CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761121Orig1s008

MULTI-DISCIPLINE REVIEW

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

NDA/BLA Multi-disciplinary Review and Evaluation

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

Application Type	Supplemental BLA
Application Number(s)	BLA 761121- S008
Priority or Standard	Standard
Submit Date	June 2, 2022
Received Date	June 2, 2022
PDUFA Goal Date	April 2, 2023
Division/Office	DHM II / OOD
Review Completion Date	April 18, 2023
Established Name	Polatuzumab vedotin-piiq
Trade Name	Polivy
Pharmacologic Class	Antibody-drug conjugate
Applicant	Genentech, Inc.
Formulation(s)	Intravenous
Dosing Regimen	1.8 mg/kg IV infusion every 21 days for 6 cycles, in combination with a rituximab product, cyclophosphamide, doxorubicin, and prednisone (R-CHP)
Applicant Proposed Indication(s)/Population(s)	In combination with a rituximab product, cyclophosphamide, doxorubicin, and prednisone (R-CHP) for the treatment of adult patients who have previously untreated diffuse large B-cell lymphoma (DLBCL)
Recommendation on Regulatory Action	Regular approval
Recommended Indication(s)/Population(s) (if applicable)	In combination with a rituximab product, cyclophosphamide, doxorubicin, and prednisone (R-CHP) for the treatment of adult patients who have previously untreated diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS) or high-grade B-cell lymphoma (HGBL) and who have an International Prognostic Index score of 2 or greater

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OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
PFDD=Patient Focused Drug Development

Glossary

1L	first-line
ABC	activated B-cell-like
acMMAE	antibody conjugated Monomethyl Auristatin E
ADA	anti-drug antibodies
ADC	antibody-drug conjugate
AE	adverse event
AEPI	adverse event of particular interest
AESI	adverse event of special interest
AR	adverse reaction
BICR	blinded independent central review
BLA	biologics license application
BR	bendamustine and rituximab
BTD	Breakthrough Therapy Designation
CAR-T	chimeric antigen receptor T-cell
CCOD	clinical cut-off date
CFR	Code of Federal Regulations
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CHP	cyclophosphamide, doxorubicin and prednisone
CMP	comprehensive metabolic panel
COA	clinical outcome assessment
COO	cell-of-origin
CR	complete response
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CT	computed tomography
DEL	double-expressor lymphoma
DFS	disease-free survival
DLBCL	diffuse large B-cell lymphoma
DEL	double-expressor lymphoma
DFS	disease-free survival
DHL	double-hit lymphoma
DILI	drug-induced liver injury
DOR	duration of response
EBV	Epstein-Barr virus
ECOG	Eastern Cooperative Oncology Group
EFS_{all}	event-free survival-all causes
EFS_{eff}	event-free survival-efficacy
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
E-R	exposure-response
EOT	end of treatment
EQ-5D-5L	EuroQol 5-Dimension, 5-Level

FACT/GOG-NTX	Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity
FACT-Lym LymS	Functional Assessment of Cancer Therapy-Lymphoma Lymphoma-specific symptoms scale
FDG-PET	fluorodeoxyglucose positron emission tomography
FL	follicular lymphoma
G	obinutuzumab
GCB	germinal center B-cell-like
G-CSF	granulocyte colony-stimulating factor
HGBL	high-grade B-cell lymphoma
HHV8	human herpesvirus 8
HSCT	hematopoietic stem-cell transplantation
HR	hazard ratio
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
IND	Investigational New Drug Application
INV	investigator
IPI	International Prognostic Index
IRC	Independent review committee
IRR	infusion-related reactions
ITT	intent-to-treat
IV	intravenous
NALT	new anti-lymphoma therapy, non-protocol anti-lymphoma therapy
NCCN	National Comprehensive Cancer Network
NE	not estimable, not evaluable
NHL	non-Hodgkin's lymphoma
NME	new molecular entity
NOS	not otherwise specified
ODAC	Oncologic Drugs Advisory Committee
OS	overall survival
OSI	Office of Scientific Investigation
ORR	objective response rate
PET-CT	positron emission tomography-computed tomography
PFS	progression-free survival
PFS24	2-year progression free survival rate
PI	prescribing information
PK	pharmacokinetics
PMR	post-marketing requirement
PMC	post-marketing commitment
PN	peripheral neuropathy
PO	orally
pola	polatuzumab vedotin-piiq
popPK	population pharmacokinetics
PRO	patient reported outcome
PT	preferred term

R	rituximab
R-CHOP	rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone
R-CHP	rituximab plus cyclophosphamide, doxorubicin and prednisone
REMS	risk evaluation and mitigation strategy
RMST	restricted mean survival time
R/R	relapsed or refractory
SAE	serious adverse event
SAP	statistical analysis plan
sBLA	supplemental BLA
SCS	Summary of Clinical Safety
SE	safety-evaluable
SEER	Surveillance, Epidemiology, and End Results
SOC	system organ class
TEAE	treatment emergent adverse event
THL	triple-hit lymphoma
TLS	tumor lysis syndrome
TTD	time to deterioration
ULN	upper limit of normal
v	version

1 Executive Summary

1.1. Product Introduction

The clinical review team recommends regular approval of polatuzumab vedotin-piiq in combination with a rituximab product, cyclophosphamide, doxorubicin, and prednisone (R-CHP) for the treatment of adult patients who have previously untreated diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS) or high grade B-cell lymphoma (HGBL) and who have an International Prognostic Index score of 2 or greater.

Polatuzumab vedotin-piiq is a CD79b-directed antibody-drug conjugate (ADC) containing a humanized, IgG monoclonal antibody against CD79b conjugated to the anti-mitotic agent, monomethyl auristatin E (MMAE). CD79b is a cell-surface antigen expressed on most mature B-cells, with ubiquitous expression in DLBCL. When internalized, the conjugate is cleaved by lysosomal enzymes to release MMAE, which disrupts the microtubule network and results in inhibited cell division and induction of apoptosis.

Polatuzumab vedotin-piiq in combination with bendamustine and rituximab (BR) received accelerated approval for the treatment of adult patients with relapsed or refractory (R/R) DLBCL NOS, after at least two prior therapies in June 2019. POLARIX (Study GO39942) is a confirmatory trial intended to verify the clinical benefit of polatuzumab vedotin, and is the basis of the recommended regular approval of polatuzumab vedotin + R-CHP in the first-line setting. The data from POLARIX also support conversion of the accelerated approval of polatuzumab vedotin + BR to regular approval.

1.2. Conclusions on the Substantial Evidence of Effectiveness

POLARIX (Study GO39942) provides substantial evidence of effectiveness of polatuzumab vedotin-piiq (pola) in combination with R-CHP in patients with previously untreated large B-cell lymphoma (LBCL). POLARIX is a multicenter, randomized, double-blinded, placebo-controlled trial evaluating the substitution of vincristine with polatuzumab vedotin in the R-CHOP regimen as front-line therapy for adult patients with LBCL. The study randomized 879 patients (84% with DLBCL NOS) in a 1:1 ratio to receive polatuzumab vedotin + R-CHP (pola+R-CHP) or R-CHOP. POLARIX met its primary endpoint, with a statistically significant improvement in investigator-assessed PFS with pola+R-CHP; the PFS hazard ratio (HR) was 0.73 (95% CI: 0.57, 0.95) with a log-rank p-value of 0.0177 (two-sided α=0.05). The point estimates of 1-year and 2-year PFS rates differed by 4.1% and 6.5%, respectively. The difference in modified EFS, a key secondary endpoint, was statistically significant, with a HR of 0.75 (95% CI: 0.58, 0.96; p-value = 0.0244). There was no improvement demonstrated in the key secondary endpoints of CR rate at the end of therapy or overall survival (OS HR 0.94; 95% CI: 0.67, 1.33 on final analysis).

In a descriptive analysis of the largest lymphoma subgroup, DLBCL NOS, the PFS HR was 0.75 (95% CI: 0.57, 0.99), and the OS HR on final analysis was 1.02 (95% CI: 0.70, 1.49). In patients with HGBL, the PFS HR was 0.48 (95% CI: 0.21, 1.08), and the OS HR was 0.42 (95% CI: 0.15, 1.19). There were insufficient data to evaluate efficacy in other LBCLs.

Based on the POLARIX results, a number of issues raised uncertainty about the benefit-risk of polatuzumab vedotin in this frontline, curative-intent setting, including the modest PFS benefit of pola+R-CHP, the OS results, limitations of other efficacy endpoints, and heterogeneity of the study

population and observed treatment effect. The application was therefore presented at an Oncology Drug Advisory Committee (ODAC) on March 9, 2023, and most committee members voted (11:2) that polatuzumab vedotin had a favorable benefit-risk profile in patients with previously untreated LBCL, including DLBCL NOS.

Although modest, the observed PFS difference between arms, supported by modified EFS, provides substantial evidence of effectiveness, demonstrates clinical benefit, and is the basis for the recommended regular approval. Because of limitations in data, the recommended indication is restricted to adult patients who have previously untreated DLBCL, NOS or HGBL and who have an International Prognostic Index (IPI) score of 2 or greater.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Efficacy: The efficacy of polatuzumab vedotin is based on investigator-assessed PFS rate in POLARIX, a double-blinded, placebo-controlled substitution trial that randomized 879 patients with previously untreated LBCL to receive pola+R-CHP or R-CHOP, followed by two cycles of rituximab alone. POLARIX met its primary endpoint, with a statistically significant improvement in investigator-assessed PFS with pola+R-CHP (HR 0.73 [95% CI: 0.57, 0.95] and log-rank p-value of 0.0177 [two-sided α=0.05]. The difference in 2-year PFS rate was 6.5% (95% CI: 0.5, 12.5). The difference in modified EFS, a key secondary endpoint, was statistically significant, with a HR of 0.75 (95% CI: 0.58, 0.96; p-value = 0.0244 with two-sided α=0.05). There was no improvement in CR rate (78% with pola+R-CHP vs. 74% with R-CHOP; p = 0.1557) or OS. On final analysis, the OS HR was 0.94 (95% CI: 0.67, 1.33) after a median follow-up of 3.3 years.

