %), as compared to 1/10 mg (16.3%). However, the increase in T cell activation from 1/10 to 1/100 mg dosages did not translate to a clinically meaningful increase in response rate and this PD effect is not considered to be clinically relevant.

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Figure 30. Median changes from pre-dose in percentage *for CD69+ CD8+ T-cells* activation in study 20160323.

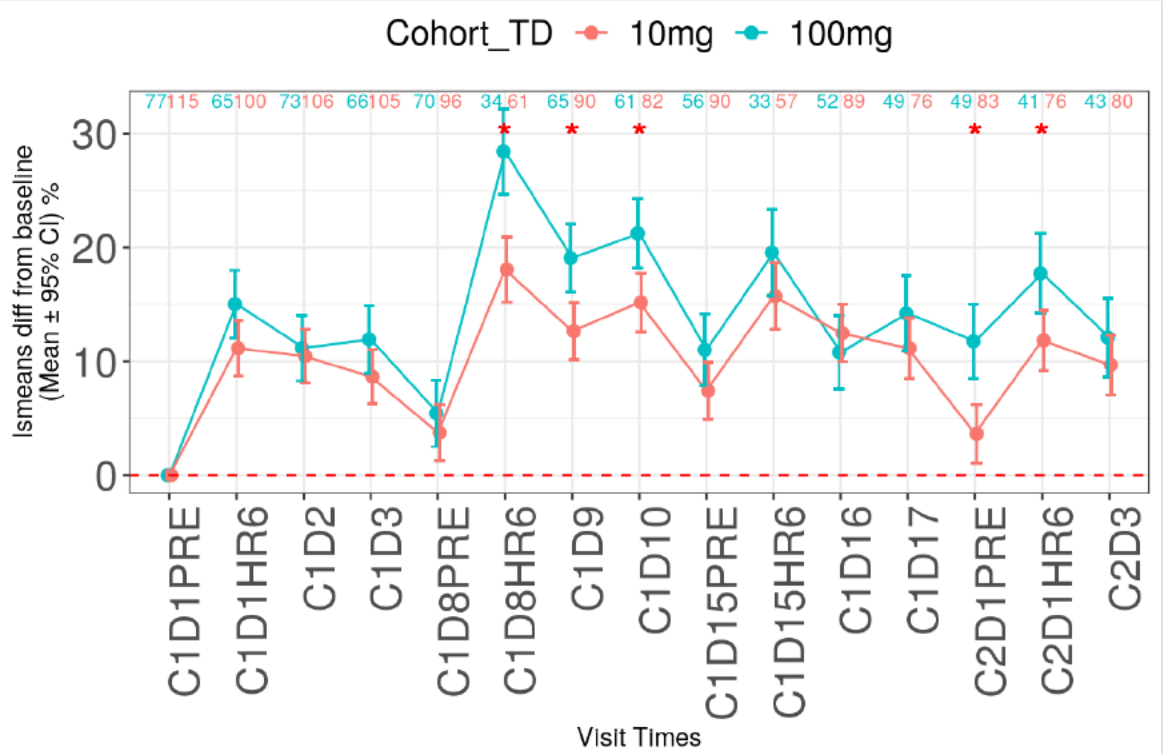


The change from baseline for CD69+ CD8+ T-cells (%CD8) (y-axis) vs. visit time point (x-axis) for patients in cohorts who received target dose <= 3mg (red), 10mg (blue), 30mg(yellow), 100mg (green). The lines are the median changes from predose (baseline) by timepoints across doses. The error bars indicate the median absolute deviation (MAD). The dots indicate the raw value of change from pre-dose (baseline) for each patient at each visit time point. C, treatment cycle; D, day of treatment cycle. Red dash line indicates the baseline level.

Figure 31. Mean changes from pre-dose in percentage of CD69+ CD8+ T-cells activation in Study 20200491.

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The change from baseline for CD69+ CD8+ T-cells (%CD8+ CD69+) (y-axis) vs. visit time point (x-axis) for patients in cohorts who received target dose 10mg (red), and 100mg. The lines are the mean changes from pre-dose (baseline) by timepoints across doses. The error bar indicates the 95% confidence interval (95% CI). The asterisks indicate the difference of lsmeans between 10mg and 100mg cohorts are significant at the visit time points per pairwise t test. C, treatment cycle; D, day of treatment cycle. Red dash line indicates the baseline level.

19.4.3. Population PK Analysis

19.4.3.1. Executive Summary

The FDA's Assessment:

The PPK analysis supports the proposed dose of 1 mg on day 1, followed by 10 mg on day 8, 15 and every 2 weeks thereafter in patients with advanced SCLC with disease progression on or after platinum-based chemotherapy. No clinically relevant differences in exposure were identified according to patient characteristics, including age, bodyweight, sex, race (Asian and White), mild or moderate renal impairment, or mild hepatic impairment. The effect of severe renal impairment and moderate to severe hepatic impairment on the PK of tarlatamab are unknown due to data limitation.

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Overall, the Applicant's PPK analyses for tarlatamab is considered acceptable for the intended analysis objectives and can reasonably well describe the observed concentration-time profile. The Applicant's analyses were verified by the reviewer, with no significant discordance identified. In addition, the developed model is deemed acceptable for deriving exposure metrics for E-R analysis and the model simulation results were acceptable to support the labeling statements regarding the general PK information and the effects of intrinsic and extrinsic factors on tarlatamab PK.

The simulated tarlatamab exposures following the Applicant's proposed retreatment plan after dose delay support their proposed repriming strategy, which is expected to effectively mitigate the incidence and severity of rebound CRS following restart of tarlatamab.

19.4.3.2. PPK Assessment Summary

The Applicant's Position:

Based on cross-study population PK analyses:

- For a 73 kg typical white individual, tarlatamab clearance, volume of distribution of central compartment, volume of distribution of peripheral compartment, and volume of distribution at steady state were estimated to be 0.65 L/day, 3.44 L, 5.06 L, and 8.5 L, respectively. The inter-individual variability for tarlatamab clearance and volume of distribution of central compartment were 43.7% and 38.7%, respectively.
- Like other biologics, body weight was found to be correlated with tarlatamab clearance, with increase in body weight associated with increase in clearance. However, at the proposed clinical regimen of 1 mg on day 1 followed by 10 mg on day 8, day 15, and Q2W thereafter, body weight had no clinically relevant impact on tarlatamab efficacy as assessed by confirmed ORR or DCR (Figures 15 and 16 of Report 157687 [Exposure-response Analysis Report] [Module 5.3.4.2]).
- Positive ADA binding status was identified as a significant time-varying covariate on tarlatamab clearance. Individuals with positive ADA binding status at any time during the study were estimated to have higher clearance. Overall, the impact of ADA was not clinically relevant as displayed by subgroup analyses for efficacy endpoints in ADA positive and ADA negative subjects in Study 20200491 (Section 11.3.1 of Study 20200491 and Integrated Summary of Immunogenicity [Module 5.3.5.3]).
- Race was found to be correlated with volume of distribution of central compartment; however, race had a negligible impact on exposures.

Tarlatamab PK were not significantly impacted by other factors such as age, sex, ethnicity, serum albumin, number of prior lines of therapies, baseline disease burden or ECOG status, or renal or hepatic function.

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General Information		
Objectives of PPK Analysis		*The objectives of the analysis were to characterize the population pharmacokinetics of tarlatamab in subjects with small cell lung cancer (SCLC), to evaluate the effects of demographic variables (covariates) on pharmacokinetic (PK) parameters, and to assess the impacts of identified covariates on tarlatamab exposures.*
Study Included		*20160323 and 20200491*
Dose(s) Included		*In these studies, tarlatamab was administered with short or extended intravenous infusion, and using no-step, one-step or two-step dosing regimens. Evaluated target doses included 0.003mg, 0.01mg, 0.03mg, 0.1mg, 0.3mg, 1mg, 3mg, 10mg, 30mg, and 100mg Q2W or 200mg Q3W (Table 2 and Table 5 of* Amgen Pharmacometrics Report: 157688)
Population Included		*Patients with small cell lung cancer*
Population Characteristics (Table 4 of Report 157688)	General	*Age median (range): 63 (32-82) years* *Weight median (range): 73 (35-149) kg* *268 (64%) male* *294 (70%) in White* *8 (1.9%) in Black* *100 (24%) in Asian* *18 (4.3%) in Other*
	Organ Impairment	*Hepatic impairment (NCI-ODWG):* *308 (73%) in Normal* *111 (26%) in Mild* *1 (0.2%) in Moderate* *Renal impairment (CKD based on eGFR):* *224 (53%) in Normal* *156 (37%) in Mild* *37 (8.8%) in Moderate* *3 Missing*
	Pediatrics (if any)	*None*
No. of Patients, PK Samples, and BLQ		*420 subjects* *399 of 8957 (4.5%) pre-dose BQL samples* *14 of 8957 (0.16%) post-dose BQL samples*
Sampling Schedule	Rich Sampling	<u>Study 20160323:</u> Intensive PK samples were collected in Parts A, C and D on days 1, 8 and 15 over a 48-hour period after the start of

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		infusion (SOI) in cycles 1 and 2 (ie. pre-infusion, end of infusion, 6, 24, 48 hours post-SOI for days 1, 8 and 15; additional sampling at 168 hours post-SOI on day 15). Sparse PK samples were collected at pre-infusion and at the end of infusion (EOI) in cycles 3 & 4, and only at pre-infusion in cycles 5-12. Sparse PK samples were collected for Parts E, F and G at pre-infusion and at EOI. For Part G, additional intensive PK samples were collected for cycle 2 only at 24, 48, 168 and 336 hours after SOI. <u>Study 20200491:</u> Sparse samples were drawn before infusion and at end of infusion on days 1, 8 and 15 of cycle 1. Starting cycle 2 through cycle 4, samples were collected at pre- and post-infusion on days 1 and 15. From cycle 5 through cycle 12, only pre-infusion samples were collected on day 1 of each cycle.
	In ITT Population	Not applicable
Covariates Evaluated	Static	*Bodyweight, age, sex, race, ethnicity, albumin, chronic kidney disease stage (CKD) score based on eGFR evaluated by Modification of Diet in Renal Disease (MDRD) formula, overall hepatic impairment scores evaluated by National Cancer Institute Organ Dysfunction Working Group criteria, ECOG score, the number of prior anticancer therapies, baseline sum of target lesion diameters*
	Time-varying	*Presence of Antidrug antibody*

Final Model	**Summary**	**Acceptability [FDA's comments]**
Software and Version	NONMEM 7.5	Acceptable
Model Structure	*Two-compartment disposition pharmacokinetic model with first order elimination*	Acceptable
Model Parameter Estimates	*Table 7 of Amgen Report 157688*	Acceptable
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	*RSE and IIV values can be found in Table 7. All shrinkage values were*	Acceptable

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	<30%. The estimated model parameters fell within the distribution of 1,000 bootstrap replicates. These results confirmed the stability of the model developed and quantified precision of the parameter estimates. Hence, the reference model was appropriately validated and deemed adequate to analyze the combined dataset (Table 8 of Amgen Report 157688).	
BLQ for Parameter Accuracy	*4.5% of PK samples that were pre-dose, 0.16% of PK samples that were postdose and 0.4% of PK samples with date-time issues were excluded from the analysis*	Acceptable
GOF, VPC	*GOF: Figure 5 of Amgen Report 157688* *pcVPC: Figures 12 and 13 of Amgen Report 157688*	Acceptable
Significant Covariates and Clinical Relevance	*Forest plot: Figure 1 of Amgen Report 157688*	No clinically relevant differences in exposure according to patient characteristics were identified, including age, bodyweight, sex, race, ethnicity, albumin, number of prior anti-cancer therapies, ECOG score, tumor burden, ADA status, mild or moderate renal impairment, or mild hepatic impairment. The effect of severe renal impairment and moderate to severe hepatic impairment on the PK of tarlatamab are unknown.

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Analysis Based on Simulation (optional)	*Section 8.2.4 of Amgen Report 157688* *Section 9.2 of Amgen Report 157688*	Additional simulations were conducted to support the proposed retreatment plan after dose delay.
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.3 PK		The proposed labeling is acceptable upon the Applicant and FDA reaching agreements to the FDA recommended revisions to the labeling, which included updates regarding formatting and clear reporting of descriptive statistics. **12.3 Pharmacokinetics** Tarlatamab pharmacokinetic parameters are presented as geometric mean (CV%) unless otherwise specified. The exposure of tarlatamab increased dose proportionally in the evaluated dose range of IMDELLTRA 1 mg to 100 mg every 2 weeks (10 times the highest approved recommended dosage). Tarlatamab steady state exposures were achieved by Cycle 2 Day 15. pharmacokinetic exposures are summarized for the recommended dosage of IMDELLTRA in Table 15. Distribution Tarlatamab steady state volume of distribution is 8.6 L (18.3%). Metabolism Tarlatamab- is expected to be metabolized into small peptides by catabolic pathways. Elimination Tarlatamab's median terminal elimination half-life (min, max) is 11.2 (4.3 to 26.5) days and the estimated systemic clearance is 0.65 L/day (44%) in patients with SCLC. Specific Populations No clinically significant differences in the pharmacokinetics of tarlatamab

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		were observed based on age (32 to 82 years), bodyweight (35 to 149 kg), sex, race (White and Asian), mild or moderate renal impairment (eGFR ≥ 30 to < 90 mL/min), or mild hepatic impairment (total bilirubin ≤ upper limit of normal (ULN) and AST > ULN). The effects of severe renal impairment (eGFR 15 to 29 mL/min), end-stage renal disease (eGFR <15 ml/min), or moderate to severe hepatic impairment (total bilirubin > 1.5 x ULN, any AST) on the pharmacokinetics of tarlatamab are unknown. Effects of Tarlatamab on CYP450 Substrates Tarlatamab causes transient release of cytokines that may suppress CYP450 enzymes and may result in an increased exposure of concomitant CYP substrates during and up to 14 days after occurrence of cytokine release syndrome [see Clinical Pharmacology (12.2)].

Amgen Pharmacometrics Report: 157688

Table 65 Summary of Demographics, Clinical Characteristics and Baseline Covariates

Subject Characteristic	Study 20160323 (n =203)	Study 20200491 (n= 217)	All subjects (n = 420)
Age (y) median (range)	63 (32-80)	64 (34-82)	63 (32-82)
Body Weight (kg) median (range)	74 (35-149)	72 (41-123)	73 (35-149)
Sex (N,%)			
Male	113 / 203 (56%)	155 / 217 (71%)	268 / 420 (64%)
Female	90 / 203 (44%)	62 / 217 (29%)	152 / 420 (36%)
Race (N,%)			
White/Caucasian	159 / 203 (78%)	135 / 217 (62%)	294 / 420 (70%)
Black	7 / 203 (3.4%)	1 / 217 (0.5%)	8 / 420 (1.9%)
Asian	21 / 203 (10%)	79 / 217 (36%)	100 / 420 (24%)
Other	16 / 203 (7.9%)	2 / 220 (0.9%)	18 / 420 (4.3%)
Ethnicity (N, %)			
Hispanic	2 / 203 (1.0%)	3 / 217 (1.4%)	5 / 420 (1.2%)

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Non-Hispanic	201 / 203 (99%)	212 / 217 (98%)	413 / 420 (98%)
Missing	0	2	2
CKD (N, %)			
Normal	107 / 203 (53%)	117 / 217 (54%)	224 / 420 (53%)
Mild CKD	78 / 203 (38%)	78 / 217 (36%)	156 / 420 (37%)
Moderate CKD	15 / 203 (7.4%)	22 / 217 (10%)	37 / 420 (8.8%)
Severe CKD	0 / 203 (0%)	0 / 217 (0%)	0 / 420 (0%)
Missing (N)	3 / 203 (1.5%)	0 / 217 (0%)	3 / 420 (0.7%)
NCI (N,%)			
Normal	152 / 203 (75%)	156 / 217 (72%)	308 / 420 (73%)
Mild liver dysfunction	51 / 203 (25%)	60 / 217 (28%)	111 / 420 (26%)
Moderate liver dysfunction	0 / 203 (0%)	1 / 217 (0.5%)	1 / 420 (0.2%)
Severe liver dysfunction	0 / 203 (0%)	0 / 217 (0%)	0 / 420 (0%)
Serum Albumin(g/L) median (range)	40.0 (4.3 – 74.0)	39.0 (25.0 – 52.0)	40.0 (4.3 – 74.0)
ECOG Baseline (N,%)			
Fully active	74 / 203 (36%)	59 / 217 (27%)	133 / 420 (32%)
Restricted	125 / 203 (62%)	158 / 217 (73%)	283 / 420 (67%)
Ambulatory	4 / 203 (2.0%)	0 / 217 (0%)	4 / 420 (1.0%)

Number of prior therapies (N, %)			
<3	143 / 203 (70%)	136 / 217 (63%)	279 / 420 (66%)
≥3	58 / 203 (29%)	81 / 217 (37%)	139 / 420 (33%)
Missing (N)	2 / 203 (1.0%)	0 / 217 (0%)	2 / 420 (0.5%)
Baseline sum of target lesion diameters (mm) median (range)	77 (10 – 758)	90 (10 – 306)	84 (10 – 758)
Missing (N)	1	0	1
Presence of anti-drug antibody (N, %)			
Negative	185 / 203 (91%)	192 / 217 (88%)	377 / 420 (90%)
Positive	15 / 203 (7.4%)	24 / 217 (11%)	39 / 420 (9.3%)
Missing	3 / 203 (1.5%)	1 / 217 (0.5%)	4 / 420 (9.3%)

*NCI: National Cancer Institute – dysfunction working group for hepatic function categories are determined as follows:

Mild liver dysfunction: if either B1 or B2 is true where B1: TB≤1.5xULN and (ALT>ULN or AST> ULN) and B2: ULN<TB ≤ 1.5xULN and (non-missing ALT or non-missing AST)

Moderate liver dysfunction: 1.5xULN<TB≤3.0 x ULN and non-missing ALT or AST

Severe liver dysfunction: 3.0 x ULN < TB and non-missing ALT or AST

TB: total bilirubin at baseline; ULN: upper limit of normal range; AST: aspartate aminotransferase; ALT: alanine aminotransferase;

**CKD: chronic kidney disease category based on eGFR uses criteria determined by the FDA Guidance:
Pharmacokinetics in Patients with Impaired Renal Function

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eGFR in mL/min = BSA normalized eGFR (mL/min/1.73m^2) x (BSA (m^2)/1.73
BSA normalized eGFR (mL/min/1.73m²) = 175 * (CRT/88.4^-1.154) * (AGE^-0.203) * (0.742 if female) * (1.212 if African American)
normal: renal function ≥ 90 mL/min; mild impairment: 60 to 89 mL/min; moderate impairment: 30 to 59 mL/min; severe impairment: 15 to 29 mL/min
***Subject (b) (6) and subject (b) (6) in study 20200491 who became ADA-positive after the record are not shown in the table.

Source: Applicant's Population PK Report 157688, Table 4.

Table 66 Parameter Estimates for the Final Model

Parameter Description (unit)	Parameter	Final Model	
		Mean	%RSE
Clearance (L/day)	CL	0.649	2.61
Volume of distribution of central compartment (L)	V1	3.44	2.72
Volume of distribution of peripheral compartment (L)	V2	5.06	6.56
Intercompartmental clearance (L/day)	Q	1.11	10.7
Covariate Effects			
Baseline bodyweight on CL (proportional change per kg)	CLBW1	0.00998	12.6
Binding ADA effect on CL (proportional change; time- varying)	CLADA1	0.215	51.4
Baseline bodyweight on V1 (proportional change per kg)	V1BW1	0.00810	16.3
Asian race on V1	V1RACECD1	-0.146	24.8
Inter Individual Variability (IIV)			
IIV for CL	IIV CL	0.437	8.50
IIV for V1	IIV V1	0.387	7.63
Correlation between CL-V1	OMEGA.2.1	0.535	11.4
Residual Error			
Exponential residual	ERR_EXP	0.575	4.94

* RSE = relative standard error.
** OMEGA and ERR_EXP are presented in standard deviation/correlation format. The relative standard errors for OMEGA and ERR_EXP are reported on the approximate standard deviation scale (SE/variance estimate)/2.
*** Covariate effects are with respect to the following reference covariates: White/Caucasian race, absence of anti-drug antibodies, 73kg baseline bodyweight

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*** RACE was assessed as a categorical covariate (Asian, White, Black, Other). Black race and Other race are retained in the model but not shown above; the effect of Black race on V1 (-0.0328, 211.1% RSE) is not significant due to small sample size; the effect of Other race on V1 (0.465, 37.3% RSE) is not interpretable as Other race includes subjects who did not report themselves as American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, or White, and subjects who declined to provide the information, and subjects whose race information was not available or unknown.

Source: Applicant's Population PK Report 157688, Table 7.

Table 67 Bootstrap Estimates and 95% Confidence Intervals

Parameter	Final Model Estimate (95CI)	Bootstrap Estimate (95CI)
CL (L/day)	0.649 (0.616, 0.682)	0.649 (0.618, 0.682)
V1 (L)	3.44 (3.25, 3.62)	3.44 (3.27, 3.63)
Q (L/day)	1.11 (0.874, 1.34)	1.11 (0.881, 1.32)
V2 (L)	5.06 (4.4, 5.71)	5.05 (4.44, 5.76)
CLADA1 (binding ADA effect on CL)	0.215 (-0.00177, 0.431)	0.216 (-0.0012, 0.488)
CLBW1 (Body weight on CL, proportional change per kg)	0.00998 (0.00752, 0.0124)	0.0099 (0.00752, 0.0125)
V1BW1 (Body weight on V1, proportional change per kg)	0.0081 (0.00551, 0.0107)	0.00819 (0.00501, 0.0113)
V1RACECD1 (Asian race on V1)	-0.146 (-0.217, -0.0752)	-0.14 (-0.215, -0.0613)
IIV:CL (OMEGA.1.1.)	0.437 (0.364, 0.51)	0.431 (0.365, 0.505)
IIV:V1 (OMEGA.2.2.)	0.387 (0.329, 0.445)	0.382 (0.326, 0.438)
COR:CL-V1 (OMEGA.2.1.)	0.535 (0.314, 0.755)	0.556 (0.308, 0.743)
RES:EXP	0.575 (0.52, 0.631)	0.575 (0.52, 0.634)

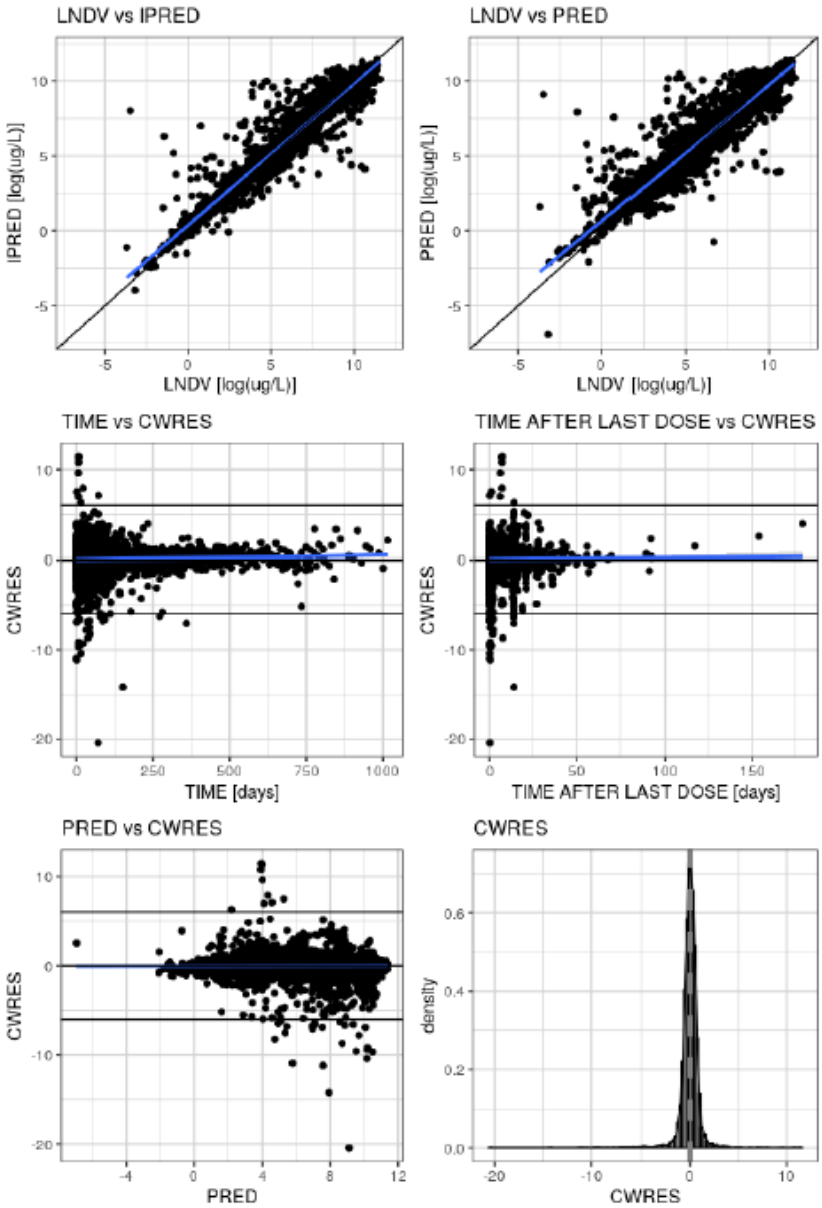
OMEGA and RES:EXP were presented in standard deviation/correlation format
RACE was assessed as a categorical covariate (Asian, White, Black, Other). Black race and Other race are retained in the model but not shown above; the effect of Black race on V1 is not significant due to small sample size; the effect of Other race on V1 is not interpretable.

Source: Applicant's Population PK Report 157688, Table 8.

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Figure 32 Goodness-of-fit Plots Based on Final Model

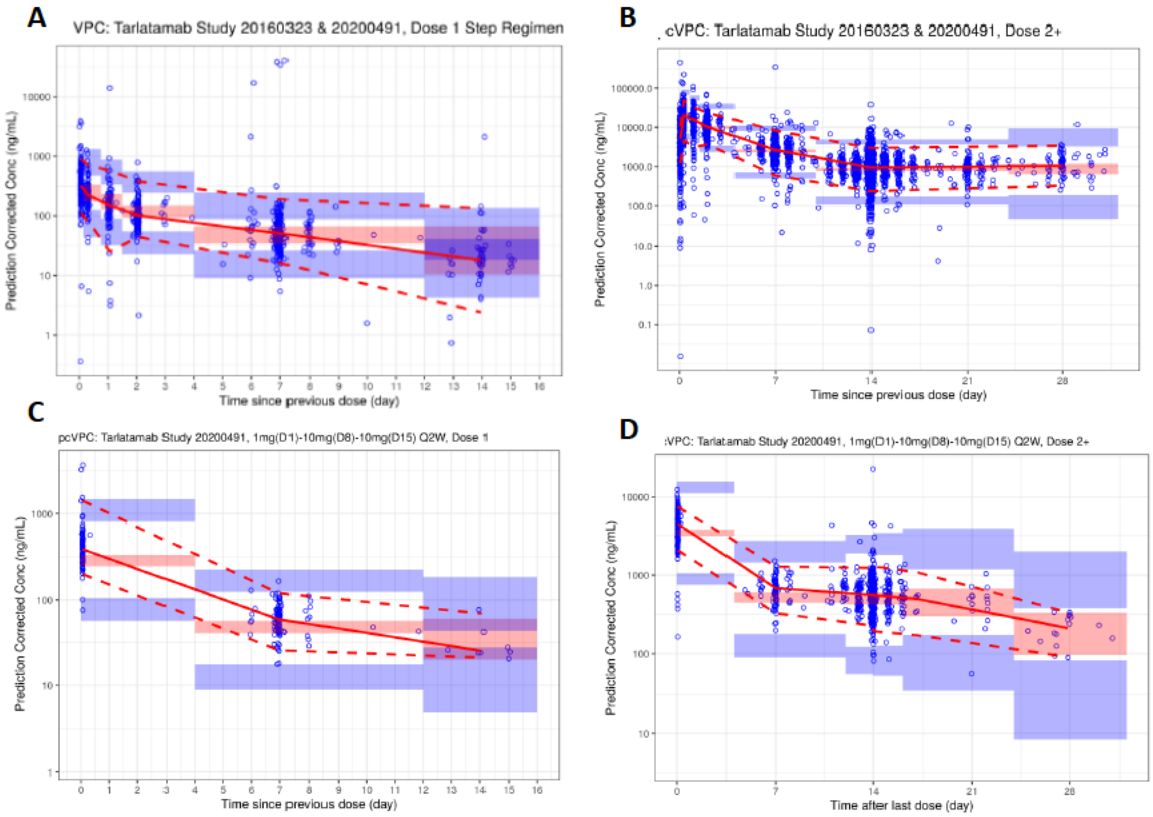


Source: Applicant's Population PK Report 157688, Figure 5.

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Figure 33 Prediction Corrected Visual Predictive Check Stratified by Dose



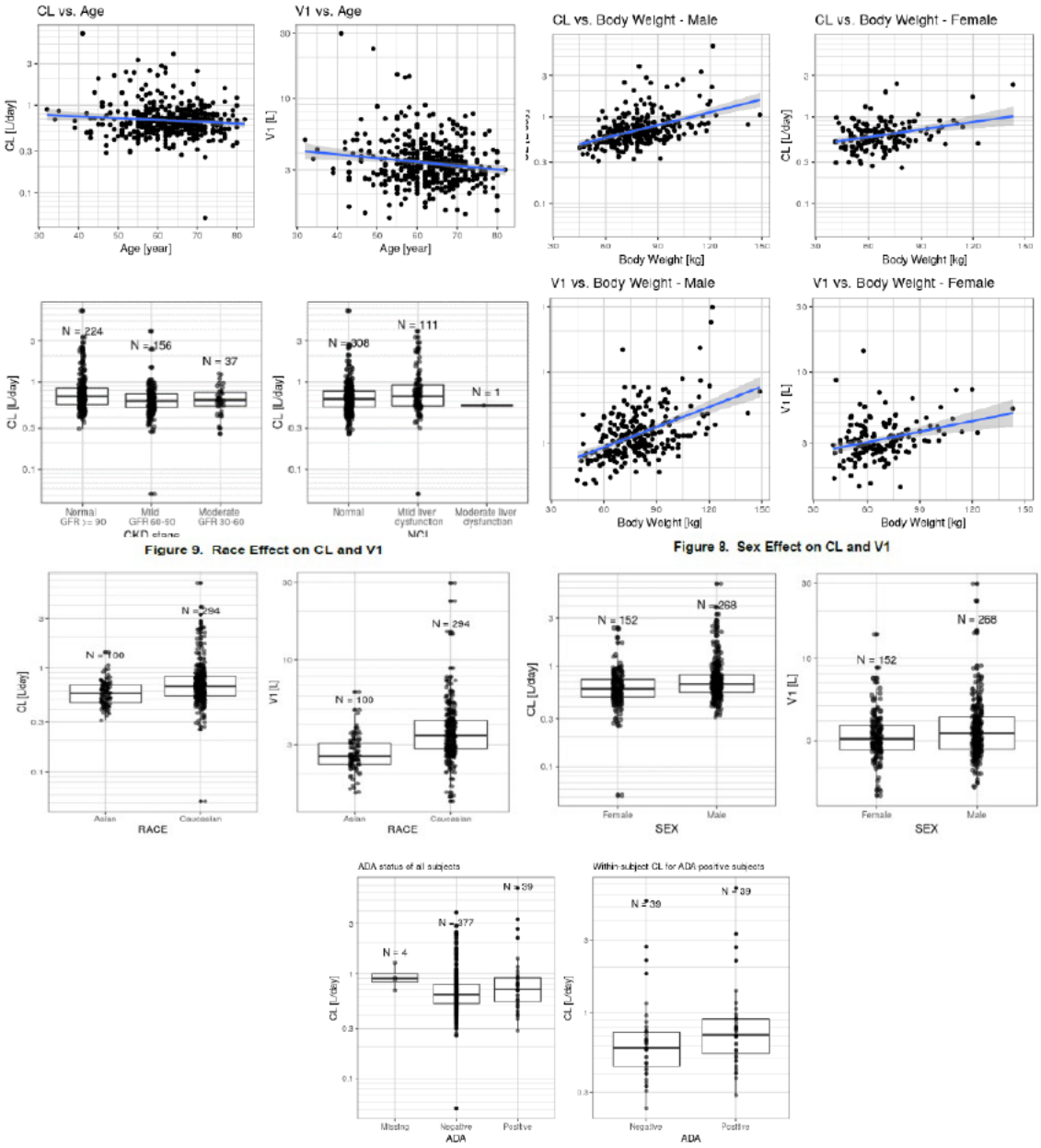
The blue circles, solid red line, and dashed red line respectively represent the data, median, and 2.5th and 97.5th percentiles of the observed data. Shaded red and blue regions respectively represent the confidence intervals about the median and 2.5th / 97.5th percentiles of the simulated data.

A: Study 20160323 & 20200491, Dose 1: Step up dose, dose range :0.003-100 mg
B: Study 20160323 & 20200491, Dose 2 and onwards, dose range :0.003-100 mg
C: Study 20200491, Dose 1: Step up dose
D: Study 20200491, Dose 2 and onwards
Source: Applicant's Population PK Report 157688, Figure 12 and 13.