Safety: In 435 patients treated with pola+R-CHP, fatal adverse reactions (ARs) occurred in 3.0% within 90 days of last treatment, primarily from infection. Serious adverse reactions (SAEs) occurred in 34%, including febrile neutropenia and pneumonia in ≥5% of recipients. ARs in ≥20% of patients, excluding laboratory abnormalities, were peripheral neuropathy, nausea, fatigue, diarrhea, constipation, alopecia, and mucositis. New or worsening Grade 3 to 4 laboratory abnormalities in ≥10% of patients were lymphopenia, neutropenia, hyperuricemia, and anemia.

Benefit/Risk: Pola+R-CHP has an overall favorable benefit/risk in adult patients with previously untreated DLBCL, NOS or HGBL and who have an IPI score of 2 or greater. There was insufficient data in patients with other LBCLs to inform benefit/risk.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• LBCL is fatal if not cured. Approximately 60% of patients with DLBCL, NOS are cured when treated with standard of care R-CHOP. The majority who relapse will die from the disease.	• There is a need for more effective yet tolerable therapies for LBCL.
Current Treatment Options	• The U.S. standard of care treatment for DLBCL, NOS is R-CHOP. More intensive regimens than R-CHOP are generally preferred in the U.S. for patients with HGBL.	• Patients with untreated LBCL have unmet medical needs.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• POLARIX is a randomized, double-blinded, placebo-controlled trial in 879 patients with previously untreated LBCL and an IPI score of 2-5 that evaluated the substitution of vincristine with polatuzumab vedotin in R-CHOP. POLARIX met its primary endpoint, with a statistically significant improvement in PFS per investigator with pola+R-CHP (HR 0.73; 95% CI: 0.57, 0.95). Sensitivity analyses were consistent with the primary analysis. • Modified EFS was also statistically significantly greater in the pola+R-CHP arm (HR 0.75; 95% CI: 0.58, 0.96). • There was no improvement in CR rate or OS (OS HR 0.94; 95% CI, 0.67, 1.33 on final analysis). At some landmark timepoints, the OS was numerically lower in the pola+R-CHP arm. • In a descriptive analysis, in DLBCL NOS, the PFS HR was 0.75 (95% CI: 0.57, 0.99), and the OS HR on final analysis was 1.02 (95% CI: 0.70, 1.49). In HGBL, the PFS HR was 0.48 (95% CI: 0.21, 1.08), and the OS HR was 0.42 (95% CI: 0.15, 1.19). There were insufficient data to evaluate efficacy in other LBCLs.	• Based on the PFS rate and supported by modified EFS in a randomized phase 3 study, pola+R-CHP has clinically meaningful efficacy in patients with previously untreated DLBCL, NOS or HGBL and who have an IPI score of 2 or greater. • The treatment effect appears heterogeneous among lymphoma subgroups. • There is adequate evidence of a positive treatment effect with the addition of polatuzumab vedotin to R-CHP, compared to R-CHOP, in the intended population.

Risk and Risk Management	• In POLARIX, safety findings were generally comparable between arms, including rates of peripheral neuropathy and dose-intensity of the chemotherapy backbone.
	• Incidences of febrile neutropenia, infection, nausea, and diarrhea were numerically higher in the pola+R-CHP arm. Fewer patients had recovery of peripheral neuropathy in the pola+R-CHP arm (58% vs. 67% with R-CHOP).
	• In 435 patients treated with pola+R-CHP,
	  ○ Fatal ARs occurred in 3.0% and SAEs occurred in 34%. ARs lead to dose reduction of polatuzumab vedotin in 6%, dose interruption in 18%, and discontinuation in 4.4%.
	  ○ ARs in ≥20% of patients, excluding laboratory abnormalities, were peripheral neuropathy, nausea, fatigue, diarrhea, constipation, alopecia, and mucositis. New or worsening Grade 3 to 4 laboratory abnormalities in ≥10% of patients were lymphopenia, neutropenia, hyperuricemia and
		• Pola+R-CHP has an acceptable safety profile in the intended population.
		• Peripheral neuropathy, infusion-related reaction, myelosuppression, and serious or opportunistic infections are included in the Warnings and Precautions.
		• Primary prophylaxis with GCSF should be mandated to mitigate complications from neutropenia.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	anemia. • Analysis of patient-reported outcomes was insufficient to inform differences in tolerability.	

1.4. Patient Experience Data

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

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

X _____

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position: Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype of non-Hodgkin's lymphoma (NHL), accounting for 30% of NHL cases (Armitage and Weisenburger 1998) and 80% of aggressive lymphomas. In 2020, 544,352 and 82,185 new NHL cases worldwide and in Northern America were estimated, respectively, with over 163,000 patients estimated to be diagnosed with DLBCL worldwide and 24,656 in Northern America (Global Cancer Observatory 2020). While DLBCL is most frequently diagnosed between the ages of 65 and 74 years (with median age of 65 years at diagnosis [SEER]), it can also occur in the younger population, including children and young adults. Overall, the incidence of DLBCL increases with age; patients with DLBCL typically present with rapidly enlarging masses at nodal or extranodal sites. Often DLBCL is asymptomatic, but it may be associated with constitutional symptoms such as fever, recurrent night sweats, weight loss, and/or local effects of lymph node enlargement, as well as those of bone marrow failure. These disease symptoms, along with treatment-related side effects, often lead to impairments in aspects of health-related quality of life including physical functioning and fatigue (Tholstrup et al. 2011). Without treatment, DLBCL is fatal with a median survival of approximately 6 months (Armitage and Weisenburger 1998).

DLBCL is a heterogeneous disease with a number of histologic, proteomic and molecular subsets with distinctive prognostic profiles, including cell-of-origin (COO) (activated B-cell-like [ABC], germinal center B-cell-like [GCB]), elevated protein expression of MYC and BCL2 seen in double-expressor lymphoma [DEL]), and gene rearrangements in MYC and BCL2 and/or BCL6 (double or triple–hit lymphoma [DHL/THL]) (Schmitz et al 2018; Scott et al 2015; Lenz et al 2008; Johnson et al 2009; Johnson et al 2012). While molecular features help to identify higher and lower risk subtypes, clinical features are also integrated into risk assessment and estimating prognosis. The International Prognostic Index (IPI) for aggressive NHL identifies five patient factors obtained at diagnosis used to stratify prognosis and overall survival (OS). One of the challenges in evaluating prognostic features is that there remains no integrated clinical and biologic prognostic system, although it has been demonstrated that among biologic subgroups, IPI can add to the predictive power of subgroups (Lenz et al 2008; Ennishi et al 2018; Schmitz et al 2018; Chapuy et al 2018; Green et al 2012). Thus, the unmet need in such a heterogeneous disease cannot be simply defined by one or the other system: there are low risk patients by IPI that have poor outcomes due to biological risk factors (e.g. ABC, DHL), and there are low risk patients by biological features who have poor outcomes due to IPI clinical risk factors.

Approximately 60% of patients are cured when treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in the frontline setting. However, DLBCL remains a disease in which a substantial number of patients are not cured by first-line (1L) treatment and most who relapse will die from the disease. Thus, optimizing the initial treatment options in the 1L curative setting would have a substantial impact on the disease outcome.

The FDA's Assessment:
FDA agrees with the Applicant's position on DLBCL but notes that the Applicant's use of the term "DLBCL" in the proposed indication and throughout the Applicant's sections in this document refers to LBCL and encompasses histologies distinct from DLBCL, including high grade B-cell lymphoma (HGBL)

with *MYC* and *BCL2* and/or *BCL6* rearrangements (also referred to as double hit or triple hit lymphoma), HGBL NOS, T-cell/histiocyte-rich LBCL, and anaplastic lymphoma kinase (ALK) positive LBCL. The DLBCL subtypes eligible for POLARIX were DLBCL NOS, Epstein-Barr virus (EBV) positive DLBCL, and human herpesvirus 8 (HHV8) positive DLBCL.

2.2. Analysis of Current Treatment Options

The standard of care therapy for DLBCL involves front line multi-agent chemotherapy with complementary mechanisms of action combined with immunotherapy. Up to 8 cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone given in 21-day intervals (R-CHOP-21), or CHOP-like chemotherapy is considered to be the standard of care therapy for patients with previously untreated DLBCL. Analyses suggest that 6 cycles is not inferior to 8 cycles (Wästerlid et al 2018; Sehn et al 2018).

Modifications to R-CHOP may be considered in certain scenarios such as limited stage disease, where fewer cycles of therapy may be considered. In the case of bulky disease, R-CHOP with consolidation radiation therapy may be considered. In patients who have poor cardiac function or are very frail or elderly with comorbidities, modifications to the chemotherapy regimen may be considered such as regimens suggested in National Comprehensive Cancer Network (NCCN) Guidelines, but these are primarily dose-attenuated, or modify R-CHOP by substitution of anthracyclines with a less cardiotoxic agent. Thus, the best outcomes are expected with R-CHOP while patient specific factors (e.g. conditioning, bulky disease) are the drivers of the modified regimens, and these modified regimens are not expected to render any efficacy benefit when compared to R-CHOP, but may represent less treatment-related toxicity in certain patient populations (NCCN 2021).

R-CHOP-like regimens that represent dose intensification may also be considered in DLBCL, which is driven by poor outcomes in higher risk patient groups such as ABC, DHL, or advanced stage disease. Regimens such as dose-adjusted etoposide plus prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab are considered in NCCN Guidelines, although the results from a randomized Phase III study did not show superiority to R-CHOP (Bartlett et al 2019). The other change to R-CHOP in the last 5 years has been the introduction of U.S. Food and Drug Administration (FDA)-approved rituximab biosimilars and rituximab hyaluronidase although these represent non-inferiority substitutions to R-CHOP. Thus, R-CHOP remains the preferred 1L regimen in NCCN Guidelines and expert recommendations (Sehn and Salles 2021).

Table 1 Applicant: Summary of the Current Treatment Options in 1L DLBCL

Product Name	Relevant Indication	Year of Approval and Type of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
FDA Approved Treatments					
RITUXAN (rituximab) Source: RITUXAN (rituximab) USPI.	For the treatment of adult patients with previously untreated DLBCL, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens	2006 Full Approval	Recommended dose is 375 mg/m^2 as an intravenous infusion administered on Day 1 of each cycle of chemotherapy for up to 8 infusions	**NHL Study 7 (n=632)** R-CHOP vs CHOP Median PFS: 3.1 years vs 1.6 years HR: 0.69 **NHL Study 8 (n=399)** R-CHOP vs CHOP Median EFS: 2.9 years vs 1.1 years HR: 0.60 **NHL Study 9 (n=823)** R-chemo vs chemo Median time to treatment failure: NE years vs NE years HR: 0.45	Grade 3 or 4 ADRs occurring more frequently in the R-CHOP arm vs CHOP arm: thrombocytopenia (9% vs. 7%) and lung disorder (6% vs. 3%). Other Grade 3 or 4 ADRs occurring more frequently in the R-CHOP arm were viral infection (NHL Study 8), neutropenia (NHL Studies 8 and 9), and anemia (NHL Study 9).

The Applicant's Position: Since the introduction of R-CHOP, the treatment standard has remained unchanged for over 20 years as the majority of randomized studies have failed to show benefit. The poor outcome of the patients not cured by R-CHOP highlights the ongoing high unmet medical need for more efficacious and better tolerated treatments for patients with previously untreated DLBCL.

The FDA's Assessment:
The FDA agrees with the Applicant's position on the treatment options for patients with previously untreated DLBCL NOS; however, there is no universal standard for previously untreated HGBL, for which more intensive regimens are generally favored in the U.S. because of concerns with inferior outcomes with R-CHOP. Central nervous system (CNS) prophylaxis is routinely considered for HGBL because of the heightened risk of CNS dissemination. Although its role is not established, high-dose therapy with SCT can also be considered for HGBL in first remission, in contrast to most cases of DLBCL NOS.

Table 2: Treatment Guidelines for Newly Diagnosed HGBL with MYC and BCL2 and/or BCL6 Translocations

• Clinical trial is recommended
• **R-CHOP** may be associated with a sub-optimal outcome. Could be considered for low-risk IPI patients.
• **Dose-adjusted EPOCH-R**
• **R-HyperCVAD** alternating with **high-dose methotrexate** and **cytarabine** *
• **R-CODOX-M** alternating with **R-IVAC** *
• Additional considerations – Central nervous system prophylaxis – Consolidation with autologous SCT can be considered
Potentially toxic regimens; performance status and comorbidities should be considered EPOCH-R: etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab R-HyperCVAD: rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone R-CODOX-M: rituximab, cyclophosphamide, vincristine, doxorubicin, and methotrexate R-IVAC: rituximab, ifosfamide, etoposide, and cytarabine Source: Modified from NCCN Guidelines for B-Cell Lymphoma

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position: The original biologics license application (BLA) (761121) was granted accelerated approval on 10 June 2019 for POLIVY® (polatuzumab vedotin-piiq) in combination with bendamustine and a rituximab product for the treatment of adult patients with relapsed or refractory (R/R) DLBCL, not otherwise specified, after at least two prior therapies.

To fulfill the accelerated approval requirement for further adequate and well-controlled clinical trials, the Applicant agreed to verify clinical benefit through either post-marketing requirement (PMR) 3630-1 (Study GO39942) or PMR 3630-2 (Study MO40598) as outlined in the BLA approval letter (Reference ID: 4446006).

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

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position: On January 7, 2011 (Serial No. 0000), the Sponsor submitted to FDA the IND 109409 for the development of polatuzumab vedotin (pola) for the treatment of B-cell malignancies. The regulatory history relevant to the proposed application is summarized in Table 3.

Table 3 Applicant: **Regulatory History of Key Interactions with FDA Regarding the Development of Pola in Combination with R-CHP in Previously Untreated DLBCL**

Date	Regulatory History
12 December 2016	Pola was granted orphan drug designation for the treatment of DLBCL (Designation request #16-5474).
12 December 2016	The Sponsor held a Type C meeting with the FDA to discuss the data supporting the proposed dose and regimen for pola of 1.8 mg/kg for 6-8 cycles to initiate Phase III trials in DLBCL (Reference ID: 4030228).
3 April 2017	The Sponsor held a Type B meeting with the FDA to discuss the proposed Phase III study in 1L DLBCL and supportive data (Reference ID: 4081102).
19 July 2017	The Sponsor received a FDA non-hold comment related to POLARIX regarding the primary PFS analysis to follow all patients for a minimum of 24 months (Serial No. 0372).
1 October 2020	The Sponsor received Type C written feedback from the FDA regarding the proposed content and format of the sBLA to enable full approval for the proposed indication in 1L DLBCL (Reference ID: 4679238).
12 October 2020	POLARIX SAP version (v)3 was submitted (Serial No. 0805). The Agency confirmed via email on 23 October 2020 that they found the proposed contents reasonable and had no additional comments.
24 September 2021	The Sponsor held a Type B Pre-sBLA meeting to discuss the clinical trial results from POLARIX, and obtain feedback on the acceptability of the results to form the basis of an sBLA for approval of POLIVY in the proposed indication.
2 December 2021	POLARIX SAP v4 was submitted (Serial No. 0873). The Agency provided Advice/Information Request (Reference ID: 4909187) dated 21 December 2021, and subsequently the Sponsor's response was submitted (Serial No. 0878).

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

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

4.1. Office of Scientific Investigations (OSI)

The FDA's Assessment:
OSI was consulted to inspect the Applicant and a clinical investigator of a US site regarding quality of oversight and conduct of the POLARIX trial.

- Genentech, Inc.: An evaluation of the Applicant's clinical trial overview was performed and comprised the following activities: oversight, clinical investigator site and monitor selection, record collection, electronic records and electronic signatures, monitoring activities by the sponsor and site monitors quality assurance, safety assessments, adverse event reporting, investigational product, transfer of regulatory obligations, contractual agreements site monitoring, electronic data capture and meeting minutes from the Independent Data Monitoring Committee. In general, the Applicant's oversight of this trial was acceptable, and no FDA Form 483 was issued.
- Clinical investigator, John Burke, M.D. / Site 307348: The FDA inspection covered the authority and administration of the clinical trial, the study protocol and amendments, study selection criteria, informed consents, investigational product controls, source data evaluation, adverse event reporting, and concomitant medication. Further, the audit comprised also a review of study subject evaluation forms, investigational drug accountability records, and sponsor monitoring activities. The inspection was generally unremarkable. No FDA Form 483 was issued at the end of the inspection.

4.2. Product Quality

The FDA's Assessment:
Not applicable, as this sBLA does not contain CMC-related changes.

4.3. Clinical Microbiology

The FDA's Assessment:
Not applicable

4.4. Devices and Companion Diagnostic Issues

The FDA's Assessment:
Not applicable

5 Nonclinical Pharmacology/Toxicology

The Applicant's Position:
No new information is provided in the current submission.

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

X	X
Primary Reviewer	Supervisor

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

The Applicant is seeking approval for polatuzumab vedotin (pola) in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP) for the treatment of previously untreated DLBCL based on results from GO39942 (POLARIX) trial. The proposed polatuzumab vedotin dosing regimen for the treatment of patients with previously untreated DLBCL is 1.8 mg/kg IV Q3W in combination with R-CHP for 6 cycles.

The efficacy evidence to support the proposed indication is primarily provided from the pivotal Phase 3 POLARIX study comparing the efficacy and safety of pola+R-CHP to those of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in patients with previously untreated DLBCL. Pola+R-CHP resulted in a progression free survival (PFS) benefit over R-CHOP, with a hazard ratio (HR) of 0.73 (95% CI: 0.57, 0.95) and log-rank p-value of 0.0177 (two-sided α=0.05). Safety was largely comparable between the two arms but with higher incidences of infection, febrile neutropenia, nausea, and diarrhea of at least 5% higher in the pola+R-CHP arm.

Additionally, the proposed dosage 1.8 mg/kg IV Q3W was assessed in study GO29044. Study GO29044 is a Phase Ib/II dose escalation study, which included a limited dose exploration of polatuzumab vedotin in combination with R-CHP in patients with previously untreated DLBCL. No meaningful conclusion can be drawn regarding the anti-tumor activity, efficacy, or safety of pola+R-CHP at polatuzumab vedotin dosages lower than 1.8 mg/kg Q3W.

The Applicant provided exposure-response (E-R) analyses to support the proposed dosage. The limited dose exploration and subsequent inclusion of only one dose level (i.e., 1.8 mg/kg) in the E-R analysis for the proposed patient population limits the characterization of polatuzumab vedotin dose-response safety and efficacy associations. As such, it is unclear what safety or efficacy outcomes to expect at dose levels lower than 1.8 mg/kg in patients with previously untreated DLBCL. The E-R analysis for efficacy did not identify any clear associations between polatuzumab vedotin exposure and overall survival (OS) or complete response (CR) although subjects with higher exposure tended to have longer PFS. For the E-R analysis for safety, higher monomethyl auristatin E (MMAE) (i.e., the unconjugated toxic payload) exposure in plasma was associated with higher rates of multiple treatment-emergent adverse events (TEAEs) in patients with previously untreated DLBCL including Grade ≥3 anemia, Grade ≥3 febrile neutropenia, Grade ≥3 infection, Grade ≥3 thrombocytopenia, and TEAEs leading to dose modifications of polatuzumab vedotin.

No major safety or tolerability concerns have been identified with the currently proposed dose of 1.8 mg/kg in the proposed patient population. TEAEs leading to dose modifications of polatuzumab vedotin and the chemotherapy backbone were comparable between the pola+R-CHP and R-CHOP arms and the relative dose intensity (RDI) was high in pola+R-CHP arm with a median RDI above 98% for all components in the chemotherapy backbone.