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Figure 34 Covariate Effects on PK Parameters

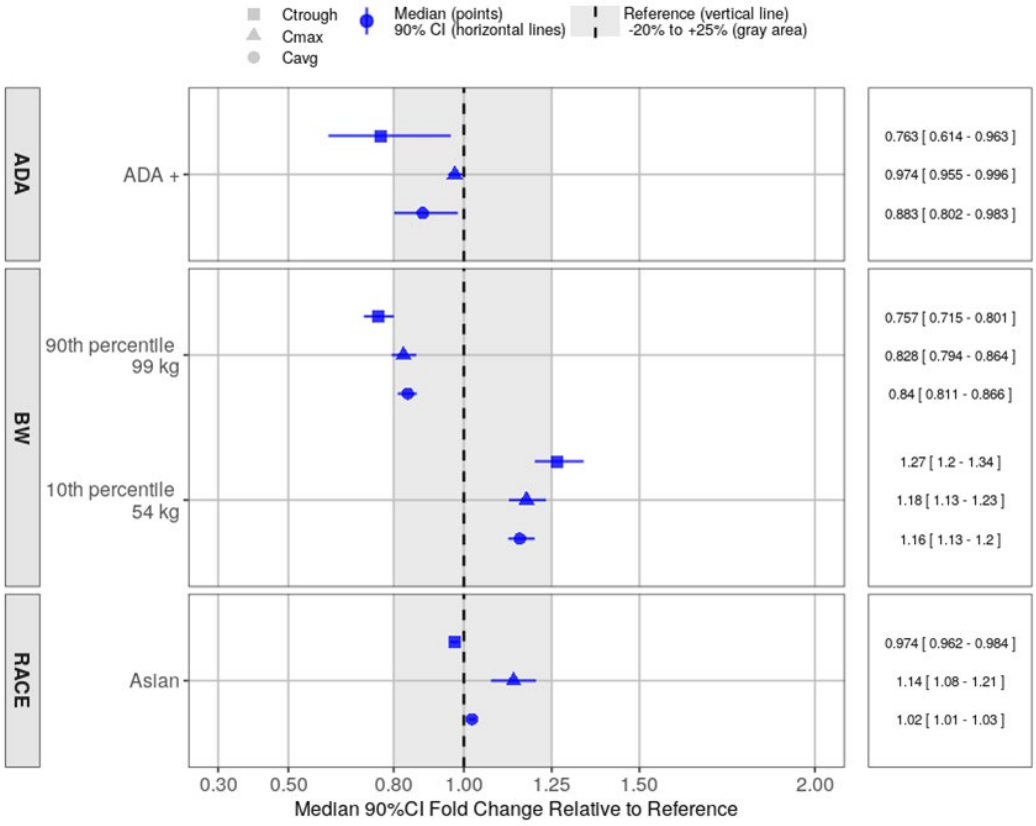


Source: Applicant's Population PK Report 157688, Figure 6-11.

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Figure 35 Forest Plot of Covariate Effects on Tarlatamab Exposures Following 1 mg D1, 10 mg on D8, D15 and Q2W Thereafter Dosing of Tarlatamab



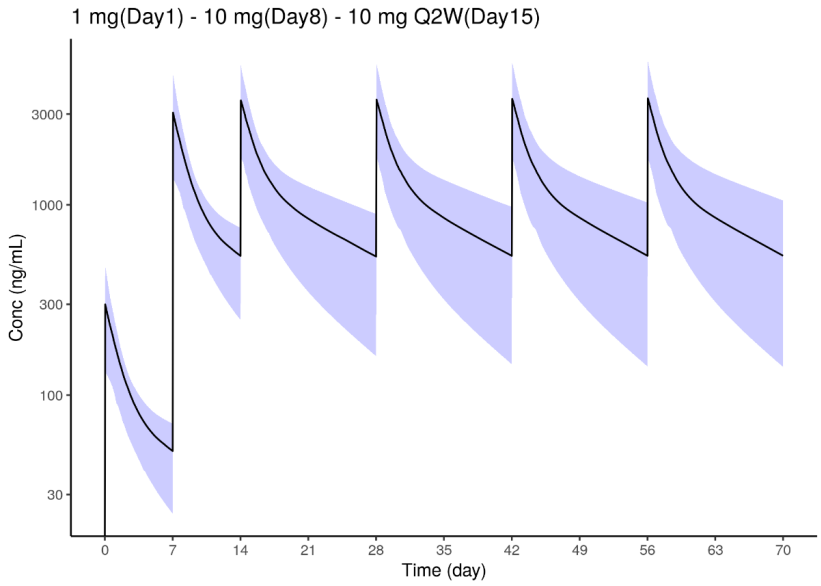
* The simulation was performed with the estimates of the final model using RxODE package in R. The parameters comprising 1,000 samples were generated from normal distributions with the respective estimated parameters and standard errors.
* Tarlatamab exposure metrics are defined as follows: Cavg is defined as Cycle 1 Cavg (average concentration over the first cycle), Cmax (maximum concentration over the first cycle), Ctrough (trough concentration at the end of first cycle).
* The impacts of covariate on Cavg, Cmax, and Ctrough were shown as □ (model-predicted Cavg, Cmax, and Ctrough) relative to the model-predicted Cavg, Cmax and Ctrough in the reference subject. The solid horizontal lines represent the 90□CI of the covariate effect. The dashed vertical line represents the reference and shaded gray region represents 80□/125□ of the reference.
* The reference subject is defined as a white subject receiving 1 mg D1, 10 mg on D8, D15 and Q2W thereafter dosing of tarlatamab with the following covariates: RACE: White/Caucasian; ADA: negative; BW: 73 kg.
* RACE was assessed as a categorical covariate (Asian, White, Black, Other). Black race and Other race are retained in the model but not shown above; the effect of Black race on exposure is not significant due to small sample size; the effect of Other race on exposure is not interpretable.

Source: Applicant's Population PK Report 157688, Figure 14.

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Figure 36 Typical Pharmacokinetic Profile of Tarlatamab Following the Proposed Clinical Regimen 1 mg D1, 10 mg on D8, D15 and Q2W Thereafter



Median is represented by solid black line. 90% prediction interval is represented by the shaded blue area.

Source: Applicant's Population PK Report 157688, Figure 15.

The FDA's Assessment:

Overall, the Applicant's PPK model is generally acceptable for the purposes of characterizing PK and predicting exposure following intravenous infusion of tarlatamab in patients with advanced SCLC with disease progression on or after platinum-based chemotherapy.

The Applicant's parameter values for the final model were generally precisely estimated. Residual standard error (RES) for all structural model parameters were low (<10.7%). RSE for covariate effect parameters were also low (<24.8%), except for the effect of ADA on CL (RSE of 51.4%). All variance parameters were also estimated precisely with RSEs lower than 11.4%. Shrinkage of the inter-individual random effects was low to moderate (<30%). The predictions and residuals are symmetrically distributed without any significant trends. The VPC plots showed acceptable model predictive performance across different studies with a slight tendency to overpredict tarlatamab concentration at 5th percentile during the elimination phase.

No clinically relevant differences in exposure according to patient characteristics were identified, including age (32-82 years), bodyweight (35-149 kg), sex, race (White and Asian), ethnicity, albumin, number of prior anti-cancer therapies, ECOG score, tumor burden, ADA

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status, mild (N=156) or moderate (N=37) renal impairment (eGFR ≥ 30 to < 90 mL/min), or mild (N=111) hepatic impairment (total bilirubin ≤ upper limit of normal (ULN) and AST > ULN).

Model Derived Tarlatamab PK Parameters

The model derived PK parameters for tarlatamab in Study 20200491 based on population PK simulations following the proposed dosage regimen (1 mg on day 1, 10 mg on day 8, 15 and q2w thereafter) were summarized in Table 4. C_{max} was defined as the concentration at the end of infusion.

Table 68 Pharmacokinetic Parameters of Tarlatamab 1/10 mg Q2W in Patients with SCLC in Study 20200491.

	PK Parameters				
	Exposure interval	Geometric mean C_{avg} (%CV)	Geometric mean C_{max} (%CV)	Geometric mean C_{trough} (%CV)	Geometric mean AUC_{tau} (%CV)
First step-up dose 1mg	D1-D8	102 (28.7%)	285 (41.1%)	47.3 (38.2%)	711 (28.7%)
First full dose 10mg	D8-D15	1050 (29%)	2900 (40.7%)	502 (39%)	7370 (29%)
Steady state 10mg Q2W	14 days	1040 (44.5%)	3400 (40.5%)	495 (73.3%)	14600 (44.5%)

Units: AUC_{tau} in ng/mL*day; C_{max}, C_{trough}, and C_{avg} in ng/mL; CV: Coefficient of variation

Source: Table 5 in Applicant's Response to FDA Information Request dated on Jan. 24, 2024.

PK analyses to support the proposed repriming strategy after dose delay

As shown in

and Figure 38, the simulated C_{trough} and C_{avg} levels remained relatively high after a 21 or 28-day dose delay following the administration of full dose of 10mg on day 8 or day 15, respectively. Although the exposure was approximately 60% lower after a 14-day delay post step-up dose administration compared to the treatment plan with no dose delay, the low incidence rate and mild CRS observed in patients following the step- up dose and with dose delay in Study 20200491(For detailed information, please refer to Table 22 in section 6.3.2.2) indicated that the exposure following a 14-day delay post step-up dose administration is sufficient to mitigate the incidence and severity of CRS following administration of 10 mg tarlatamab. These analysis

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results support the Applicant's proposed repriming strategy after dose delay.

Table 69 Exposure comparison between the Applicant's proposed retreatment plan after dose delay and the treatment plan with no dose delay

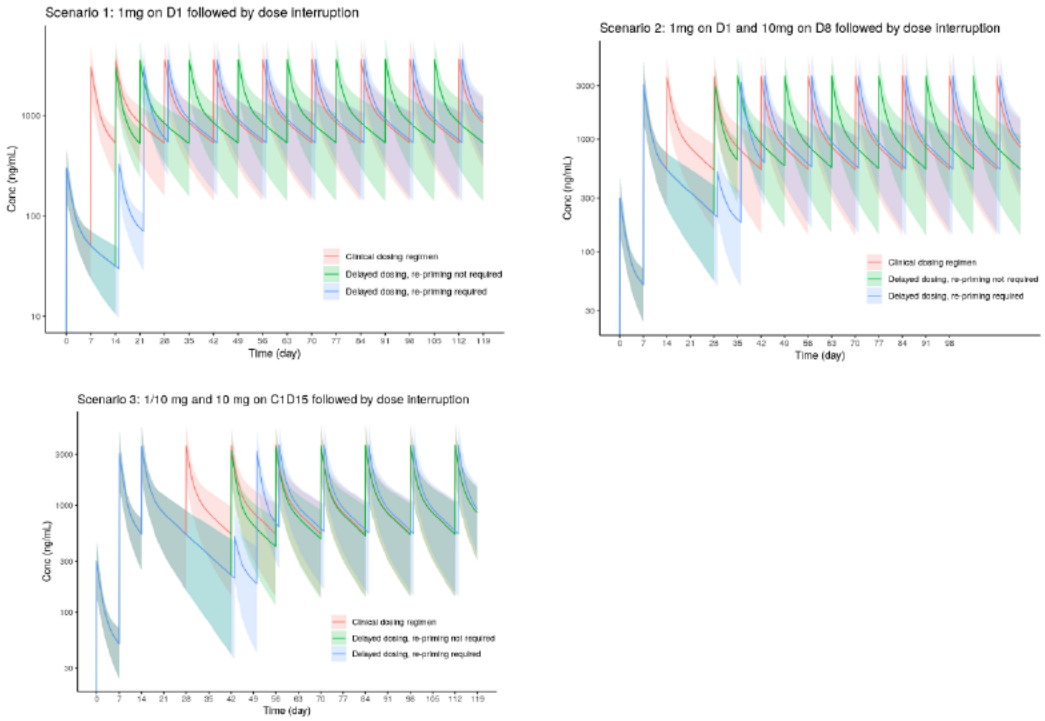
Last dose administered	Duration since last dose	Proposed treatment plan	Ctrough,proposed/ Ctrough,reference	Cavg,proposed/ Cavg,reference
Step-up dose 1 mg	≤ 14 days	10 mg	0.61	0.68
Cycle 1 day 8 10 mg	≤ 21 days	10 mg	4.10	5.57
Cycle 1 day 15 10 mg Q2W thereafter	≤ 28 days	10 mg	4.10	6.61

Ctrough,proposed and Cavg,proposed: simulated geometric mean Ctrough or Cavg on day 14, 21 or 28 since last dose administered based on the Applicant's proposed retreatment plan after dose delay.

Ctrough,reference and Cavg,reference:: simulated geometric mean Ctrough or Cavg on day 14, 21 or 28 since last dose administered based on the Applicant's proposed treatment plan with no dose delay.

Source: summary of the data from Table 8-11 in Applicant's Response to FDA Information Request issued Jan. 11, 2024.

Figure 37 Simulated tarlatamab PK profiles following the proposed treatment plan with no dose delay and the retreatment plan after dose delays



Source: Figure 20-22 in Applicant's Response to FDA

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

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Information Request issued Jan. 11, 2024.

19.4.4. Exposure-Response Analysis

19.4.4.1. ER (efficacy) Executive Summary

The FDA's Assessment:

The E-R efficacy analysis generally supports the proposed dosage of tarlatamab (10 mg) in patients with advanced SCLC with disease progression on or after platinum-based chemotherapy.

The exposure efficacy analysis suggested that higher tarlatamab exposure associated with higher ORR across the dose range of 3 to 100 mg, evaluated in studies 20160323 and 20200491. The ORR appeared to plateau at doses of 10 mg and above. The secondary endpoints (DCR, PFS, OS, BTSR) also demonstrated similar efficacy across the evaluated dose range of 3 to 100 mg. These analyses based on secondary endpoints are considered to be exploratory due to difficulty of interpretation in the absence of an appropriate control arm. Except for the sum of tumor diameter at baseline (BTSR) being identified as a covariate associated with higher hazard for OS, no other covariates were identified to have a clinically meaningful impact on ORR, DCR, PFS, OS and BTSR.

Overall, there are no clinically significant exposure-response relationships for efficacy over the exposure range observed between 10 mg and 100 mg. This flat ER relationship for efficacy is consistent with similar ORRs observed in 10 mg and 100 mg treatment arm in the pivotal trial.

19.4.4.2. ER (efficacy) Assessment Summary

The Applicant's Position:

Using pooled data across Studies 20160323 and 20200491, the relationship between model-estimated averaged concentration over the first cycle and key efficacy endpoints were explored. These analyses confirmed that the exposures associated with the proposed dosing regimen of 10 mg Q2W maximizes the efficacy of tarlatamab.

General Information	
Goal of ER analysis	*Characterize the relationships between tarlatamab serum exposures and key efficacy endpoints, including objective response rate (ORR) (complete response [CR] and partial response [PR]), disease control rate (DCR, comprising CR, PR or stable disease [SD]), progression-free survival (PFS), overall survival (OS), duration of*

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		response (DOR), and best tumor size response (BTSR, based on percentage change in sum of target lesion diameters from baseline)
Study Included		*The dataset for ER analyses consisted of 412 subjects with small cell lung cancer (SCLC) receiving at least one dose of tarlatamab in the monotherapy setting in the phase 1 Study 20160323 and phase 2 Study 20200491*
Endpoint		*Primary: ORR* *Secondary: DCR, PFS, OS, DOR, BTSR*
No. of Patients (total, and with individual PK)		*412*
Population Characteristics	General	*Age median (range): 63 (32-82) year* *Weight median (range): 73 (35-149) kg* *263 (64%) male* *286 (69%) White* *8 (1.9%) Black or African American* *100 (24%) Asian* *18 (4.4%) Other*
	Pediatrics (if any)	*Not Applicable*
Dose(s) Included		*0.003, 0.01, 0.03, 0.1, 0.3, 1, 3, 10, 30, 100 mg Q2W; 200 mg Q3W*
Exposure Metrics Explored (range)		*The PK exposure metrics, including $C_{avg,\ first\ cycle}$, $C_{trough,first\ cycle}$ and $C_{max,first\ cycle}$, were derived from the population pharmacokinetic analysis for tarlatamab based on the model-predicted concentration-time profiles depending on the respective subjects dose, regimen, and PK covariates. These exposure metrics were comparable to steady state exposures.*
Covariates Evaluated		*Age, body weight, sex, race, ethnicity, liver metastasis, brain metastasis, smoking status, number of prior lines of anticancer therapy, prior PD-1 or PD-L1 inhibitor theray, sum of target lesion diameters, presence of ADA, chronic kidney disease category (CKD) based on estimated glomercular filtration rate, National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria for hepatic dysfunction.*
Final Model Parameters	**Summary**	**Acceptability [FDA's comments]**
Model Structure	*Cox regression model: PFS, OS, DOR*	Acceptable

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	Emax model: ORR, DCR *Imax model: BTSR*	
Model Parameter Estimates	*Tables 2 to 5 of* Amgen Pharmacometrics Report 157687	Acceptable
Model Evaluation	*Base model selection was based on* objective function value (OFV), Akaike information criterion (AIC), and/or Bayesian information criterion (BIC). Once the base model was determined and the ER relationship was identified as significant, a forward inclusion and backward elimination method was implemented to explore potential covariates that could significantly affect the ER relationship in a multivariate fashion.	Acceptable
Covariates and Clinical Relevance	*Sum of target lesion diameters (baseline; independent of exposures) was found to be significantly associated with higher hazard for OS.* *Subgroups of the significant covariates identified in tarlatamab population PK analysis (Report 157688) were evaluated on efficacy.* None of the covariates evaluated in this analysis resulted in clinically meaningful change in efficacy and therefore do not warrant a dose adjustment.	The alternative tarlatamab exposure metrics, Cavg,event (average concentration up to the time of first response, progression or end of treatment) and Cavg,ss (average concentration at steady state) were used to conduct additional ER analysis for efficacy endpoints (ORR, DCR,PFS,OS and BTSR). The consistent results were obtained using the Cavg,event or Cavg,ss exposure metrics for evaluating the exposure efficacy relationships, when compared with the exposure efficacy relationships obtained using Cavg,first cycle.