The population pharmacokinetic (PPK) analysis is largely consistent with the previous analysis. Following the proposed 1.8 mg/kg IV Q3W dosage, there are no clinically significant differences in the exposure of antibody-conjugated MMAE (acMMAE) or unconjugated MMAE based on intrinsic or extrinsic factors including weight (38.4 to 148 kg), age (19 to 80 years), sex, Asian (19.6%) or White (53.1%) racial category, mild hepatic impairment, or mild to moderate renal impairment. Current labeling recommends avoiding use in moderate or severe hepatic impairment, as the effects of moderate or severe hepatic impairment on the PK of polatuzumab vedotin are not fully characterized but could lead to elevated concentrations of the payload and therefore higher rates of AEs. The PPK analysis supports the proposed body weight-based dosing regimen of 1.8 mg/kg in the indicated patient population.

Recommendation:
The Office of Clinical Pharmacology has reviewed the information contained in BLA761121 supplement 8. This BLA supplement is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations and comments are summarized below:

REVIEW ISSUE	RECOMMENDATIONS/COMMENTS
Pivotal or supportive evidence of effectiveness	Higher acMMAE exposure was associated with better PFS and the E-R efficacy analysis generally supported the proposed dosage of polatuzumab vedotin, 1.8 mg/kg IV Q3W, in combination with R-CHP. Although higher acMMAE and MMAE exposure were both associated with higher rates of multiple treatment-emergent adverse events (TEAEs), no major safety or tolerability concerns have been identified with the currently proposed dosage of 1.8 mg/kg Q3W in the proposed patient population. The totality of the evidence supports the approval of polatuzumab vedotin dosage 1.8 mg/kg Q3W in combination with R-CHP for previously untreated DLBCL.
General dosing instructions	The proposed dosage of polatuzumab vedotin is 1.8 mg/kg administered as an intravenous infusion every 21 days for 6 cycles in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Following the proposed 1.8 mg/kg IV Q3W dosage, there were no clinically significant differences in acMMAE or MMAE exposure based on intrinsic or extrinsic factors. No new dose adjustment is recommended based on body weight (38 to 148 kg), sex, age (19 to 80 years), Asian (19.6%) or White (53.1%) racial category, mild hepatic impairment, or mild to moderate renal impairment. Patients with treatment-emergent anti-drug antibodies (n=6) had 30% lower exposure to unconjugated MMAE

REVIEW ISSUE	RECOMMENDATIONS/COMMENTS
	than patients without anti-drug antibody (ADA; n=416). However due to low occurrence (1.4%) of ADA in the POLARIX trial, the effect of ADA on PK is uncertain and the effect of ADA on safety or efficacy is unknown.
Labeling	The proposed labeling is acceptable upon the Applicant and FDA reaching agreements to the FDA-recommended revisions to the labeling.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's Position: The clinical pharmacology of pola was characterized to support pola for the treatment of R/R DLBCL in BLA 761121. The clinical pharmacology program of pola in 1L DLBCL included pharmacokinetic (PK) analysis, exposure-response (E-R) (efficacy/safety/tolerability) analysis, and assessment of immunogenicity. The key clinical pharmacology conclusions from the pivotal POLARIX (GO39942) study and the supportive Study GO29044 are summarized below:

- The co-administration of pola (1.8 mg/kg Q3W) in combination with R-CHP resulted in no considerable changes in the PK of each of the drugs:
  - PK results in POLARIX were consistent with the known PK of pola (pola plasma concentration in combination with R-CHP was comparable to the concentration of the pola monotherapy).
  - No clinically relevant drug interactions between pola and rituximab (R) and CHP for the proposed label combination.
- The previously developed population PK models provide adequate description of acMMAE and unconjugated MMAE concentrations following intravenous administration of pola in combination with CHP in patients with previously untreated DLBCL in POLARIX.
- No clinically meaningful exposure-efficacy or exposure-safety relationships were identified when pola was administered in combination with R-CHP to patients with 1L DLBCL.
- Positive ADA response does not appear to have a clinically relevant impact on pola PK exposures in POLARIX. Due to the limited number of anti-pola antibody-positive patients, no conclusions can be drawn concerning a potential effect of immunogenicity on safety or efficacy. However, no obvious correlation has been identified between ADA response and safety and the emergence of ADAs to pola did not appear to impact efficacy of ongoing and sustained disease remission despite development of ADAs in some patients.

The FDA's Assessment:
FDA generally agrees with Applicant's position that polatuzumab vedotin's PK, exposure, and E-R associations have been characterized in patients with previously untreated DLBCL. There is no formal PK comparison in patients with R/R or previously untreated DLBCL, and PPK analysis was conducted separately for each population. In a cross-study comparison, exposure did not significantly differ (i.e., within approximately 20% difference) between R/R DLBCL and previously untreated DLBCL. The limited dose exploration and subsequent inclusion of only one dose level (i.e., 1.8 mg/kg) in the E-R analysis for the proposed patient population limits the ability to characterize polatuzumab vedotin dose-response

safety and efficacy associations. As such, it is unclear what safety or efficacy outcomes to expect at dose levels lower than 1.8 mg/kg in patients with previously untreated DLBCL. The E-R efficacy analysis showed that higher acMMAE exposure was associated with better PFS based on data from patients with previously untreated DLBCL in POLARIX, although no E-R associations were identified for CR rate or OS. E-R safety analysis showed higher acMMAE and MMAE exposure was associated with higher rates of several TEAEs including Grade ≥3 anemia, Grade ≥3 febrile neutropenia, Grade ≥3 infection, Grade ≥3 thrombocytopenia, and TEAEs leading to dose modification of polatuzumab vedotin.

While the optimized dose of polatuzumab vedotin remains uncertain due to limited dose finding and inclusion of only one dose level (i.e., 1.8 mg/kg) in the E-R analysis, no major safety or tolerability concerns have been identified with the currently proposed dose of 1.8 mg/kg in the proposed patient population. TEAEs leading to dose modifications of polatuzumab vedotin and the chemotherapy backbone were comparable between the pola+R-CHP and R-CHOP arms. The relative dose intensity (RDI) was high in pola+R-CHP arm with median RDI above 98% for all components in the chemotherapy backbone. Refer to Section 6.3 for additional details.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data: POLARIX evaluated pola administered at a fixed dose of 1.8 mg/kg by IV infusion Q3W in combination with R-CHP in previously untreated patients with DLBCL. The 1.8 mg/kg Q3W regimen used in POLARIX is the current approved treatment regimen in R/R DLBCL, which was based on data from nonclinical studies, clinical data from the original registrational Study GO29365 in R/R DLBCL, supported by data from Study GO29044 which tested the safety, anti-tumor activity and pharmacokinetics of escalating body weight–based doses (1.0 , 1.4, and 1.8 mg/kg) Q3W of pola in patients with B-cell NHL.

Justification of pola dose and regimen (1.8 mg/kg Q3W for 6 cycles) when administered as part of the pola+R-CHP combination in patients with previously untreated DLBCL is based upon pola PK, tolerability, safety and efficacy from pivotal Phase III POLARIX study and supportive GO29044 study and E-R analyses using data from pivotal Phase III POLARIX study.

In POLARIX and supportive Study GO29044, co-administration of 1.8 mg/kg Q3W pola with R-CHP resulted in no clinically relevant change in the steady-state PK of co-administrated drugs (Section 6.2.1).

In the Phase Ib/II Study GO29044 evaluating the recommended Phase II dose of pola at 1.8 mg/kg Q3W for 6–8 cycles with R-CHP in patients with previously untreated DLBCL, the safety profile (including hematologic toxicity, infections, and neurotoxicity) was comparable to that seen in the R-CHOP arm of the contemporary study BO21005 (Vitolo et al 2017; Tilly et al 2019). PK studies did not demonstrate alterations to cyclophosphamide or doxorubicin PK when combined with pola, and dose intensity of R-CHP was also maintained with the incorporation of pola at 1.8 mg/kg (Shemesh et al 2020; Tilly et al 2019). Efficacy by positron emission tomography (PET), as measured by investigator-assessed response by modified Cheson (2007) criteria, was promising, with 78% achieving CR and 91% achieving overall response (OR) at the end of treatment.

The positive efficacy results and manageable safety profile for the POLARIX study supporting pola dosing regimen of 1.8 mg/kg Q3W are presented in Section 8.

The E-R analysis of 1.8 mg/kg Q3W of pola for 6 cycles in combination with R-CHP based on POLARIX suggested that a higher pola exposure may be associated with a higher incidence of some safety endpoints (e.g., Grade (Gr) $\geq$ 2 peripheral neuropathy (PN), Gr $\geq$ 3 anemia and Gr $\geq$ 3 thrombocytopenia) and a lower pola exposure may be associated with lower efficacy on progression-free survival (PFS) and EFS_{eff} (event-free survival due to efficacy). Pola dose modifications due to Adverse Event (AE) were not correlated with acMMAE or unconjugated MMAE exposures. Dose intensity for pola, rituximab, doxorubicin, and cyclophosphamide was correlated with pola exposure with an overall high dose intensity (mean, median, and geometric mean >96%) across each tertile of pola exposure (Section 6.3.1).

The Applicant's Position: The recommended pola dosing regimen and schedule for patients with previously untreated DLBCL is pola 1.8 mg/kg Q3W administered intravenously in combination with R-CHP. This is the same dose and schedule as approved for pola in combination with BR in R/R DLBCL. Collectively, PK, safety/tolerability, efficacy and E-R analyses support the selected pola dose and regimen in combination with R-CHP in patients with previously untreated DLBCL as an appropriate dosage regimen that balances PFS benefits with managing risks of developing AEs.

The FDA's Assessment:
FDA agrees with the proposed polatuzumab vedotin dosing regimen of 1.8 mg/kg Q3W with R-CHP in previously untreated DLBCL from a clinical pharmacology perspective. The limited dose exploration and subsequent inclusion of only one dose level (i.e., 1.8 mg/kg) in the E-R analysis for the proposed patient population limits the ability to characterize polatuzumab vedotin dose-response safety and efficacy associations. It is unclear what safety or efficacy outcomes to expect at lower dose levels.

The E-R analysis for efficacy identified that presence of bulky disease at baseline and acMMAE exposure had statistically significant associations with better PFS. The E-R analysis for efficacy did not identify any clear associations between acMMAE AUC and overall survival or probability of complete response. The E-R analysis for safety identified that both acMMAE and MMAE were associated with multiple treatment-emergent adverse events (TEAEs) and TEAEs leading to dose modifications of polatuzumab vedotin.

No major safety or tolerability concerns were identified for the proposed regimen. RDI of all drugs was similar between the pola+R-CHP and R-CHOP arms with median RDI of greater than 98%. FDA performed additional analysis on rates of TEAE leading to dose modification including reduction, interruption, and discontinuation, and did not identify significant differences in the rates of TEAE leading to dose modifications between the pola+R-CHP and R-CHOP arms.

The dose-finding study GO29044 does not adequately characterize the safety, anti-tumor activity, and efficacy of escalating body weight-based doses (i.e., 1.0 , 1.4, and 1.8 mg/kg) of pola+R-CHP Q3W in patients with previously untreated DLBCL because there were too few patients per dose cohort. The current dose selection of polatuzumab vedotin at 1.8 mg/kg Q3W for previously untreated DLBCL is based on limited dose-finding in a small number of patients. Given the limited dose exploration and the small number of patients at dosages lower than 1.8 mg/kg Q3W (2 subjects at 1 mg/kg and 3 subjects at 1.4 mg/kg), the evaluation of any potential differences in the efficacy and safety profiles of the lower dose levels in combination with R-CHP is difficult.

Refer to Section 6.3 for additional details.

6.2.2.2. Therapeutic Individualization

Data: The previously developed popPK models describe acMMAE and unconjugated MMAE concentrations following intravenous administration of pola in combination with CHP in patients with previously untreated DLBCL in POLARIX (Section 6.3.1).

Following 1.8 mg/kg Q3W dosing, body weight, age, sex, race, region, renal function impairment, mild hepatic impairment, and disease characteristics, IPI score, DLBCL subgroup, DEL by IHC, LDH were not associated with clinically relevant differences on post hoc estimated acMMAE and unconjugated MMAE exposures (Section 6.3.1).

Patients with moderate hepatic impairment have similar acMMAE exposures to patients with normal hepatic function but higher unconjugated MMAE exposures (46% higher for Cycle 6 area under concentration-time curve [AUC] and 35% for Cycle 6 Cmax [maximum serum concentration]). Based on the logistical regression of unconjugated MMAE exposures with the probability of AESIs, an increase of unconjugated MMAE AUC from 13.8 to 20.7 ng*day/mL (50% increase) and unconjugated MMAE Cmax from 1.33 to 2 ng/mL (50% increase) is not expected to increase the incidence of AESIs more than ~20%.

The Applicant's Position: Given the totality of data, including observed efficacy and safety in POLARIX, starting dose adjustment per these covariates evaluated in POLARIX PopPK analysis is not warranted.

The higher unconjugated MMAE exposures in patents with moderate hepatic impairment is not expected to have a clinically relevant impact on safety based on the exposure-safety analysis results. Thus, no starting dose adjustment is warranted for patients with mild hepatic impairment. No conclusions can be drawn for patients with moderate hepatic impairment (N=9) or severe hepatic impairment (N=1) due to limited data.

The FDA's Assessment:
FDA agrees with the Applicant's position that no dose adjustment is recommended based on intrinsic or extrinsic factors including body weight, age, sex, White or Asian racial category, mild hepatic impairment, or mild or moderate renal impairment.

Compared to patients with normal hepatic function, the geometric mean exposure of acMMAE was 11% higher in patients with previously untreated DLBCL and mild hepatic impairment. The geometric mean exposure of unconjugated MMAE was 40% higher in patients with relapsed or refractory DLBCL and mild hepatic impairment. No dose adjustment is recommended for patients with mild hepatic impairment.

The PPK analysis included 1 to 3 quantifiable PK samples per analyte (i.e., acMMAE and unconjugated MMAE) from each of 9 patients with moderate hepatic impairment and 1 patient with severe hepatic impairment. The data were insufficient to adequately characterize differences in PK or exposure according to moderate or severe hepatic impairment. The labeling states that use of polatuzumab vedotin should be avoided in patients with moderate or severe hepatic impairment because patients with moderate or severe hepatic impairment may have higher polatuzumab vedotin exposure, and the impacts on clinical outcomes and the magnitude of exposure increase are not known.

In the POLARIX study, ADA positive status was found in 1.4% (6/422) of patients. According to the PPK analysis, patients with treatment-emergent ADA (n=6) had 30% lower exposure to unconjugated MMAE than patients without treatment-emergent (TE) ADA (n=416). Due to low occurrence of ADA, the effect of ADA on PK is uncertain and the clinical relevance of the impact of ADA on efficacy and safety are

unknown.

Refer to Section 18.3.2.2 for detailed assessment of PPK analysis.

6.2.2.3. Outstanding Issues

The Applicant's Position: None

The FDA's Assessment:
FDA agrees there are no outstanding issues from a clinical pharmacology perspective.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:
Pola Pharmacokinetics Results in POLARIX: A total of 434 POLARIX-enrolled patients who had at least one PK-measurable sample post-dose for at least one analyte (acMMAE, unconjugated MMAE and total antibody) were included in the PK analysis (PK cut-off date 16 March 2021). In the pola+R-CHP arm, the geometric mean PK concentration at 30 minutes post-dose on C4D1 compared to 30 minutes post-dose on C1D1 was higher for acMMAE (639 ng/mL vs. 576 ng/mL) and for total antibody (42.0 μg/mL vs. 33.6 μg/mL). For unconjugated MMAE, the post dose geometric mean concentration on Cycle 4 Day 1 tended to be lower compared to Cycle 1 Day 1 post dose (0.189 ng/mL vs 0.327 ng/mL). The geometric mean post-dose pola concentrations on Cycle 1 Day 1 and Cycle 4 Day 1 and pre-dose C4D1 pola geometric mean concentration were generally similar to corresponding values from other pola studies.

Population PK of Pola in Combination with R-CHP in POLARIX: A two-analyte (acMMAE-MMAE) integrated PopPK analysis (Report 1090510) based on PK data from 460 NHL patients from Studies DCS4968g, GO27834, GO29044, and GO29365 (excluding Arms G and H) was previously established to characterize the PK properties of acMMAE and unconjugated MMAE. The current PopPK analysis used the legacy pop-PK model structure to characterize pola PK observed in POLARIX by external validation and was conducted using pola PK data from the pola+R-CHP investigational arm in POLARIX. The legacy PopPK model provides an adequate description of acMMAE and unconjugated MMAE concentrations following the IV administration of pola in patients with previously untreated DLBCL.

Following 1.8 mg/kg Q3W dosing in POLARIX, body weight, age, sex, race (Asian versus non-Asian), region (Asia country versus non-Asia country), renal function impairment (mild or moderate impairment), mild hepatic impairment, disease characteristics (bulky disease, Ann Arbor stage, ECOG PS, IPI score, DLBCL subgroup, DEL by IHC, LDH) were not associated with clinically relevant difference of acMMAE and unconjugated MMAE exposures.

Exposure-Response (E-R) Analysis: The pola exposure-efficacy and exposure-safety analyses on data from previously untreated DLBCL patients treated with pola+R-CHP are summarized below. The E-R analyses included 429 previously untreated DLBCL patients from the pola+R-CHP arm of the POLARIX study.

Exposure-safety relationship:

- Higher acMMAE exposures (AUC and C_{max}) were significantly correlated with higher incidence of Gr ≥2 PN, Gr ≥3 anemia (only AUC), and Gr ≥3 thrombocytopenia ($p < 0.05$). The covariate analyses

were performed only for the acMMAE AUC models. The forward inclusion identified increased baseline hemoglobin (HGB) and increased LDH as the significant covariates associated with increased probability of Gr ≥3 anemia at α=0.01 level. The E-R relationship ($p < 0.05$) remained significant in the presence of these covariates. Only HGB was retained in the model at α=0.001 level during the backward elimination.

- Higher unconjugated MMAE exposures (AUC, C_{max}) were significantly correlated with higher incidence of Gr ≥3 neutropenia, Gr ≥3 infections and infestations, Gr ≥3 anemia, Gr ≥3 thrombocytopenia, and Gr ≥3 febrile neutropenia ($p < 0.05$). The covariate analyses were performed only for the unconjugated MMAE AUC models. The forward inclusion identified increased HGB as a significant covariate associated with increased probability of Gr ≥ 3 anemia, and Asian race as a significant covariate associated with increased probability of Gr ≥3 neutropenia at α=0.01 level. The E-R relationship remained significant in the presence of these covariates in the model; both covariates were retained in the final model at α=0.001 level during the backward elimination.
- acMMAE and unconjugated MMAE exposures (AUC, C_{max}) were not significantly correlated with probability of dose modification due to AEs and time to first dose modification due to AE.
- There were statistically significant correlations between increased acMMAE/unconjugated MMAE exposures (AUC, C_{max}) and decreased dose intensity of pola, rituximab, doxorubicin, and cyclophosphamide ($p < 0.05$). However, given an overall high dose intensity (mean, median, and geometric mean >96%) across each tertile of the acMMAE and unconjugated MMAE exposure, these statistically significant associations between exposure and dose intensity were not considered clinically relevant.
- For all other safety endpoints assessed, there were no statistically significant correlations with the exposure of acMMAE or unconjugated MMAE.

Exposure-efficacy relationship:

- The Cox analysis suggested a significant correlation (p=0.01 by Cox regression) between acMMAE AUC and PFS, with higher exposure leading to a longer PFS. The forward inclusion identified baseline bulky disease and B cell count as significant covariates at α=0.01 level. The E-R relationship remained significant in the presence of those covariates in the model. Only bulky disease remained in the final model at α=0.001 level during the backward elimination.
- The Cox analysis suggested a significant correlation (p=0.01 by Cox regression) between acMMAE AUC and EFS_{eff}, with higher exposure leading to a longer EFS_{eff}. The forward inclusion identified baseline bulky disease as a significant covariate at α=0.01 level. The E-R relationship remained significant in the presence of this covariate in the model. Only bulky disease remained in the final model at α=0.001 level during the backward elimination.
- The Cox analysis suggested no significant correlation between acMMAE AUC and interim OS.
- Probability of CR at the end of treatment did not correlate with acMMAE exposure (AUC).