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Simulation for Specific Population	*Not applicable*	
Visualization of E-R relationships	*Figures 3 to 9 and Figure 11 of* Amgen Pharmacometrics Report 157687	Acceptable
Overall Clinical Relevance for ER	The results of ER analysis suggest that the proposed clinical regimen of 10 mg Q2W reaches the plateau of efficacy in this patient population (Figure 1 of Amgen Report 157687). None of the covariates evaluated in this analysis resulted in clinically meaningful change in efficacy and therefore do not warrant a dose adjustment.	Overall, the Applicant's ER analyses for efficacy are deemed acceptable.
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics		The efficacy of tarlatamab was evaluated at two dose levels, 10 and 100 mg, in the dose expansion cohorts in study 20200491. The following statement was included in section 12.2. *"There are no clinically significant exposure-response relationships for efficacy over the exposure range observed between 10 mg and 100 mg. (10 times the highest approved recommended dosage)."*

Amgen Pharmacometrics Report: 157687

Table 70 Summary of Demographics, Clinical Characteristics and Baseline Covariates

Variable	**20160323**, N = 195[1]	**20200491**, N = 217[1]	**Overall**, N = 412[1]
Age (year)			
Mean (SD)	62 (9)	63 (9)	63 (9)
Median (Minimum-Maximum)	63 (32-80)	64 (34-82)	63 (32-82)

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Weight (kg)			
Mean (SD)	76 (20)	74 (16)	75 (18)
Median (Minimum-Maximum)	74 (35-149)	72 (41-123)	73 (35-149)
Sex			
Male	108 / 195 (55%)	155 / 217 (71%)	263 / 412 (64%)
Female	87 / 195 (45%)	62 / 217 (29%)	149 / 412 (36%)
Race			
American Indian or Alaska Native	0 / 195 (0%)	0 / 217 (0%)	0 / 412 (0%)
Asian	21 / 195 (11%)	79 / 217 (36%)	100 / 412 (24%)
Black or African American	7 / 195 (3.6%)	1 / 217 (0.5%)	8 / 412 (1.9%)
Native Hawaiian or Other Pacific Islander	0 / 195 (0%)	0 / 217 (0%)	0 / 412 (0%)
White	151 / 195 (77%)	135 / 217 (62%)	286 / 412 (69%)
Other	16 / 195 (8.2%)	2 / 217 (0.9%)	18 / 412 (4.4%)
Ethnicity			
Hispanic	2 / 195 (1.0%)	3 / 217 (1.4%)	5 / 412 (1.2%)
Non-Hispanic	193 / 195 (99%)	212 / 217 (98%)	405 / 412 (98%)
(Missing)	0 / 195 (0%)	2 / 217 (0.9%)	2 / 412 (0.5%)
ADA status			
Negative	180 / 195 (92%)	191 / 217 (88%)	371 / 412 (90%)
Positive	15 / 195 (7.7%)	26 / 217 (12%)	41 / 412 (10.0%)
Baseline sum of target lesion diameters (mm)			
Mean (SD)	119 (85)	107 (67)	113 (76)
Median (Minimum-Maximum)	100 (15-643)	95 (11-320)	97 (11-643)
(Missing)	34	27	61
Smoking status			
Never	18 / 193 (9.3%)	14 / 217 (6.5%)	32 / 410 (7.8%)
Current	34 / 193 (18%)	32 / 217 (15%)	66 / 410 (16%)
Former	141 / 193 (73%)	171 / 217 (79%)	312 / 410 (76%)
(Missing)	2	0	2
Number of prior anticancer therapies			
NHXACTHR=1	51 / 195 (26%)	4 / 217 (1.8%)	55 / 412 (13%)
NHXACTHR=2	87 / 195 (45%)	132 / 217 (61%)	219 / 412 (53%)
NHXACTHR=3	29 / 195 (15%)	45 / 217 (21%)	74 / 412 (18%)
NHXACTHR > 3	26 / 195 (13%)	36 / 217 (17%)	62 / 412 (15%)
(Missing)	2 / 195 (1.0%)	0 / 217 (0%)	2 / 412 (0.5%)

Variable	**20160323, N = 1951**	**20200491, N = 2171**	**Overall, N = 4121**
Brain metastasis at screening			
No brain metastasis	145 / 195 (74%)	159 / 217 (73%)	304 / 412 (74%)
Brain metastasis	50 / 195 (26%)	58 / 217 (27%)	108 / 412 (26%)

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Liver metastasis at screening			
No liver metastasis	107 / 195 (55%)	140 / 217 (65%)	247 / 412 (60%)
Liver metastasis	88 / 195 (45%)	77 / 217 (35%)	165 / 412 (40%)
Prior PD-1/PD-L1 administration			
No prior PD-1/PD-L1 admin	78 / 195 (40%)	58 / 217 (27%)	136 / 412 (33%)
Prior PD-1/PD-L1 admin	117 / 195 (60%)	159 / 217 (73%)	276 / 412 (67%)
Chronic kidney disease (CKD) stage at baseline			
Normal	105 / 195 (54%)	117 / 217 (54%)	222 / 412 (54%)
Mild	73 / 195 (37%)	78 / 217 (36%)	151 / 412 (37%)
Moderate	14 / 195 (7.2%)	22 / 217 (10%)	36 / 412 (8.7%)
Severe	0 / 195 (0%)	0 / 217 (0%)	0 / 412 (0%)
Kidney failure	0 / 195 (0%)	0 / 217 (0%)	0 / 412 (0%)
(Missing)	3 / 195 (1.5%)	0 / 217 (0%)	3 / 412 (0.7%)
NCI-ODWG			
Normal	145 / 195 (74%)	156 / 217 (72%)	301 / 412 (73%)
Mild liver dysfunction	50 / 195 (26%)	60 / 217 (28%)	110 / 412 (27%)
Moderate liver dysfunction	0 / 195 (0%)	1 / 217 (0.5%)	1 / 412 (0.2%)
Severe liver dysfunction	0 / 195 (0%)	0 / 217 (0%)	0 / 412 (0%)
(Missing)	0 / 195 (0%)	0 / 217 (0%)	0 / 412 (0%)

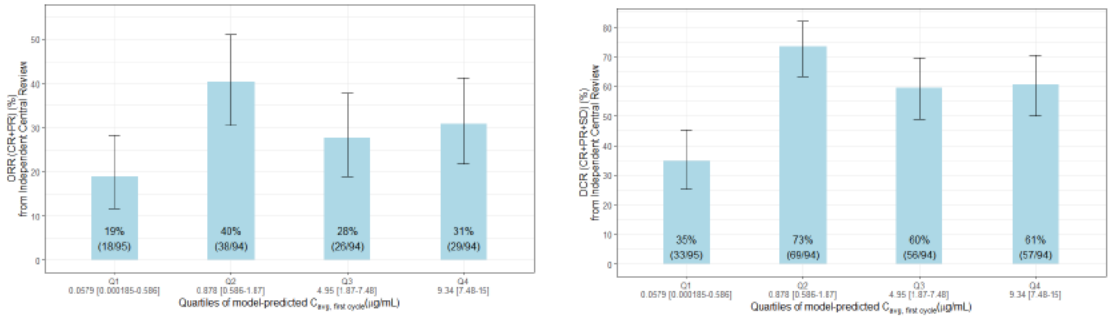
CKD: chronic kidney disease category based on eGFR uses criteria determined by the FDA Guidance: Pharmacokinetics in Patients with Impaired Renal Function eGFR in mL/min = BSA normalized eGFR (mL/min/1.73m^2) x (BSA (m^2)/1.73. BSA normalized eGFR (mL/min/1.73m^2) = 175 * (CRT/88.4^-1.154) *(AGE^-0.203) * (0.742 if female) * (1.212 if African American);
NCI-ODWG: National Cancer Institute – dysfunction working group for hepatic function categories are determined as follows: Mild liver dysfunction: if either B1 or B2 is true where B1: TB≤1.5xULN and (ALT>ULN or AST> ULN) and B2: ULN<TB ≤ 1.5xULN and (non-missing ALT or non-missing AST).
Moderate liver dysfunction: 1.5xULN<TB≤3.0 x ULN and non-missing ALT or AST. Severe liver dysfunction: 3.0 x ULN < TB and non-missing ALT or AST. TB: total bilirubin at baseline; ULN: upper limit of normal range; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

Source: Applicant's ER Report 157687, Table 1.

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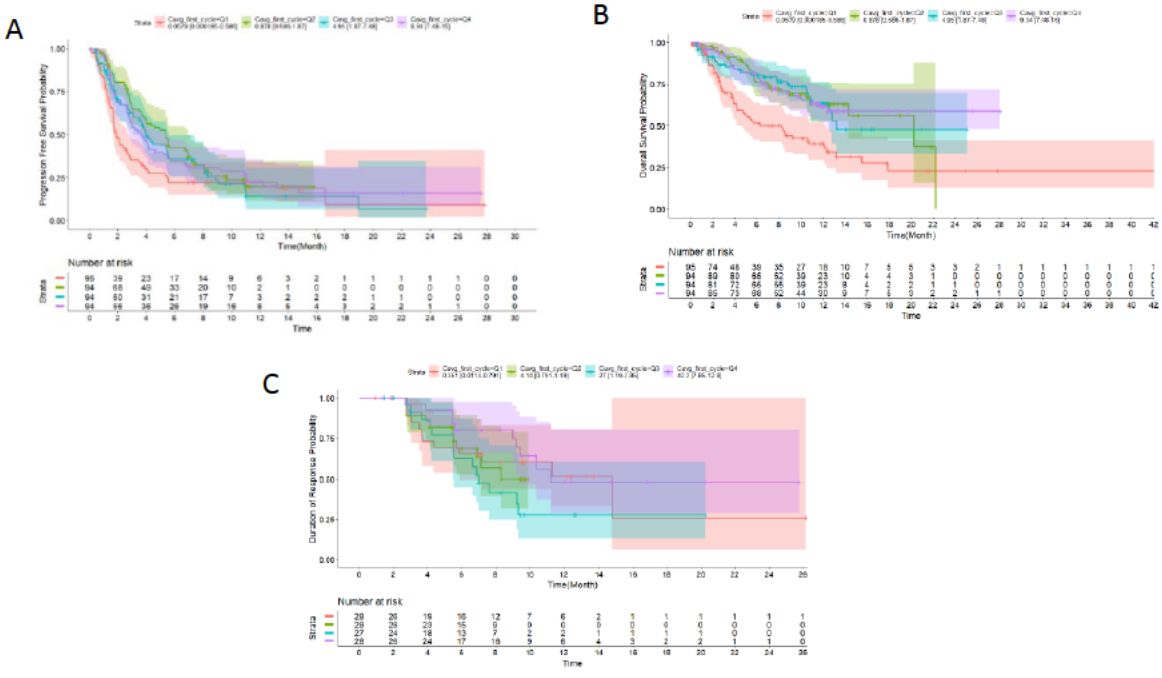
Figure 38 Relationships Between ORR and DCR vs. Model-predicted Cavg,first cycle Quartiles



Cavg,firstcycle=model-estimated averaged concentration over the first cycle presented as Median [range] for each Quartile (Q) ; ORR= objective response rate; DCR=disease control rate; The 95% confidence intervals shown in the figure were estimated by Clopper–Pearson method.

Source: Applicant's ER Report 157687, Figure 3.

Figure 39 Kaplan–Meier Plot of Progression Free Survival (A), Overall Survival (B) and Duration of Response (C) Stratified by Model-predicted Cavg, first cycle Quartiles

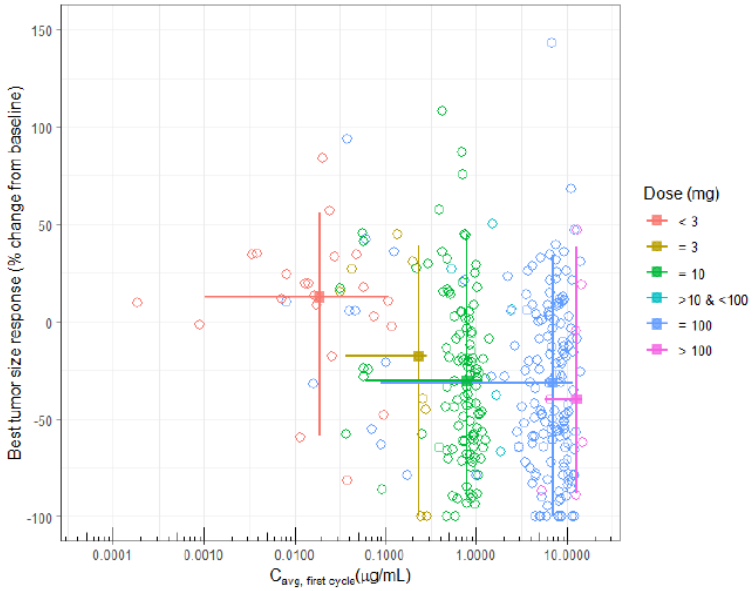


Cavg, first cycle=model-estimated averaged concentration over the first cycle

Source: Applicant's ER Report 157687, Figure 4,5 and 6.

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Figure 40 Best Tumor Size Response by Independent Assessor vs. Model-predicted tarlatamab Cavg,first cycle



Cavg, first cycle = model-estimated average concentration over the first cycle; BTSR = Best tumor size reduction (% change from baseline); Open circles represent individual subject's best tumor size response (% change from baseline) and the corresponding Cavg, first cycle. Solid squares represent the median of best tumor size response (% change from baseline) and corresponding median of Cavg, first cycle for < 3 mg, 3 mg, 10 mg, 100 mg and > 100mg target dose, and different target dose groups were represented in different colors. Vertical and horizontal lines represent 5th and 95th percentiles of the best tumor size response (% change from baseline) and Cavg, first cycle in <3 mg, 3 mg, 10 mg, 100 mg and >100 mg target dose, respectively.

Source: Applicant's ER Report 157687, Figure 7.

Table 71 Summary of Univariate Analysis between $C_{avg, first\ cycle}$ and ORR/DCR

Univariate Analysis for ORR		
	Estimate	95% CI
Log-linear Model: AIC: 455.522 ; BIC: 463.386 ; OFV: 451.522		
β0: Intercept of log odds	-1.87	[-2.65, -1.09]
β1: Slope of log odds change with an increase in LN(Cavg, first cycle in ng/mL) by 1	0.137	[0.0346, 0.239]
Emax Model: AIC: 446.690 ; BIC: 454.554 ; OFV: 442.690		
Emax: maximum ORR from drug effect	0.339	[0.286, 0.397]
EC50: Cavg, first cycle (ng/mL) achiving 50% of maximum ORR		
Univariate Analysis for DCR		

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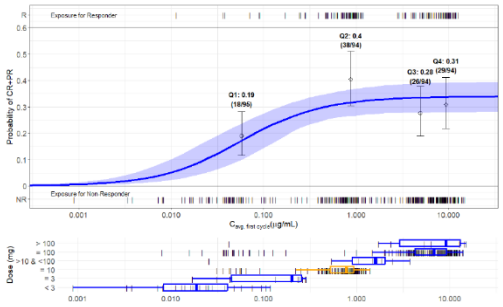
	Estimate	95% CI
Log-linear Model: AIC: 502.004 ; BIC: 509.868; OFV: 498.004		
Large correlation (-0.967) between parameter estimates was found between β0 and β1		
β0: Intercept of log odds	-1.26	[-2.07, -0.449]
β1: Slope of log odds change with an increase in LN(Cavg, first cycle in ng/mL) by 1	0.216	[0.105, 0.327]
Emax Model: AIC: 502.030 ; BIC: 509.894 ; OFV: 498.030		
Emax: maximum DCR from drug effect	0.650	[0.587, 0.707]
EC50: Cavg, first cycle (ng/mL) achiving 50% of maximum DCR	49.4	[20.9, 117]

estimated averaged concentration over the first cycle; ORR = objective response rate;
DCR =disease control rate; AIC = Akaike information criterion; BIC = Bayesian information criterion; OFV =objective function value

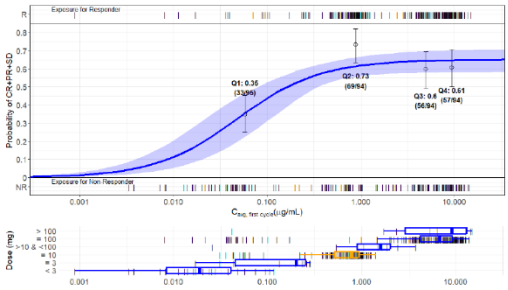
Source: Applicant's ER Report 157687, Table 2.

Figure 41 Model-predicted ORR (A) and DCR (B) and their distribution by tarlatamab Cavg,first cycle quartiles

A



B



Cavg, first cycle = model-estimated averaged concentration over the first cycle; ORR= objective response rate; DCR = disease control rate; In the upper panel: vertical error bars and open circles represent 95% CI and mean of probability of observed ORR or DCR by model-simulated Cavg, first cycle quartiles, respectively. The blue line and blue shaded area represent the model predicted probability curves with 95% prediction bands. The short vertical lines in the upper and lower band represent individuals' Cavg, first cycle; In the lower panel: distributions of Cavg, first cycle, stratified by dose (mg) were summarized by boxplots. The hinges of horizontal boxplots represent inter-quartile range (IQR, meaning 25th to 75th percentiles) of Cavg, first cycle, the whiskers of horizontal boxplots represent the largest and smallest Cavg, first cycle, no more than 1.5*IQR from the right and left hinges, respectively. The short vertical lines represent individuals' Cavg, firstcycle.

Source: Applicant's ER Report 157687, Figure 8 and 9

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Table 72 Results of Cox Regression Analyses for PFS, OS and DOR

Response Variable	Predictor Variable	Estimate	Standard Error	P-value
Progression Free Survival, PFS	LN (Cavg, first cycle)	0.919	0.0303	0.00564
Overall Survival, OS	LN (Cavg, first cycle)	0.849	0.0338	0.00000125
Duration of Response,DOR	LN (Cavg, first cycle)	1.03	0.0916	0.742

Source: Applicant's ER Report 157687, Table 3.

Table 73 Summary of multivariate Regression Analysis Results for PFS and OS

Response Variable	Predictor Variable	Estimate	Standard Error	P-value
Progression Free Survival, PFS	LN (Cavg, first cycle)	0.919	0.0303	0.00564
Overall Survival, OS	LN (Cavg, first cycle)	0.849	0.0339	0.00000149
	Sum of tumor diameter (baseline)	1.00	0.000851	0.00000835

Source: Applicant's ER Report 157687, Table 4.

The FDA's Assessment:

The E-R efficacy analyses supports the proposed dosage of tarlatamab (10 mg) in patients with advanced SCLC with disease progression on or after platinum-based chemotherapy.

ORR (Primary endpoint)

Graphical analyses for ORR suggested an efficacy benefit for patients with tarlatamab $C_{avg,first\ cycle}$ above Q1 (Figure 39 and Figure 40). Exposure efficacy analyses indicated a positive relationship between tarlatamab exposure and ORR, with higher ORR observed at higher exposure levels. The ORR appeared to plateau at dose of 10 mg and above. The model estimated ORR probabilities were 26.2, 31.4 and 33.6% at doses of 3, 10 and 100 mg Q2W, respectively (Figure 42). Additionally, the estimated DCR probabilities were 52.0%, 60.8% and 64.5%, respectively (Figure 42). The corresponding tarlatamab median $C_{avg,first\ cycle}$ values were

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0.2, 0.773 and 6.77 ug/mL at doses of 3, 10 and 100 mg Q2W, respectively. No significant covariate was identified for both ORR and DCR.
Additionally, the exposure metrics ($C_{avg, first\ cycle}$) used in this exposure efficacy analysis were derived from the PPK analysis based on the patients' actual tarlatamab dosing records over the first cycle and patient specific covariates identified in the PPK analysis. Considering the first response (PR or better) was assessed approximately 6 weeks after the initial treatment of tarlatamab (Figure 13 in section 8.1.2), the $C_{avg\ during\ first\ cycle}$ has integrated the treatment modification information including any treatment discontinuation or dose interruption during the first cycle. Therefore, $C_{avg, first\ cycle}$ is an appropriate exposure metric for evaluating the relationship between tarlatamab exposure and ORR. Based on the identified E-R relationship, the entire exposure range following administration of 1/10 mg has likely already reached a level of exposure that may lead to a plateau response (Figure 42). This is consistent with the observed data which indicated that dose interruptions did not appear to impact the tarlatamab responses in the 1/10 mg cohort (For the detailed information, please refer to Table 23 in Section 6.3.2.2).

DCR, PFS, OS, DOR and BTSR (secondary endpoints)

Overall, E-R analyses indicated that, across the evaluated exposure range, the secondary efficacy endpoints (DCR, PFS, OS and BTSR) were significantly associated with tarlatamab $C_{avg,first\ cycle}$ and appeared to reach a plateau with exposure at 10 mg Q2W. This is consistent with the results obtained for the primary efficacy endpoint (ORR).

The univariate CoxPH analyses for time-to-events (PFS and OS) also indicated significant associations between tarlatamab $C_{avg,first\ cycle}$ and PFS and OS (Table 71). The E-R trend for DOR is not statistically significant possibly due to the limited sample size (~28 patients in each quartile). The multivariate COX regression analyses identified the sum of tumor diameter at baseline as a covariate that was significantly associated with higher hazard for OS. No other significant covariates were identified for PFS (Table 72). Of note, FDA does not consider these endpoints interpretable in the absence of an appropriate control arm (see Section 8.1.2) and these analyses are considered to be exploratory.

Please note that the efficacy of tarlatamab was evaluated at two dose levels, 10 and 100 mg, in the dose expansion cohorts in study 20200491. There was no clinically significant E-R relationship for efficacy over the exposure range between 10 and 100 mg.

19.4.4.3. ER (safety) Executive Summary

The FDA's Assessment:

The E-R safety analysis generally supports the proposed dosage of tarlatamab (10 mg) in patients with advanced SCLC with disease progression on or after platinum-based chemotherapy.

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The E-R safety analyses indicated that there was an exposure-response relationship between tarlatamab exposure and neutropenia or neurologic toxicity including ICANS with a higher risk of any grade neutropenia or neurologic toxicity including ICANS at higher exposure.

Multivariate logistic regression analyses indicated that the higher sum of tumor lesion diameter at baseline and exposure to prior anti-PD1 treatment were associated with higher probability of neurologic toxicity including ICANS, while the ECOG status at baseline was associated with higher probability of neutropenia.

In addition, the observed proportion of patients experiencing neutropenia and neurologic toxicity including ICANS following a 100 mg target dose, was higher than those observed in 10 mg target dose. This dose-response trend was consistent with the estimated E-R relationship for safety.

19.4.4.4. ER (safety) Assessment Summary

The Applicant's Position:

No clear trends for exposure-response relationships were identified for grade ≥ 3 adverse events, grade ≥ 3 treatment-related adverse events, and grade ≥ 3 adverse events of interest of neurological events, ICANS, and CRS. A shallow trend was observed for higher percentage of subjects experiencing grade ≥ 3 neutropenia with increasing tarlatamab exposures. No clinically relevant impact on QTc interval was observed at the proposed clinical regimen of 10 mg Q2W.

The results of the exposure-response analysis suggest that the proposed clinical regimen of 10 mg Q2W reaches the plateau of efficacy with a limited impact on neutropenia and provides a reasonable balance of benefit-risk in this patient population. None of the covariates evaluated in this analysis resulted in clinically meaningful changes in the drug's effect on efficacy and therefore do not warrant a dose adjustment.

General Information	
Goal of ER analysis	*Characterize relationships between tarlatamab serum exposures and key safety endpoints, including overall treatment-emergent adverse event (TEAE), treatment-related adverse event (TRAE) and selected TEAE of neutropenia, TEAE of neurological events, TEAE of immune effector cell-associated neurotoxicity syndrome (ICANS), and TEAE of cytokine release syndrome (CRS)*
Study Included	*The dataset for ER analyses consisted of 412 subjects with small cell lung cancer (SCLC) receiving at least one dose of tarlatamab in the monotherapy setting in the phase 1 Study 20160323 and phase 2 Study 20200491*

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Population Included		*SCLC patients*
Endpoint		*Maximal grade of TEAE, TRAE, and Event of Interest: TEAE of neutropenia, neurological events, immune effector cell-associated neurotoxicity syndrome (ICANS) and cytokine release syndrome (CRS).*
No. of Patients (total, and with individual PK)		*412*
Population Characteristics	General	*Age median (range): 63 (32-82) year* *Weight median (range): 73 (35-149) kg* *263 (64%) male* *286 (69%) White* *8 (1.9%) Black or African American* *100 (24%) Asian* *18 (4.4%) Other*
	Organ impairment	*Hepatic impairment (NCI-ODWG):* *Normal: 301 (73%), Mild LD: 110 (27%) , Moderate LD: 1 (0.2%)* *Renal impairment (CKD based on eGFR):* *Normal: 222 (54%), Mild: 151 (37%), Moderate: 36 (8.7%), Missing: 3 (0.7%)*
	Pediatrics (if any)	*Not Applicable*
	Geriatrics (if any)	*Age ≥ 75: n = 33 (8.01%)*
Dose(s) Included		*0.003, 0.01, 0.03, 0.1, 0.3, 1, 3, 10, 30, 100 mg Q2W; 200 mg Q3W*
Exposure Metrics Explored (range)		*The exposure metrics, including $C_{avg,\ first\ cycle}$, $C_{trough,first\ cycle}$ and $C_{max,first\ cycle}$, were derived from the population pharmacokinetic analysis for tarlatamab based on the model-predicted concentration-time profiles depending on the respective subjects dose, regimen, and PK covariates.*
Covariates Evaluated		*Age, body weight, sex, race, ethnicity, liver metastasis, brain metastasis, smoking status, number of prior lines of anticancer therapy, prior PD-1 or PD-L1 inhibitor therapy, sum of target lesion diameters, presence of ADA, chronic kidney disease category (CKD) based on estimated glomerular filtration rate, National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria for hepatic dysfunction.*
Final Model Parameters	**Summary**	**Acceptability**

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		[FDA's comments]
Model Structure	*Logistic regression: Grade 3+ TEAE, Grade 3+ TRAE, Grade 3+ TEAE of neutropenia, neurological event, ICANS, CRS, and neutropenia*	Acceptable
Model Parameter Estimates	Table 7 of Amgen Pharmacometrics Report: 157687	Acceptable
Model Evaluation	*ER relationships were assessed by Wald test. Associations were considered significant if the p-value was less than 0.05. When an ER relationship for a safety endpoint was identified to be significant, a stepwise method was implemented to identify potential covariates based on BIC.*	Acceptable
Covariates and Clinical Relevance	*No significant covariate was identified*	Acceptable
Simulation for Specific Population	Not Applicable	
Visualization of E-R relationships	*Figures 12 and 13 of* Amgen Pharmacometrics Report: 157687	The additional exposure safety analysis for neurologic toxicity including ICANS was conducted using tarlatamab exposure metrics, Cavg, ss and Cmax, ss.
Overall Clinical Relevance for ER	*Tarlatamab exposure was associated with Grade 3+ neutropenia. No covariate was found to be significant for Grade 3+ neutropenia.*	The ER relationship for CRS cannot be adequately evaluated solely based on the data in safety dataset. This is because the step-up dosing regimen was utilized to mitigate the CRS risk at the dose of 3 mg and above, as a result, the ER analysis

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		results for CRS derived from the safety dataset may be confounded by the mitigation approach and may not accurately reflect the true relationship between tarlatamab exposure and CRS risk.
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics		The safety of tarlatamab was evaluated at two dose levels, 10 and 100 mg, in the dose expansion cohorts in study 20200491. The following statement was included in section 12.2. "There is an exposure-response relationship between tarlatamab exposure and neutropenia or neurologic toxicity including ICANS with a higher risk of any grade neutropenia or neurologic toxicity including ICANS at higher exposure."

Amgen Pharmacometrics Report: 157687

Table 74 Frequencies of Adverse Events by Exposure Quartiles

	Cavg, first cycle median [range] in µg/mL				
	Q1 0.0599 [0.000185,0.603]	Q2 0.865 [0.619,1.12]	Q3 4.35 [1.13,6.94]	Q4 9.24 [6.94,15]	Overall 1.12 [0.000185,15]
	Nevent/Nsubject Rate [95%CI]				
TEAE	71/103 68.9[59.1,77.7]	51/103 49.5[39.5,59.5]	69/103 67[57,75.9]	62/103 60.2[50.1,69.7]	253/412 61.4[56.5,66.1]
TRAE	43/103 41.7[32.1,51.9]	19/103 18.4[11.5,27.3]	49/103 47.6[37.6,57.6]	35/103 34[24.9,44]	146/412 35.4[30.8,40.3]
Neutropenia	4/103 3.88[1.07,9.65]	5/103 4.85[1.59,11]	10/103 9.71[4.75,17.1]	17/103 16.5[9.92,25.1]	36/412 8.74[6.19,11.9]
Neurological event	10/103 9.71[4.75,17.1]	9/103 8.74[4.07,15.9]	13/103 12.6[6.89,20.6]	6/103 5.83[2.17,12.2]	38/412 9.22[6.61,12.4]
ICANS	3/103 2.91[0.605,8.28]	1/103 0.971[0.0246,5.29]	5/103 4.85[1.59,11]	4/103 3.88[1.07,9.65]	13/412 3.16[1.69,5.34]
	Cmax, first cycle, median [range] in µg/mL				
	Q1 0.351 [0.001,3.27]	Q2 4.06 [3.28,5.44]	Q3 24.9 [5.46,32.6]	Q4 39.5 [32.6,81.4]	Overall 5.45 [0.001,81.4]

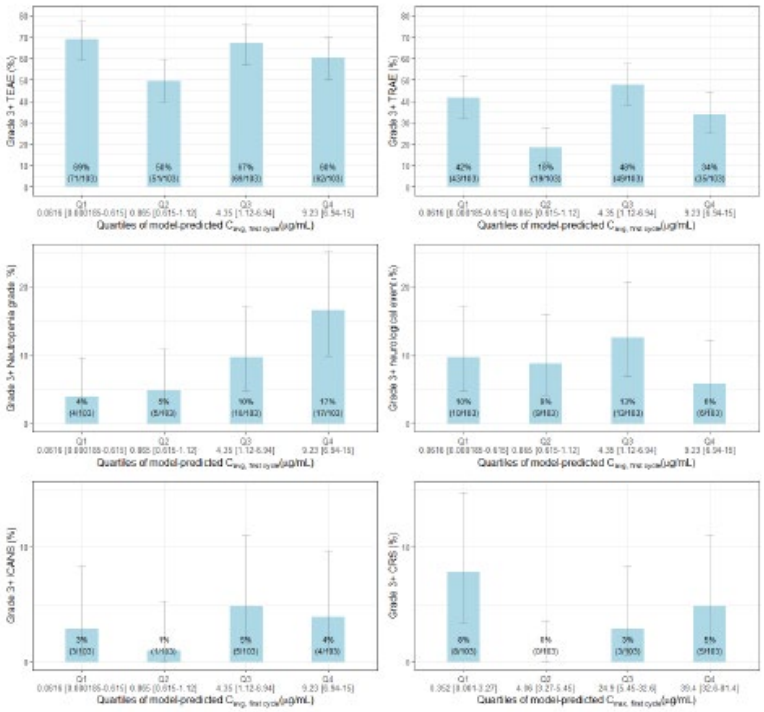
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	Nevent/Nsubject Rate [95%CI]				
	8/103	0/103	3/103	5/103	16/412
CRS	7.77[3.41,14.7]	0[0,3.52]	2.91[0.605,8.28]	4.85[1.59,11]	3.88[2.24,6.23]

TEAE = Treatment Emergent Adverse Event; TRAE = Treatment Related Adverse Event; ICANS = immune effector cell-associated neurotoxicity syndrome; CRS = cytokine release syndrome.