The Applicant's Position: The information from prior clinical studies contributing to the clinical pharmacology evaluation of pola was included in the original BLA (R/R DLBCL). The new clinical pharmacology information includes an evaluation of pola PK and E-R (efficacy/safety) relationship using data from previously untreated DLBCL patients in the POLARIX study (pola+R-CHP treatment).

Observed pola PK and PopPK analysis confirmed similar PK for R/R NHL (DLBCL+FL) patients receiving pola as 2L therapy (one prior line of therapy) and 3L+ therapy (two or more prior lines of therapy) versus 1L DLBCL treated with pola+R-CHP.

E-R analysis based on POLARIX study suggested that a higher exposure may be associated with higher incidence of some safety endpoints (e.g., Gr ≥2 PN, Gr ≥3 anemia and Gr ≥3 thrombocytopenia) and a lower exposure may be associated with lower efficacy on PFS and EFS_{eff}. Overall, the E-R analyses and the favorable benefit risk profile of the POLARIX study support the proposed dosing regimen of 1.8 mg/kg pola Q3W up to 6 cycles in combination with R-CHP for treating patients with 1L DLBCL.

It is acknowledged that the E-R analysis is limited by the data from a single dose level of pola (1.8 mg/kg Q3W up to 6 cycles), as evaluated in POLARIX. It is known that the E-R relationships for biologics with only one dose level might be confounded due to the potential for the extent of disease to impact the PK of a therapeutic antibody. Given that extent of disease may also be related to both safety and efficacy, it is not possible to distinguish between an effect of PK on disease versus an effect of disease on PK (Wang et al. 2017; Dai et al. 2020). Therefore, the positive E-R relationships observed in POLARIX should be interpreted with caution.

The FDA's Assessment:

FDA agrees with the proposed polatuzumab vedotin dosage of 1.8 mg/kg Q3W for 6 cycles with R-CHP in patients with previously untreated DLBCL. No major safety or tolerability concerns have been identified with the currently proposed dose of 1.8 mg/kg in the proposed patient population. TEAEs leading to dose modifications of polatuzumab vedotin and the chemotherapy backbone were comparable between the pola+R-CHP and R-CHOP arms and the relative dose intensity (RDI) was high in pola+R-CHP arm with a median RDI above 98% for all components in the chemotherapy backbone.

The Applicant's supportive study GO29044 tested the safety and efficacy of escalating body weight-based doses (i.e., 1.0, 1.4, and 1.8 mg/kg) of polatuzumab vedotin Q3W in patients with R/R and newly diagnosed B-cell NHL. As shown in **Table 4**, the ORR values for the limited number of subjects at all doses in dose escalation were 100%. Given the small number of patients, it is difficult to discern any preliminary efficacy or safety difference in lower dosages (e.g., 1.4 mg/kg) when compared to the selected polatuzumab vedotin RP2D at 1.8 mg/kg Q3W. The relationships between polatuzumab vedotin dose and clinical efficacy or safety are not fully characterized in combination with R-CHP for previously untreated DLBCL.

Table 4: Efficacy and Safety Result in GO29044 for Subjects with Previously Untreated DLBCL Who Received Pola+R-CHP

Polatuzumab vedotin Dose in mg/kg, n (%)	Dose Escalation			Dose Expansion
	1.0 mg/kg N=2	1.4 mg/kg N=3	1.8 mg/kg N=5	1.8 mg/kg N=40
Grade ≥3 AE	1 (50%)	1 (33%)	4 (80%)	25 (63%)
Serious AE	0	1 (33%)	3 (60%)	15 (38%)
Grade ≥3 Neutropenia	1 (50%)	0	3 (60%)	9 (23%)
Grade ≥3 Infection	0	0	3 (60%)	2 (5%)
ORR	2 (100%)	3 (100%)	5 (100%)	36 (90%)

AE = adverse event; ORR = overall response rate; pola+R-CHP = polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone.
Source: Study GO29044 CSR

FDA agrees that the current E-R analysis is limited by the inclusion of data from only a single dose level. The current E-R analysis of safety and efficacy includes data from 429 patients with previously untreated DLBCL in POLARIX who received 1.8 mg/kg polatuzumab vedotin Q3W in combination with R-CHP. The limited dose exploration and subsequent inclusion of only one dose level (i.e., 1.8 mg/kg) in the E-R analysis for the proposed patient population limits the ability to characterize polatuzumab vedotin dose-response safety and efficacy associations. As such, it is unclear what safety or efficacy outcomes to expect at dose levels lower than 1.8 mg/kg in patients with previously untreated DLBCL.

The E-R analysis for efficacy did not identify any clear associations between acMMAE AUC and overall survival or probability of complete response. Cox proportional hazard modeling identified that presence of bulky disease at baseline and acMMAE exposure had statistically significant associations with PFS. Refer to Section 18.3.3.2 for detailed E-R efficacy analysis.

In the E-R safety analysis, higher MMAE and acMMAE exposure were both associated with higher rates of multiple TEAEs. Higher MMAE exposure was associated with higher rates of Grade ≥3 neutropenia, Grade ≥3 febrile neutropenia, Grade ≥3 infections, Grade ≥3 anemia, Grade ≥3 thrombocytopenia, Grade ≥3 lymphocyte count decreased, Grade ≥3 hemoglobin decreased, Grade ≥3 platelet count decreased, Grade ≥3 leukocyte count decreased, and TEAE leading to dose modification of any drug in the pola+R-CHP regimen and dose modification of polatuzumab vedotin. Higher acMMAE exposure was associated with higher rates of Grade ≥2 peripheral neuropathy, Grade ≥3 anemia, Grade ≥3 thrombocytopenia, Grade ≥3 hemoglobin decreased, and TEAE leading to dose modification of any drug in the pola+R-CHP regimen and dose modification of polatuzumab vedotin. E-R safety associations were generally stronger with MMAE exposure in plasma compared to acMMAE, which is consistent with the mechanism of action of polatuzumab vedotin as MMAE is the unconjugated toxic payload.

No clear associations were identified between acMMAE or MMAE exposure and Grade ≥3 hyperglycemia, Grade ≥3 cardiac arrhythmias, or Grade ≥3 hepatic toxicity. The number of patients who experienced these safety events was relatively small. Refer to Section 18.3.3.4 for detailed E-R safety analysis.

FDA agrees that dose intensity of the chemotherapy backbone was similar in the pola+R-CHP arm versus the R-CHOP arm. As shown in **Table 5**, RDI was high (mean, median, and geometric mean >98%) for each component in pola+R-CHP and was similar to that of the R-CHOP arm. Of note, RDI does not reflect dose delay or discontinuation because patients with early discontinuation were censored at the end of the last completed cycle. For example, 91.7% of subjects in the pola+R-CHP arm received all six planned doses of polatuzumab vedotin and 88.5% of subjects in the R-CHOP arm received all six planned doses of vincristine (see Section 8.2.2).

To further assess the difference between planned dosage and actual dosage, FDA compared rates of dose modifications due to TEAE across arms. There were no significant differences observed in the rates of TEAEs leading to dose modification of polatuzumab vedotin, vincristine, rituximab, or any drug between the pola+R-CHP arm versus R-CHOP arm, as displayed in **Table 6**.

Table 5: Summary of Relative Dose Intensity in POLARIX in the ITT Population

RDI %	R-CHOP (N= 438)					POLA+R-CHP (N=435)				
	RTX n=435	CYC n=433	DOX n=433	VIN n=436	PRED n=438	RTX n=431	CYC n=431	DOX n=431	POLA n=432	PRED n=435
Mean (%)	99.1	98.6	98.7	98.5	98.4	99.0	98.5	98.5	98.1	98.4
Median (%)	100	100	100	100	100	100	100	100	99.8	100
Min-Max (%)	84-108	65-109	64-109	63-103	20-123	64-116	64-106	65-106	64-111	26-127

Dose intensity is the actual dose received divided by the expected dose. Expected dose is based on the maximum dose allowed per protocol and the actual number of cycles for which treatment was received. Patients with early discontinuation were censored at the end of the last completed cycle.
CYC=cyclophosphamide; DOX=doxorubicin; ITT = intent to treat; Pola=Polatuzumab vedotin; PRED=prednisone; RTX=rituximab; RDI=relative dose intensity; VIN=vincristine
Source: POLARIX CSR Table 9

Table 6: Summary of TEAE Leading to Dose Modifications in POLARIX E-R Safety Population

	Any Drug*		Polatuzumab vedotin or placebo		Vincristine or placebo		Rituximab	
Type of Dose Modification	Pola + R-CHP n=429	R-CHOP n=432	Pola + R-CHP n=429	R-CHOP n=432	Pola+ R-CHP n=429	R-CHOP n=432	Pola + R-CHP n=429	R-CHOP n=432
Dose interruption	23.8%	25.7%	14.0%	14.4%	13.8%	13.9%	22.4%	24.1%
Dose reduction	9.3%	13.2%	5.6%	10.4%	5.6%	10.4%	0%	0%
Drug discontinuation	6.1%	6.7%	4.2%	5.1%	4.2%	5.1%	4.4%	4.9%
Any dose modification	34.7%	38.2%	22.1%	27.1%	21.7%	26.6%	25.9%	26.6%

*Any drug refers to polatuzumab vedotin/placebo, vincristine/placebo, rituximab, doxorubicin, cyclophosphamide, or prednisone.
Pola+R-CHP = polatuzumab vedotin combination with rituximab, cyclophosphamide, doxorubicin, and prednisone; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; TEAE = treatment emergent adverse event.
Source: Reviewer's analysis

6.3.2. Clinical Pharmacology Questions

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

Data: Findings from exposure-efficacy analyses for pola at 1.8 mg/kg Q3W in POLARIX suggested that increased acMMAE AUC may be associated with longer PFS and EFS_{eff} and a pola exposure decrease may be associated with lower efficacy. It is acknowledged that the E-R analysis is limited by the data from a single dose level of 1.8 mg/kg.

The Applicant's Position: Yes. The clinical pharmacology information along with the efficacy results from POLARIX and GO29044 pola+R-CHP treated patients with 1L DLBCL provide evidence of effectiveness.

The FDA's Assessment:
FDA agrees that the clinical pharmacology data from POLARIX supports polatuzumab vedotin 1.8 mg/kg Q3W in combination with R-CHP in patients with previously untreated DLBCL.

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

Data: PK, safety/tolerability, efficacy and E-R analyses collected from POLARIX and supportive study GO29044 support the selected pola dose and regimen (1.8 mg/kg Q3W for 6 cycles) in combination with R-CHP in patients with previously untreated DLBCL as an appropriate dosage regimen that balances PFS benefits with managing risks of developing AEs. The details are provided in section 6.3.1.

The Applicant's Position: Yes. The proposed dose of pola 1.8 mg/kg IV of pola Q3W is effective and has a manageable safety profile based on the available data from the previously approved R/R DLBCL application, the pivotal POLARIX study, and the supportive GO29044 study for the patients with previously untreated DLBCL.

The FDA's Assessment:
FDA agrees with the proposed regimen of polatuzumab vedotin 1.8 mg/kg IV Q3W in combination with R-CHP in patients with previously untreated DLBCL. Refer to Section 6.3.1 for additional information on polatuzumab vedotin dose selection.

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

The Applicant's Position:
No, there is no alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors (Section 6.2.2.2).

The FDA's Assessment:
FDA agrees with the Applicant's position. Following the proposed dosage of 1.8 mg/kg IV Q3W, no clinically significant differences in acMMAE or MMAE plasma exposure were identified according to body weight (38.4 to 148.2 kg), age (19 to 80 years), sex (males vs. females), Asian (20%) or White (53%) racial category, mild hepatic impairment (total bilirubin 1 to 1.5 × ULN and any AST or any AST greater than ULN), or mild to moderate renal impairment (CrCl 30 to 89 mL/min). No alternative dosage is recommended according to these patient factors. Refer to Section 6.2.2.2 for additional details.

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

Data: There have been no dedicated clinical biopharmaceutic studies (i.e., bioavailability and food effect) for pola because pola is administered intravenously (bioavailability=1.0) and no food effect would be expected with parenteral administration. The potential for drug-drug interactions with concomitant medications was assessed as part of the original BLA and the appropriate guidance is provided in the label. No additional analyses have been performed.

Drug -drug interaction between pola and R-CHP was not evaluated in the POLARIX PopPK analysis since all patients in Arm A received pola+R-CHP.

R-CHP did not appear to have an impact on the PK of pola when given in combination based on observed data and PopPK analysis. The PK of pola in the pivotal POLARIX study and supportive Study GO29044 are in line with the other studies of pola. PopPK analysis of POLARIX further supports the pola PK similarity among different studies.

In the supportive Study GO29044, pola did not appear to have an impact on the PK of cyclophosphamide or doxorubicin when given in combination based on observed data. No significant difference in cyclophosphamide or doxorubicin PK was observed for DLBCL patients receiving 1.8 mg/kg of pola + R/G-CHP based on similar cross-cycle exposure comparisons of each analyte both prior to and after administration of pola.

The Applicant's Position: There was no evidence for drug-drug or food-drug interaction between pola and R-CHP.

The FDA's Assessment:
FDA agrees with Applicant's assessment. No formal drug-drug interaction study was conducted to investigate the impact of R-CHP on polatuzumab vedotin PK. The observed acMMAE, total antibody, and unconjugated MMAE concentrations were compared across studies GO29365 and POLARIX. The concentration for pre-dose on Cycle 4 Day 1 (C4D1), and post-dose on Cycle 1 Day 1 (C1D1) were similar between the two studies despite different concomitant medication of R-CHP versus bendamustine plus rituximab (**Table 7**).

Table 7: Observed Mean (SD) Polatuzumab Vedotin PK Concentration Comparisons Across Studies

Analyte	Visit	POLARIX 1.8 mg/kg polatuzumab vedotin IV Q3W (+R-CHP)	GO29365 1.8 mg/kg polatuzumab vedotin IV Q3W (+ BR)	Ratio of POLARIX/ GO29365
acMMAE (ng/mL)	C1D1 30-min post dose	603(153)	653(237)	0.923
	C4D1 pre-dose	18.2(12.0)	23.2(8.59)	0.784
	C4D1 post-dose	657 (175)	659(156)	0.997
Total antibody (ug/mL)	C1D1 30-min post dose	36.1 (11.0)	33.9(11.7)	1.06
	C4D1 pre-dose	5.44(3.20)	5.41(1.79)	1.01
	C4D1 post-dose	44.4(14.5)	39.2(7.30)	1.13
Unconjugated MMAE (ng/mL)	C1D1 30-min post dose	0.424(0.335)	0.590(1.08)	0.719
	C4D1 pre-dose	0.144(0.116)	0.186(0.118)	0.774
	C4D1 post-dose	0.222(0.142)	0.256(0.118)	0.867

acMMAE = antibody-conjugated monomethyl auristatin E; BR = bendamustine and rituximab; C1D1 = cycle 1 day 1; MMAE = monomethyl auristatin E; pola = polatuzumab vedotin; Q3W = every 3 weeks; SD = standard deviation; R-CHP = rituximab plus cyclophosphamide, doxorubicin and prednisone.
Source: BLA 761121 supplement 8 summary of clinical pharmacology studies Table 2

FDA also agrees with the Applicant's assessment that polatuzumab vedotin is unlikely to have an impact on the PK of cyclophosphamide or doxorubicin when given in combination. In study GO29044, cyclophosphamide and doxorubicin were administered on Day 1 of Cycle 1, with polatuzumab vedotin administered on Day 2 of Cycle 1; while during Cycle 3, polatuzumab vedotin, cyclophosphamide and doxorubicin were co-administered on Day 1. In **Table 8**, Cycle 1 C_{max} and C_{trough} (C_{23hr} or C_{24hr}) of cyclophosphamide and doxorubicin prior to polatuzumab vedotin administration were similar to those in the Cycle 3. These results suggest that polatuzumab vedotin is unlikely to have a clinically relevant impact on PK of cyclophosphamide and doxorubicin when given in combination.

Table 8: Summary of Mean (SD) Cyclophosphamide, Doxorubicin Concentration Prior and Following Administration of Polatuzumab Vedotin in Combination with R-CHOP in Patient with DLBCL

Victim Drug (Dose)	Parameter	N	GO29044 Before polatuzumab vedotin dosing C1D1 Mean Concentration µg/mL (SD)	N	GO29044 After polatuzumab vedotin dosing C3D1 Mean Concentration µg/mL (SD)	Ratio
Cyclophosphamide (750 mg/m^2)	C_{max}	22	37.5 (24.4)	28	34.8 (6.14)	0.93
	C_{23hr}	25	2.98 (1.39)	19	3.17 (1.66)	1.1
Doxorubicin (50 mg/m^2)	C_{max}	23	35.4 (13.6)	27	29.3 (10.9)	0.82
	C_{24hr}	25	9.13 (2.51)	20	8.68 (2.05)	0.95

SD = standard deviation.
Source: Study GO29044 CSR, table 50 and 51

X	X
Primary Reviewer Yue Xiang Robyn Konicki	Team Leader Ruby Leong Jiang Liu

7 Sources of Clinical Data

7.1. Table of Clinical Studies

The Applicant's Position:

Table 9 Applicant: Listing of Clinical Trials Relevant to the sBLA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Key Endpoints	Treatment Duration/Follow Up	No. of patients enrolled	Study Population	No. of Centers, Countries
Controlled Studies to Support Efficacy and Safety								
GO39942 (POLARIX)[a]	NCT03274492	Phase III, multicenter, randomized, double-blind, placebo-controlled	A) Pola 1.8 mg/kg + placebo for vincristine, R-CHP q 21 days x 6 cycles. B) Placebo for pola+R-CHOP q 21 days x 6 cycles. Rituximab 375 mg/m^2 as monotherapy in Cycles 7 and 8 in both arms.	Primary endpoint: Inv-assessed PFS Key Secondary: • EFS_{eff} by the investigator[b] • CR rate at EOT by FDG-PET by BICR [b] • OS [b]	After completion of therapy, all patients will be followed up to 5 years. After 5 years, patients will be followed only for survival and initiation of NALT.	**Total 1L DLBCL=879**[c] A) Pola+R-CHP=440 B) R-CHOP=439	Previously untreated patients with CD20-positive DLBCL.	211 centers in 22 countries, in 3 regions.
Supportive Study								
GO29044	NCT01992653	Phase Ib/II, open-label, multicenter, multiple treatment arms (Pola+R/G-CHP)	Dose-escalation: Pola 1.0–1.8 mg/kg+R-CHP q 21 days × 6–8 cycles Pola 1.4–1.8 mg/kg +G-CHP q 21 days × 6–8 cycles. Expansion: Pola 1.8 mg/kg +R-CHP q 21 days × 6–8 cycles Pola 1.8 mg/kg +G-CHP q 21 days × 6–8 cycles.	Primary endpoint: MTD Key Secondary: CR rate by PET-CT, ORR, CR rate by CT scan, DOR, PFS, EFS, and OS in patients with previously untreated DLBCL.	Patients received a total of 6-8 cycles (q21 days) of pola+R-CHP or pola+G-CHP. After completion of therapy, 2 years of follow-up.	**Total 85** patients enrolled: 75[d] safety and efficacy evaluable patients had previously untreated DLBCL: pola+R-CHP n=50; pola+G-CHP n=25	Dose-escalation newly diagnosed or R/R B-NHL (≤1 prior line of systemic therapy)· Expansion previously untreated DLBCL with IPI 2–5.	11 centers in 2 countries: (France and US)

[a]Modules 1, 2 and 5 of the sBLA are based on the POLARIX primary analysis (CCOD June 28, 2021) as previously agreed with the Agency per the Type C Content & Format Written Responses and follow up correspondences (Reference ID: 4679238; correspondence on 23 October 2020, Serial No. 0809; correspondence on 8 December 2020, Serial No. 0816).
Following the Pre-sBLA meeting, the Applicant reached agreement with the Agency for an update of POLARIX safety and OS data with approximately 8 months of additional follow up from the primary analysis (CCOD February 2022) provided as supplemental reports with the sBLA. The final OS analysis will be available during review of the sBLA as agreed with the Agency. [b]Key secondary endpoints per the hierarchical testing procedure (to control the overall type I error rate at a one-sided 0.025 level of significance). [c]The global study population is the basis of the pivotal study and represents the ITT population. [d]Safety and efficacy evaluable population in 1L DLBCL patients (n=75). A total of 82 patients were safety evaluable, as n=7 were other NHL histologies. Of the 75 DLBCL patient, 66 patients were treated with pola 1.8 mg/kg and 9 treated at doses <1.8 mg/kg.