Source: Table 6 in Applicant's ER report 157687

Figure 42 Proportion of Subjects Experiencing Grade ≥ 3 Safety Events by Tarlatamab Exposure Quartiles



Source: Figure 12 in Applicant's ER report 157687

Table 75 Results of Logistic Regression Analyses for Safety Events

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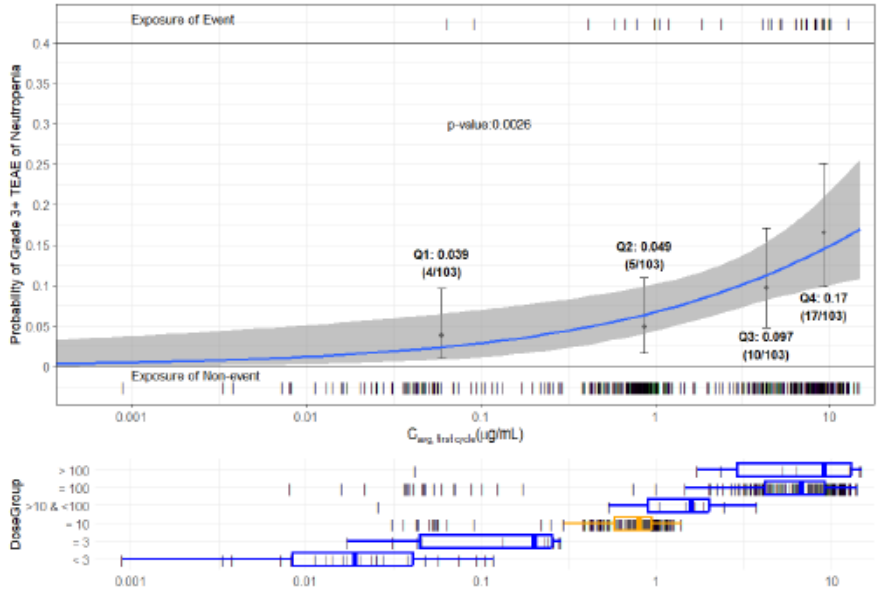
Reference ID: 5382024

Safety Event	Predictor Variable	Estimate	Standard Error	P-value
Grade 3+ TEAE	LN($C_{avg, first\ cycle}$)	-0.0224	0.0516	0.664
Grade3+ TRAE	LN($C_{avg, first\ cycle}$)	0.0297	0.0527	0.573
Grade3+ Neutropenia	LN($C_{avg, first\ cycle}$)	0.385	0.128	0.00260
Grade3+ Neurological event	LN($C_{avg, first\ cycle}$)	-0.0595	0.0823	0.470
Grade3+ ICONS	LN($C_{avg, first\ cycle}$)	0.0958	0.157	0.542
Grade 3+ CRS	LN($C_{avg, first\ cycle}$)	-0.268	0.107	0.0120

TEAE = Treatment Emergent Adverse Event; TRAE = Treatment Related Adverse Event; ICANS = immune effector cell-associated neurotoxicity syndrome; CRS = cytokine release syndrome. LN = natural log.

Source: Table 7 in Applicant's ER report 157687

Figure 43 Model Predicted Probability of Grade 3+ neutropenia and Observed Grade 3+ neutropenia events versus tarlatamab Cavg, first cycle



$C_{avg, first\ cycle=}$ model-estimated averaged concentration over the first cycle; Upper panel: Vertical error bars and open circles represent 95% CI and mean of probability of grade 3+ neutropenia, respectively. The blue line and shaded area represent the model predicted probability curves with 95% prediction bands for grade 3+ neutropenia. The short vertical lines in the upper and lower band represent individuals' $C_{avg, first\ cycle}$. In lower panel: distributions of $C_{avg, first\ cycle}$, stratified by dose (mg) were summarized by boxplots. The hinges of horizontal boxplots represent inter-quartile range (IQR, meaning 25th to 75th percentiles) of $C_{avg, first\ cycle}$,

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the whiskers of horizontal boxplots represent the largest and smallest $C_{avg, first\ cycle}$, no more than 1.5*IQR from the right and left hinges, respectively. The short vertical lines represent individuals' $C_{avg, first\ cycle}$.

Source: Figure 13 in Applicant's ER report 157687

The FDA's Assessment:

The E-R safety analysis generally supports the proposed dosage of tarlatamab (10 mg) in patients with advanced SCLC with disease progression on or after platinum-based chemotherapy.

Applicant's exposure safety analyses are considered acceptable. In response to the FDA's IR, the Applicant conducted several additional analyses to further explore safety-related aspects of the treatment with tarlatamab in patients with advanced SCLC with disease progression on or after platinum-based chemotherapy. These analyses showed that there was a positive E-R relationship between tarlatamab exposure and neutropenia or neurologic toxicity including ICANS with a higher risk of any grade neutropenia or neurologic toxicity including ICANS at higher exposure.

The E-R analyses for CRS could be potentially confounded by the mitigation approach (step-up dosing regimen) utilized to manage the CRS risk at doses of 3 mg and above. Consequently, the analysis results may not accurately reflect the true relationship between tarlatamab exposure and CRS risk.

No apparent trend between tarlatamab exposure metrics and the incidence rate of any grade ICANS was identified.

Additionally, a comparison of overall neurologic toxicity including ICANS between 10 and 100 mg target doses indicated a consistent relationship between tarlatamab dose, exposure and neutropenia or neurologic toxicity including ICANS.

CRS

Based on the data from Study 20200491, the overall CRS incidence rates were 30% for Grade 1, 20% for Grade 2 and 1% for Grade 3 following administration of 1/10 mg tarlatamab, while the CRS incidence rates were slightly higher following administration of 1/100 mg tarlatamab with Grade 1 at 35%, Grade 2 at 24% and Grade 3 at 5%. The analyses conducted by the Applicant showed no clear trends in E-R relationships for Grade ≥ 3 CRS. However, these findings are not considered reliable due to the limited number of patients (16/412) who experienced Grade ≥ 3 CRS in safety dataset.

The additional E-R analyses for Grade ≥ 1 and Grade ≥ 2 CRS suggested a slightly positive trend, with a higher CRS rate at higher exposure levels. This relationship may indicate that 1 mg may

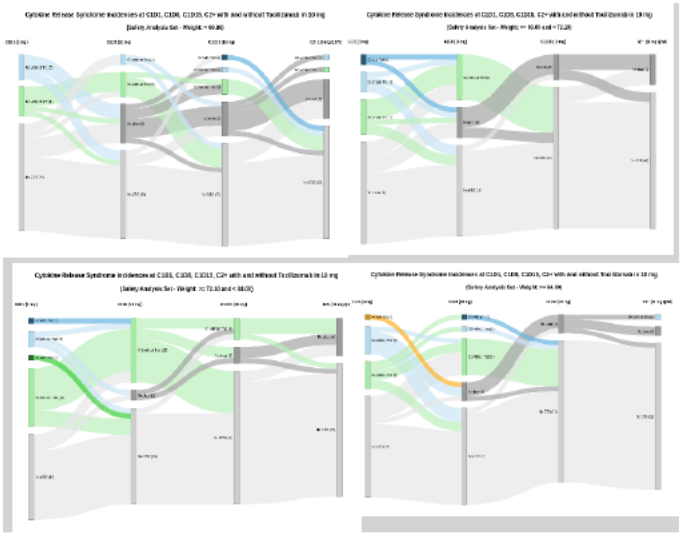
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not adequately stimulate the immune system for a higher target dose of 100 mg when compared to a lower target dose of 10 mg. However, it should be noted the derived E-R relationship for CRS based on the tarlatamab safety dataset may be confounded by the mitigation approach of the 1 mg step-up dose that had been utilized to mitigate the CRS risk at the dose of 3 mg and above and may not accurately reflect the true relationship between tarlatamab exposure and CRS risk.

To visualize the impact of body weight, age and DDL3 on the CRS risk following administration of 1/10 mg tarlatamab, sankey plots were generated for CRS grade and tocilizumab use by BW quartiles, age quartiles and DLL3 cut point based on the data from Study 20200491 (1/10 mg) in response to the FDA's IR. As shown in Figure 45, Figure 46, and Figure 47, no apparent trend of CRS incidence rate or severity was found by age quartiles, BW quartiles or DLL3 cut points.

Figure 44 Cytokine Release Syndrome Incidences at C1D1, C1D8, C1D15, C2+ with and without Tocilizumab Stratified by Body Weight Following Administration of 1/10 mg Tarlatamab.



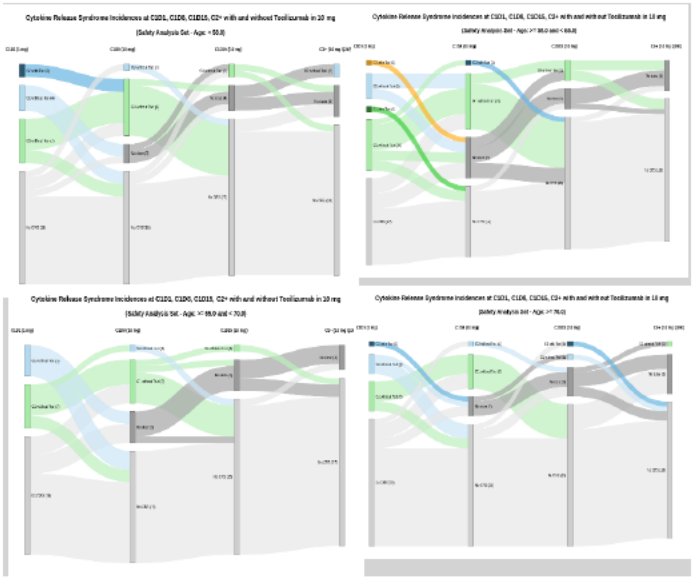
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Source: Figure 2, 3, 4 and 5 in Applicant response to FDA's IR dated on Jan.4, 2024

Figure 45 Cytokine Release Syndrome Incidences at C1D1, C1D8, C1D15, C2+ with and without Tocilizumab Stratified by Age Following Administration of 1/10 mg Tarlatamab.

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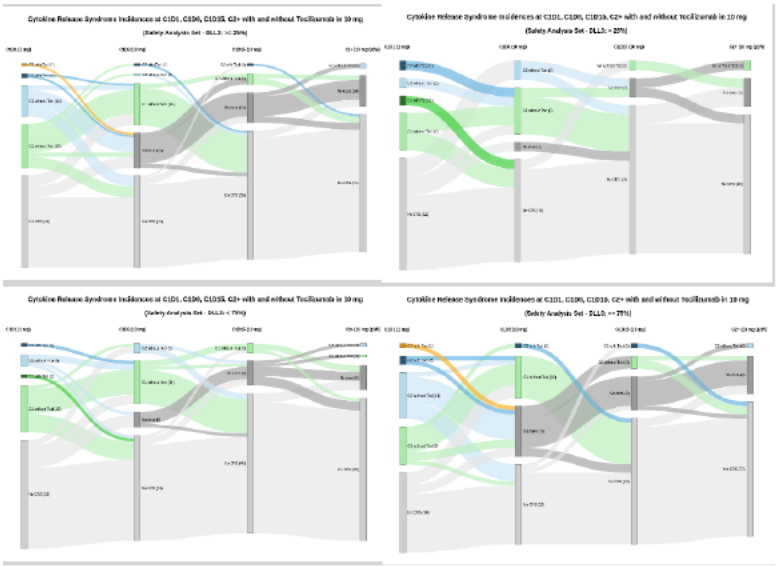
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Source: Figure 6, 7, 8 and 9 in Applicant response to FDA's IR dated on Jan.4, 2024

Figure 46 Cytokine Release Syndrome Incidences at C1D1, C1D8, C1D15, C2+ with and without Tocilizumab Stratified by DLL3 Cut Point Following Administration of 1/10 mg Tarlatamab.



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Source: Figure 10, 11, 12, and 13 in Applicant response to FDA's IR dated on Jan.4, 2024

Neutropenia

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The Applicant's exposure safety analyses indicated a shallow positive trend, with a higher percentage of patients experiencing Grade ≥ 3 neutropenia as tarlatamab exposures during the first treatment cycle increased.

Considering that the majority of neutropenia events occurred later beyond the first treatment cycle, the E-R relationships for Grade ≥ 1, Grade ≥ 2 and Grade ≥ 3 neutropenia were assessed using the different exposure metrics, C_{avg}, C_{max} and $C_{trough,}$ which were derived according to the following conditions.

--C_{max} and C_{trough} were derived from the last dosing interval before the event time of neutropenia AEs.

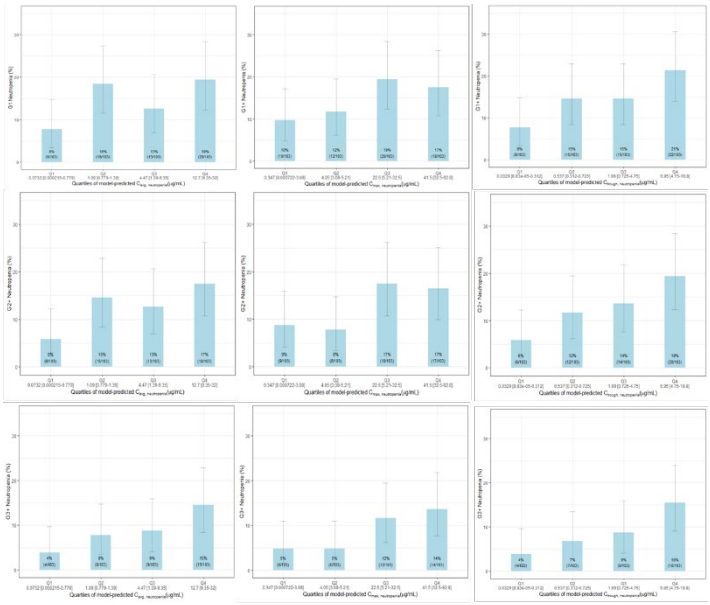
--C_{avg} was calculated from the last complete dosing interval over 2 weeks before the event time of neutropenia AEs.

As shown in Figure 48, the incidence rate for Grade ≥ 1, Grade ≥ 2 and Grade ≥ 3 neutropenia were found to be correlated with the exposure to tarlatamab, with a higher incidence rate of neutropenia observed at higher levels of tarlatamab exposure. It appears that C_{trough} was the exposure metric most strongly associated with the likelihood of neutropenia events, as evident from the lowest Akaike information criterion (AIC) value compared to C_{avg} and C_{max}.
Multivariate logistic regression analyses indicated that ECOG status at baseline was associated with higher probability of neutropenia. Figure 49 showed the model predicted mean probability and observed Grade ≥ 1, Grade ≥ 2 and Grade ≥ 3 neutropenia events with increasing tarlatamab exposure.

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Figure 47 Proportion of Subjects Experiencing Neutropenia Events (Grade ≥ 1, Grade ≥ 2 and Grade ≥ 3) by Tarlatamab Exposure Quartiles

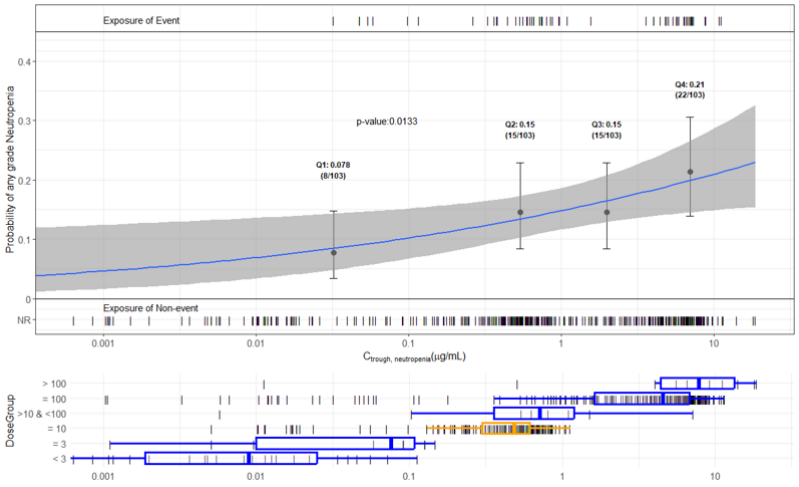


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Source:

Grade ≥ 1 Neutropenia: Table 6 in Applicant response to FDA's IR dated on Jan.24, 2024
Grade ≥ 2 and Grade ≥ 3 Neutropenia: Reviewer's analysis

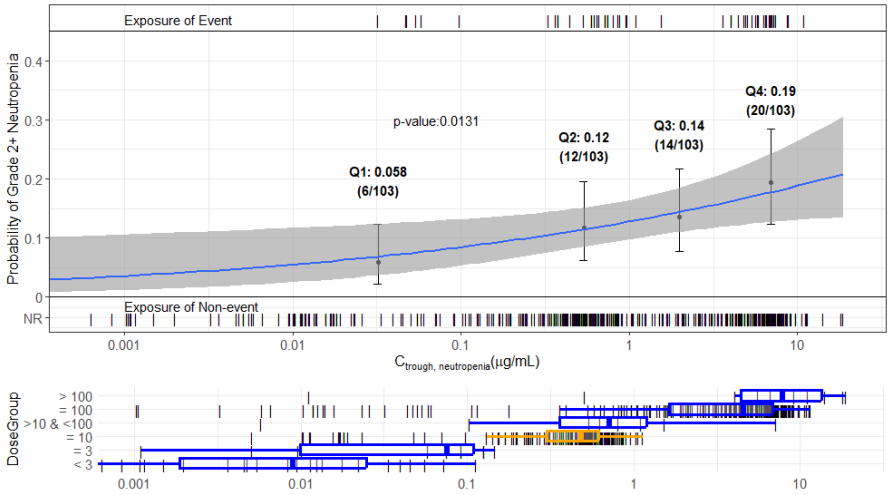
Figure 48 Model Predicted Probability of Grade ≥ 1, Grade ≥ 2 and Grade ≥ 3 Neutropenia and Observed Grade ≥ 1 Grade ≥ 2 and Grade ≥ 3 Neutropenia Events Versus Tarlatamab $C_{trough,}$ neutropenia.



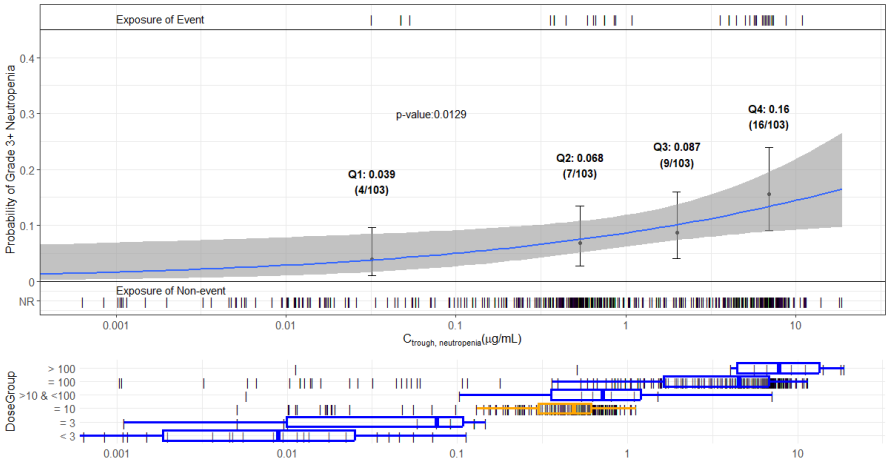
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Source: Figure 17 in Applicant response to FDA's IR dated on Jan.24, 2024

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Source: Reviewer's analysis



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Source: Reviewer's analysis

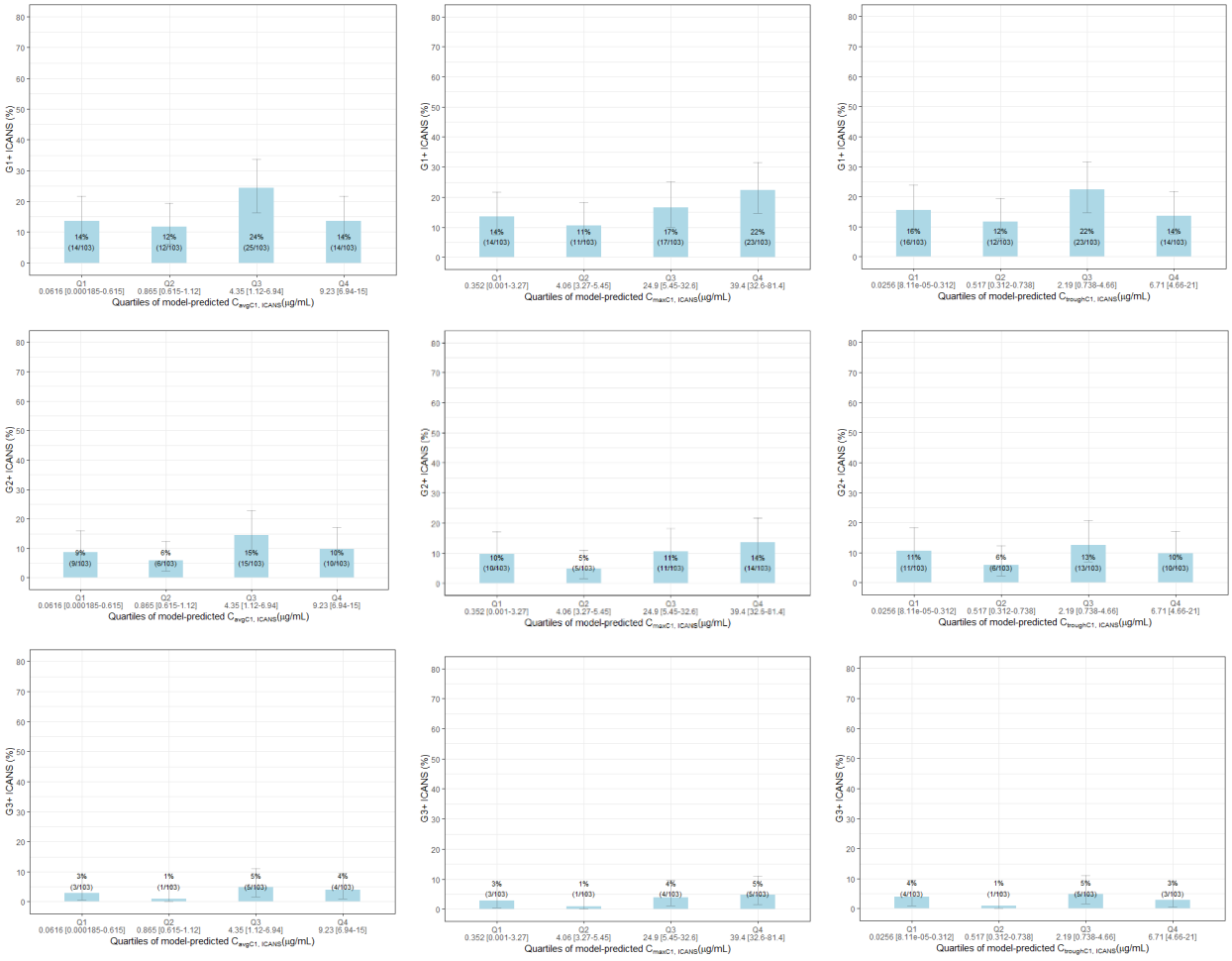
ICANs

There was no apparent trend between tarlatamab exposure metrics and the incidence rate of any grade ICANS (Figure 5049).

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Figure 49 Proportion of Subjects Experiencing ICANS Events (Grade ≥ 1, Grade ≥ 2 and Grade ≥ 3) by Tarlatamab Exposure Quartiles



Source: Reviewer's analysis

Neurologic toxicity including ICANS

In response to the FDA's IR, the Applicant conducted the exposure safety analysis for neurologic toxicity including ICANS (Grade≥1, Grade≥2 and Grade≥3) using tarlatamab exposure metrics, $C_{avg, ss}$ and $C_{max, ss}$, which were derived according to the following conditions.

-- $C_{avg,ss}$: average concentration over the dosing interval based on nominal dosing on Cycle 2 Day 1

-- $C_{max,ss}$: maximum concentration over the dosing interval based on nominal dosing on Cycle 2

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Day 1.

As shown in Figure 51, a positive exposure response relationship was observed for patients experienced Grade ≥ 1 and Grade ≥ 2 neurologic toxicity including ICANS. No trend was found for patients experiencing Grade ≥ 3 neurologic toxicity including ICANS. Consistent with the findings from graphical analysis, a statistically significant relationship was identified between tarlatamab exposure and Grade ≥ 1 and Grade ≥ 2 neurologic toxicity including ICANS. Higher tarlatamab exposure was associated with a greater incidence rate of Grade ≥ 1 and Grade ≥ 2 neurologic toxicity including ICANS. No statistically significant positive exposure response relationship for Grade ≥ 3 neurologic toxicity including ICANS was identified, likely due to the limited number of patients (41/412) who experienced Grade ≥ 3 neurologic toxicity including ICANS in the safety dataset.

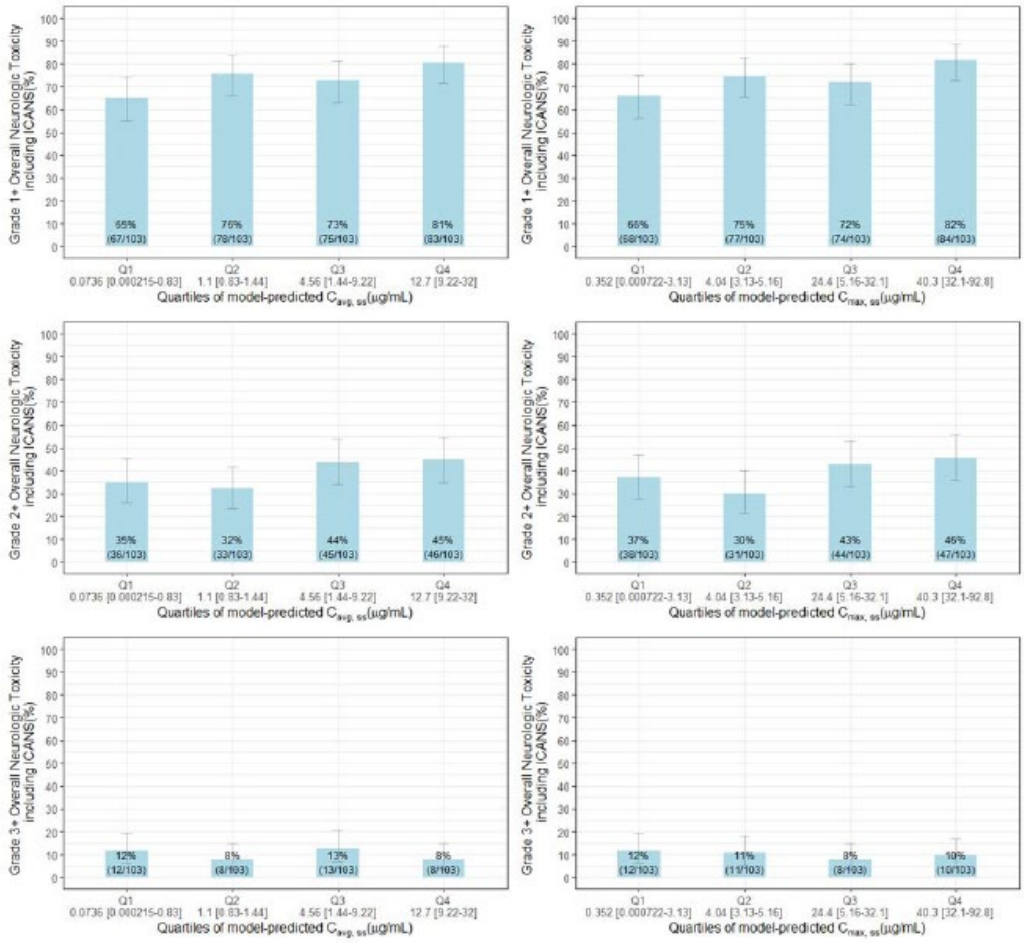
Multivariate logistic regression analyses indicated that the higher sum of tumor lesion diameter at baseline and exposure to prior anti-PD1 treatment were associated with higher probability of neurologic toxicity including ICANS.

In addition, it was observed that a higher proportion of patients experienced Grade ≥ 1(78%) and grade ≥ 2(46%) neurologic toxicity including ICANS following a 100 mg target dose, relative to 10 mg target dose (69% for Grade ≥1 and 31% for Grade ≥2 events). This trend was consistent with the estimated E-R relationship when $C_{avg,ss}$ was employed as a predictor variable. The predicted mean probability of experiencing Grade ≥1 and Grade ≥2 neurologic toxicity including ICANS at median $C_{avg,ss}$ corresponding to either 10 mg or 100 mg dose levels is comparable to the observed data (Table 75).

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Figure 50 Proportion of Subjects Experiencing Overall Neurologic Toxicity including ICANS (Grade ≥1, Grade ≥2 and Grade ≥ 3) by Tarlatamab Cavg,ss, and Cmax,ss Quartiles



Q1, Q2, Q3, and Q4 represent the four quartiles of $C_{avg,ss}$ or $C_{max,ss}$. Blue bar and error bars represent mean and 95% CI (estimated by Clopper-Pearson method) of the safety events in Q1, Q2, Q3, and Q4, respectively.

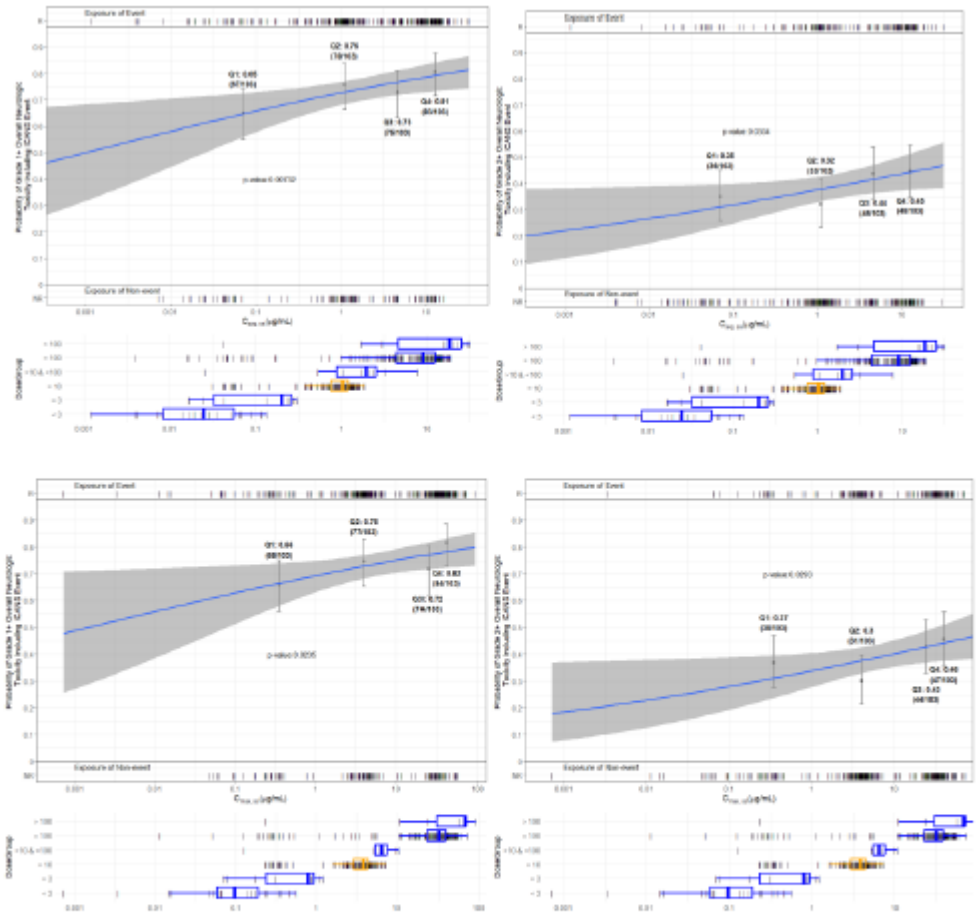
Source Figure 2 in Applicant response to FDA's IR dated on Mar.19, 2024

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Figure 51 Predicted Mean Probability and Observed Overall Neurologic Toxicity Including ICANS Events (Grade≥ 1 and Grade ≥ 2) Versus Tarlatamab Cavg,ss and Cmax,ss

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Upper panel; $C_{avg, ss}$ = model-estimated averaged concentration at steady state; Lower panel; $C_{max, ss}$ = model-estimated maximal concentration at steady state.
Vertical error bars and open circles represent 95% CI and mean probability of grade 1+ or grade 2+ events, respectively. Blue line and shaded area represent mean and 95% prediction interval of the model-simulated probability of grade 1+ or grade 2+ events, respectively. Short vertical lines in the upper and lower band represent individuals' $C_{avg, ss}$ (upper panel) or $C_{max, ss}$ (lower panel).

Source Figure 3 in Applicant response to FDA's IR dated on Mar.19, 2024

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Table 76 Predicted Mean Probability and Observed overall neurologic toxicity including ICANS (Grade ≥ 1, Grade ≥ 2, and Grade ≥ 3) at 10 mg and 100 mg dose levels (Pooled data across studies 20160323 and 20200491)

Response Variable	Percentage of Subjects experiencing an event by target dose % (N)		Predicted mean probability of experiencing an event at estimated median Cavg,ss % [CI]	
	10 mg	100 mg	10 mg	100 mg
Total number of subjects	157	202	--	--
G1+ Overall Neurologic Toxicity including ICANS[a]	69.4 (109)	78.2 (158)	72.8 [68.4-77.2]	78.4 [73.3-83.6]
G2+ Overall Neurologic Toxicity including ICANS[a]	31.2 (49)	46 (93)	37.6 [32.8-42.5]	43.3 [37.0-49.7]
G3+ Overall Neurologic Toxicity including ICANS[a]	8.3 (13)	9.9 (20)	No statistically significant positive relationship identified	
G1+ Neutropenia[b]	14.7 (23)	16.3 (33)	12.5 [9.99-15.7]	19.4 [15.0-23.1]
G2+ Neutropenia[b]	11.4 (18)	15.3 (31)	10.4 [8.06-13.8]	17.4 [12.8-20.9]
G3+ Neutropenia[b]	6.4 (10)	11.9 (24)	6.32 [4.32-9.94]	13.2 [8.32-16.4]

Source:
a: Table 3 in Applicant response to FDA's IR dated on Mar.19, 2024
b: Reviewer's analysis

19.4.4.5. Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position:

No clear trends for exposure-response relationships were identified for grade ≥ 3 adverse events, grade ≥ 3 treatment-related adverse events, and grade ≥ 3 adverse events of interest of neurological events, ICANS, and CRS. A shallow trend was observed for higher percentage of

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subjects experiencing grade ≥ 3 neutropenia with increasing tarlatamab exposures. No clinically relevant impact on QTc interval was observed at the proposed clinical regimen of 10 mg Q2W.

The results of the exposure-response analysis suggest that the proposed clinical regimen of 10 mg Q2W reaches the plateau of efficacy with a limited impact on neutropenia and provides a reasonable balance of benefit-risk in this patient population. None of the covariates evaluated in this analysis resulted in clinically meaningful changes in the drug's effect on efficacy and therefore do not warrant a dose adjustment.

The FDA's Assessment:

FDA agrees based on results from study 20200491 and study 2016323, tarlatamab represents a therapeutic approach intended for addressing unmet medical needs in patient with SCLC, a life-threatening condition.

FDA agrees that the proposed dose regimen of 1 mg on cycle 1 day 1, followed by 10 mg on cycle 1 day 8, 15 and every 2 weeks did not raise any significant safety concerns. CRS risk was effectively mitigated by a single 1 mg step-up dose and retreatment plans after dose delay. The E-R efficacy and safety relationships generally support the proposed dosage regimen.

However, a positive E-R relationship was identified between tarlatamab exposure and neutropenia or neurologic toxicity including ICANS with a higher risk of any grade neutropenia or neurologic toxicity including ICANS at higher exposure. Therefore, the appropriate risk management strategies may be necessary to ensure a favorable risk/benefit balance.

A positive E-R relationship between tarlatamab exposure and efficacy endpoints was observed across the dose levels evaluated (3-100 mg). The efficacy appears to reach plateau at doses of 10 mg and above, supporting the proposed target doses.

Furthermore, FDA agrees that no clinically relevant impact on QTc interval was observed. Although Applicant's analysis determines a statistically significant positive C-QTc relationship, this relationship is very shallow, not clinically significant, and unlikely to be due to interaction with hERG channel since tarlatamab is a large therapeutic protein.

19.5. Additional Analyses Conducted by FDA

The summary of method validation and in-study performance for plasma samples are presented in Table 76 and Table 77. FDA agrees the bioanalytical methods are acceptable based on the current Bioanalytical Method Validation Draft FDA Guidance for Industry.

Table 77. Summary method performance of a bioanalytical method to measure tarlatamab in human serum.

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Bioanalytical method validation report name, amendments, and hyperlinks	Quantification of AMG 757 in Human Serum by ECL Assay (MET-406436) Validation Report.125850 (version 1.0 and 2.0)		
Method description	MET-406436 Version 1.0; An Electro-chemiluminescence (ECL)-based assay for the Quantification of tarlatamab in Human Serum		
Materials used for calibration curve & concentration	Prepared in human serum at nominal tarlatamab concentrations of 400, 133, 44.4, 14.8, 4.94, 1.65, 0.549, 0.183, 0.0610, 0.0203 and 0.00677 ng/mL		
Validated assay range	0.0203 to 133 ng/mL tarlatamab		
Material used for QCs & concentration	Prepared in human serum at nominal tarlatamab concentrations of 133, 100, 2.00, 0.0650 and 0.0203 ng/mL		
Minimum required dilutions (MRDs)	n/a (analysis in 100% serum)		
Source & lot of reagents (LBA)	Capture reagent [redacted] (b) (4) lot: PL-55265 (Amgen Inc.) Detection Reagent [redacted] (b) (4) lot: PL-54405 (Amgen Inc.)		
Regression model & weighting	5-parameter fit (weighting $1/y^2$)		
Validation parameters	**Method validation summary**		**Acceptability**
Standard calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	9	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-5 to 7%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 6%	Yes
QCs performance during accuracy & precision	**Cumulative accuracy (%bias) in 5 QCs**	-10 to 1%	Yes
	Inter-batch %CV	≤ 15%	Yes
	Total Error (TE)	≤ 25%	Yes

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Selectivity & matrix effect	A total of 10 individual lots (healthy: 2 males, 2 females; 4 SCLC patients, 1 hemolytic and 1 lipemic) of human serum samples were tested unspiked and spiked at the LLOQ (0.0203 ng/mL), LQC (0.0650 ng/mL) and ULOQ (133 ng/mL) levels. No matrix effect was observed as 80% of the spiked samples recovered within the acceptance criteria.	Yes
Interference & specificity	Recombinant DLL-3 was spiked at concentrations of 2, 20, 200, 2.000, and 20.000 pg/mL in LQC (0.0650 ng/mL tarlatamab) and HQC (100 ng/mL tarlatamab) samples. Interference from recombinant DLL-3 was observed at concentrations of 20 pg/mL and higher. No impact of pembrolizumab (50 to 250 µg/mL), (b) (4) (50 to 1000 µg/mL), Etanercept (0.1 to 5 µg/mL) and Tocilizumab (10 to 250 µg/mL) on the quantification of tarlatamab was observed.	Yes
Hemolysis effect	One hemolytic serum was tested unspiked and spiked at the LLOQ (0.0203 ng/mL), LQC (0.0650 ng/mL) and ULOQ (133 ng/mL) levels. No matrix effect was observed.	Yes
Lipemic effect	One lipemic serum was tested unspiked and spiked at the LLOQ (0.0203 ng/mL), LQC (0.0650 ng/mL) and ULOQ (133 ng/mL) levels. No matrix effect was observed.	Yes
Dilution linearity & hook effect	Dilution linearity was performed by analyzing 2 QCs containing 1330 ng/mL tarlatamab as 10-, 100-, 1000-, and 10000-fold dilutions. The %bias of all diluted samples ranged from -23 to 17%. No hook effect was observed.	Yes
Bench-top/process stability	Stability was demonstrated for 2 hours at RT. Stability at 2-8°C for 24 hours could not be shown.	Yes
Freeze-Thaw stability	Tarlatamab in human serum is stable up to 3 freeze-thaw cycles (-80°C +/- 10°C and RT). ULOQ (133 ng/mL), MQC (2.00 ng/mL) and LLOQ (0.0203 ng/mL) were tested.	Yes
Long-term storage	Long-term stability of tarlatamab in human serum can be guaranteed for up to 12 months at -80°C +/- 10°C and at -20°C +/- 5°C for up to 9 months.	Yes

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	ULOQ (133 ng/mL), MQC (2.00 ng/mL) and LLOQ (0.0203 ng/mL) were tested.	
Parallelism	Parallelism was demonstrated in four clinical samples, as back-calculated concentrations between all samples in a dilution series were within 30% CV.	Yes
Carry over	Positioning within or across reader sectors had no impact on tarlatamab quantification at high and low concentrations.	Yes
Method performance in study 20160323 (per Interim Report, Study ongoing)		
Assay passing rate	257 out of 303 analytical runs (85%) met the method acceptance criteria.	Yes
Standard curve performance	• Cumulative bias range: -2 to 2% (from LLOQ to ULOQ) • Cumulative precision: ≤ 14% CV (from LLOQ to ULOQ)	Yes
QC performance	• Cumulative bias range: -1 to 4% • Cumulative precision: ≤ 17% CV • TE: ≤ 18%	Yes
Method reproducibility	Incurred sample reanalysis was performed in 5% of study samples (278) and 79% of samples met the pre-specified criteria.	Yes
Study sample analysis/ stability	Study samples were stored for a maximum of 12 months at -80 +/- 10°C until analysis. 51 samples were stored longer than 12 months and were therefore not analyzed.	

Table 78. Summary of method MET-406436 modifications and cross-validation results.

Bioanalytical method validation report name and hyperlink	Validation Report.154752 (outsourcing to (b) (4)	
Changes in method	• Calibration curve concentrations modified: 180, 90.0, 45.0, 22.5, 11.3, 5.63, 2.81, 1.41, 0.703, 0.352 and 0.176 ng/mL tarlatamab • Watson LIMS used for data evaluation (instead of SoftMax Pro)	
New validated assay range if any	0.352 to 90.0 ng/mL tarlatamab	
Validation parameters	**Cross-validation performance**	**Acceptability**

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Standard calibration curve performance during accuracy & precision	Cumulative accuracy (%bias) from LLOQ to ULOQ	-2 to 3%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 4%	Yes
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs	-9 to 3 %	Yes
	Inter-batch %CV	≤ 11%	Yes
	Percent total error (TE)	≤ 16%	Yes
Cross-validation	30 QC samples (six sets of five levels of QCs (ULOQ, HQC, MQC, LQC and LLOQ) were tested. The relative percent difference between the reference and the comparator lab was less than 30%. 30 patient sera collected in clinical study 20160323 were tested. 84% of the evaluable samples were comparable with concentrations measured in the original assay run (< 20%Diff from original level)	NA	NA
Selectivity & matrix effect	A total of 37 individual lots (10 normal human serum; 7 diseased sera (SCLC), 10 hemolytic and 10 lipemic) of human serum samples were tested unspiked and spiked at the LLOQ (0.352 ng/mL) and HQC (67.5 ng/mL) levels. No matrix effect was observed (pass rate: > 80%).		Yes
Interference & specificity	Recombinant DLL-3 was spiked at concentrations of 1000, 500, 250, 100, and 10 pg/mL in ULOQ (90 ng/mL), HQC (67.5 ng/mL), MQC (10.0 ng/mL), LQC (1.00 ng/mL) and LLOQ (0.352 ng/mL) tarlatamab samples. No interference for recombinant DLL-3 was observed at all 5 levels of QCs.		Yes
Hemolysis effect	Ten hemolytic sera were tested unspiked and spiked at the LLOQ (0.352 ng/mL) and HQC (67.5 ng/mL) levels. No matrix effect was observed (pass rate: 80%).		Yes
Lipemic effect	Ten lipemic sera were tested unspiked and spiked at the LLOQ (0.352 ng/mL) and HQC (67.5 ng/mL) levels. No matrix effect was observed (pass rate: 90%).		Yes
Dilution linearity & hook effect	50000 ng/mL, 1000 ng/mL and 600 ng/mL tarlatamab was diluted 1:10, 1:100, 1:1000 and 1:10000.		Yes

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	The %bias of all diluted samples ranged from -14 to 16%. No hook effect was observed.	
Bench-top/process stability	Stability was demonstrated for 24 hours 46 minutes at RT and at 2-8°C for 22 hours and 59 minutes.	Yes
Freeze-Thaw stability	Tarlatamab in human serum is stable up to 5 freeze-thaw cycles (-80°C +/- 10°C and RT). HQC (67.5 ng/mL) and LQC (1.00 ng/mL) were tested.	Yes
Long-term storage	Long-term stability of tarlatamab in human serum can be guaranteed for up to 407 days at -80 +/- 10°C and at -20°C +/- 5°C for up to 186 days. DL-A (50000 ng/mL), HQC (67.5 ng/mL) and LQC (1.00 ng/mL) were tested.	Yes
Method performance in study 20200491 (per interim Report, Study ongoing)		
Assay passing rate	148 out of 170 analytical runs (87%) met the method acceptance criteria	Yes
Standard curve performance	• Cumulative bias range: 0 to 1% (from LLOQ to ULOQ) Cumulative precision: ≤ 3% CV (from LLOQ to ULOQ)	Yes
QC performance	• Cumulative bias range: -6 to 5% • Cumulative precision: ≤ 10% CV TE: ≤ 16%	Yes
Method reproducibility	Incurred sample reanalysis was performed in 7% of study samples (211) and 92% of samples met the pre-specified criteria	Yes
Study sample analysis/ stability	Study Samples were stored for a maximum of 407 days at -80 +/- 10°C until analysis. 2 samples were stored longer than 407 days.	

19.6. Safety Analyses Conducted by FDA

The FDA's Assessment:

No additional safety analyses were conducted beyond those described above in Section 8.2.

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Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Yue Xiang, PhD	CDER/OTS/OCP/DCPII	Sections: 6	**Select one:** _X_Authored ___Approved
	Signature: Yue Xiang -S Digitally signed by Yue Xiang -S Date: 2024.05.10 09:54:12 -04'00'			
Clinical Pharmacology Team Leader	Hong Zhao, PhD	CDER/OTS/OCP/DCPII	Sections: 6, 19.4	**Select one:** __Authored _X_Approved
	Signature: Hong Zhao -S Digitally signed by Hong Zhao -S Date: 2024.05.10 11:11:30 -04'00'			
Clinical Pharmacology/ Pharmacometrics Team Leader	Youwei Bi, PhD	CDER/OTS/OCP/DPM	Sections:6, 19.4	**Select one:** ___Authored _X_Approved
	Signature: Ye Xiong -S Digitally signed by Ye Xiong -S Date: 2024.05.10 12:00:51 -04'00'			
Clinical Pharmacology/ Pharmacometrics Reviewer	Jianghong Fan, PhD	CDER/OTS/OCP/DPM	Sections: 6, 19.4	**Select one:** _X_Authored ___Approved
	Signature: Jianghong Fan -S Digitally signed by Jianghong Fan -S Date: 2024.05.10 11:48:28 -04'00'			
Clinical Pharmacology Division Director	Nam Atiqur Rahman, PhD	CDER/OTS/OCP/DCPII	Sections: 6, 19.4	**Select one:** ___Authored _X_Approved
	Signature: Nam A. Rahman -S Digitally signed by Nam A. Rahman -S Date: 2024.05.10 15:03:48 -04'00'			

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Clinical Reviewer	Yufan Liu, PharmD	CDER/ OND/OOD/DOII	Sections: 1-4, 7-13, 19.1, 19.2	**Select one:** _X_Authored ___Approved
	Signature: Yufan Liu -S Digitally signed by Yufan Liu -S Date: 2024.05.13 11:36:09 -04'00'			
Clinical Reviewer	Jeannette Nashed, BSN, MSN, CRNP	CDER/ OND/OOD/DOII	Sections: 1.2, 4.1, 8.2, 12	**Select one:** _X_Authored ___Approved
	Signature: Jeannette C. Nashed -S Digitally signed by Jeannette C. Nashed -S Date: 2024.05.10 13:37:01 -04'00'			
Clinical Team Leader	Amy Barone, MD	CDER/OND/OOD/DOII	Sections: All	**Select one:** _X_Authored _X_Approved
	Signature: See signature in DARRTS.			
Cross-Disciplinary Team Leader (CDTL)	Amy Barone, MD	CDER/OND/OOD/DOII	Sections: All	**Select one:** _X_Authored _X_Approved
	Signature: See signature in DARRTS.			
Supervisory Associate Director (Clinical)	Erin Larkins, MD	CDER/OND/OOD/DOII	Sections: All	**Select one:** _X_Approved
	Signature: See signature in DARRTS.			

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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Statistical Reviewer	Mengdie Yuan, PhD	CDER/OTS/OB/DBV	Sections: 8	**Select one:** _X_ Authored ___ Approved
	Signature: Mengdie Yuan -S Digitally signed by Mengdie Yuan -S Date: 2024.05.10 12:34:11 -04'00'			
Statistical Team Leader	Anup Amatya, PhD	CDER/OTS/OB/DBV	Sections: 8	**Select one:** ___ Authored _X_ Approved
	Signature: Anup K. Amatya -S Digitally signed by Anup K. Amatya -S Date: 2024.05.10 09:58:26 -04'00'			
Nonclinical Reviewer	Melissa Pegues, PhD	CDER/OND/OOD/DHOT	Sections: 5	**Select one:** _X_ Authored _X_ Approved
	Signature: Melissa A. Pegues -S Digitally signed by Melissa A. Pegues -S Date: 2024.05.10 14:25:59 -04'00'			
Nonclinical Team Leader	Claudia Miller, PhD	CDER/OND/OOD/DHOT	Sections: 5	**Select one:** _X_ Authored _X_ Approved
	Signature: Claudia Miller -S Digitally signed by Claudia Miller -S Date: 2024.05.15 11:00:18 -04'00'			
Nonclinical Director	Haleh Saber, PhD	CDER/OND/OOD/DHOT	Sections: 5	**Select one:** _X_ Approved
	Signature: Haleh Saber -S Digitally signed by Haleh Saber -S Date: 2024.05.10 14:49:01 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology/ Genomics Reviewer	Sarah Dorff, PhD	CDER/OTS/OCP/DTPM	Sections: 6	**Select one:** _X_ Authored _X_ Approved
	Signature: Sarah E. Dorff -S Digitally signed by Sarah E. Dorff -S Date: 2024.05.10 13:46:53 -04'00'			
Statistical Director	Shenghui Tang, PhD	CDER/OTS/OB/DBV	Sections: 8	**Select one:** ___ Authored _X_ Approved
	Signature: Shenghui Tang -S Digitally signed by Shenghui Tang -S Date: 2024.05.10 13:41:14 -04'00'			
Associate Director for Labeling (ADL)	Barbara Scepura, MSN	CDER/OND/OOD/DOII	Sections: 11	**Select one:** _X_ Authored _X_ Approved
	Signature: Barbara A. Scepura -S Digitally signed by Barbara A. Scepura -S Date: 2024.05.10 09:49:11 -04'00'			

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/s/

AMY K BARONE
05/15/2024 05:27:02 PM

ERIN A LARKINS
05/15/2024 05:57:55 PM
Supervisory Associate Director, DO2

PAUL G KLUETZ
05/15/2024 09:38:45 PM