The FDA's Assessment:
FDA agrees with the Applicant's listing of trials.

8 Statistical and Clinical Evaluation

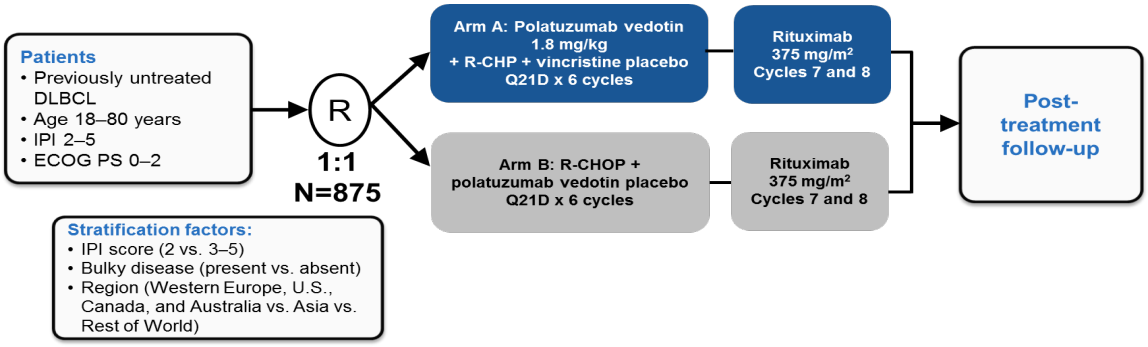
8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Pivotal Study POLARIX (GO39942)

Trial Design

POLARIX is a Phase III, multicenter, randomized, double-blind, active-control, placebo-controlled, two-arm study to compare the efficacy, safety, and PK of pola+R-CHP with those of R-CHOP in patients with previously untreated DLBCL (see Figure 1).

Figure 1 Applicant: Study Design for POLARIX



Pola+R-CHP (investigational arm [A]): pola 1.8 mg/kg IV, placebo for vincristine IV, rituximab 375 mg/m2 IV, cyclophosphamide 750 mg/m2 IV, doxorubicin 50 mg/m2 IV each given on Day 1 and prednisone 100 mg/day orally (PO) given on Days 1–5 of every 21-day cycle for 6 cycles. Rituximab 375 mg/m2 IV was given as monotherapy in Cycles 7 and 8.

R-CHOP (control arm [B]): placebo for pola IV, vincristine 1.4 mg/m2 IV (maximum 2 mg/dose), rituximab 375 mg/m2 IV, cyclophosphamide 750 mg/m2 IV, and doxorubicin 50 mg/m2 IV each, given on Day 1 and prednisone 100 mg/day PO given on Days 1–5 of every 21-day cycle for 6 cycles. Rituximab 375 mg/m2 IV was given as monotherapy in Cycles 7 and 8.

Trial Location: Western Europe, US, Canada, Australia, Asia and Rest of World

Choice of Control: Active control with R-CHOP and pola placebo.

Diagnostic Criteria: Patients with previously untreated CD20–positive DLBCL.

Key Inclusion Criteria:

- Patients with previously untreated CD20–positive DLBCL, included one of the following diagnoses by 2016 WHO classification of lymphoid neoplasms: DLBCL, not otherwise specified (NOS) included GCB type, ABC type; T-cell/histiocyte-rich large B-cell lymphoma; Epstein-Barr virus–positive DLBCL, NOS; ALK-positive large B-cell lymphoma; HHV8-positive DLBCL, NOS; High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements (double-hit or triple-hit lymphoma); High-grade B-cell lymphoma, NOS
- IPI score of 2–5
- ECOG Performance Status of 0, 1, or 2 with life expectancy ≥12 months

- Aged 18–80 years at the time of signing Informed Consent Form
- Adequate hematologic and end organ function

Key Exclusion Criteria:

- Contraindication to any of the individual components of R-CHOP, including prior receipt of anthracyclines, or history of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies, or known sensitivity or allergy to murine products
- Prior organ transplantation
- Grade >1 PN by clinical examination or demyelinating form of Charcot-Marie-Tooth disease
- History of indolent lymphoma or diagnosis of the following: follicular lymphoma (FL) grade 3B; B–cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma (grey-zone lymphoma); primary mediastinal (thymic) large B–cell lymphoma; Burkitt lymphoma; CNS lymphoma (primary or secondary involvement), primary effusion DLBCL, and primary cutaneous DLBCL
- Any of the following abnormal laboratory values (unless any of these abnormalities were due to underlying lymphoma):
  - INR or PT $> 1.5 \times$ upper limit of normal (ULN) in the absence of therapeutic anticoagulation
  - PTT or aPTT $> 1.5 \times$ ULN in the absence of a lupus anticoagulant
  - Serum AST and ALT $\geq 2.5 \times$ ULN
  - Total bilirubin $\geq 1.5 \times$ ULN (patients with documented Gilbert disease could be enrolled if total bilirubin is $\leq 3.0 \times$ ULN)
  - Serum creatinine clearance < 40 mL/min
- Positive test results for chronic hepatitis B infection
- Known history of HIV seropositive status
- Pregnant or lactation patients or patients intended to become pregnant during study

Study Treatments/Dose Modification/Dose Discontinuation: The fixed dose and schedule of pola and R-CHP/R-CHOP are approved dosages for each drug.

Assignment to Treatment: Patients were randomized 1:1 via an interactive voice or web-based response system (IxRS) to one of the two treatment arms using a permuted-block randomization method. Randomization was stratified according to the following stratification factors: IPI score (IPI 2 versus IPI 3–5); Bulky disease, defined as one lesion ≥ 7.5 cm (present versus absent); Geographical region (Western Europe, United States, Canada, and Australia versus Asia versus rest of World [remaining countries]). No crossover was allowed.

Blinding: This was a double-blinded study. A placebo for vincristine was administered to the experimental arm and a placebo for pola was administered to the control arm; the appearance of the placebo was comparable to the active agent.

Dose modification, dose discontinuation: Dose modifications, dose delays, and drug discontinuations were required and permitted based on safety and laboratory evaluation. For the blinded vincristine or blinded pola, symptoms of neuropathy (peripheral sensory, motor neuropathy, constipation or ileus) and hyperbilirubinemia was used in the assessment to decrease, withhold, or discontinue treatment.

Administrative Structure: An unblinded independent Data Monitoring Committee (iDMC) monitored accumulating patient safety data in the treatment arms. All summaries and analyses by treatment arm for the iDMC review were prepared by an external independent Data Coordinating Center (iDCC). Blinded independent central review was used to determine complete response (CR) rate at treatment completion.

Procedures and Schedule: Table 10 represents key procedures and their schedule.

Table 10 Applicant: Schedule of Key Procedures

Assessment	Screening (days)	Treatment Period	Treatment completion visit	Post-treatment
Day/visit	−28 to 1	Cycle 1-Cycle 8	N/A	N/A
Adverse event (AE) assessment	x	x	x	x
Physical exam, laboratory assessment including CBC, CMP, viral serologies, vital signs, ECOG performance status	x	x	x	x
Study treatment administration		x		
B symptoms, FACT/GOG-NTX	x	x	x	x
EORTC QLQ-C30, FACT-Lym LymS, EQ-5D-5L (PRO)	x	Cycle 1, 2, 3, 5	x	every 6 months x 2 years, every 12 months x 3 years
CT and/or PET-CT	x	After Cycle 4, before Cycle 5	x	every 6 mo x 2 years, every 12 mo x 3 years
Concomitant medication assessment	x	x	x	

Source: Adapted from Protocol GO39942 (POLARIX), Appendix 1.

Study visits occurred at screening, Day 1 of each cycle, at treatment completion. Post treatment, visits are scheduled every 3 months for the first 2 years, then every 6 months for the next 3 years. Each study visit includes a physical examination, AE assessment, general laboratory assessment, ECOG PS assessment, and up to treatment completion, concomitant medication assessment. Disease response by CT and/or PET-CT was assessed at screening, before cycle 5, and at treatment completion. In the follow up period, disease response is every 6 months for the first 2 years, then every 12 months for the subsequent 3 years. The schedule of PRO assessments is also included in Table 10 above.

Concurrent Medications: Permitted concomitant medications included oral contraceptives, hormone-replacement therapy, and other supportive care medications. Granulocyte colony-stimulating factor (G-CSF) prophylaxis was required for all patients; anti-infective prophylaxis was permitted based on investigator preference. Other than the prednisone given as study treatment or pre-phase treatment, corticosteroids were allowed for the treatment of conditions other than lymphoma (e.g., asthma). Intrathecal CNS prophylaxis was permitted; systemic CNS prophylaxis was prohibited (e.g. IV methotrexate). Prohibited therapies included other anti-tumor therapy not defined as study treatment, radiotherapy prior to completing study treatment, or other concurrent investigational agents.

Subject completion, discontinuation, or withdrawal: All patients enrolled in the study are included in the ITT population. All patients who received any study treatment are included in the safety-evaluable (SE) population. The primary and secondary efficacy analyses were performed on the ITT population; safety results are performed on the SE population. Subjects who withdrew from study at any time in the study were not replaced.

The FDA's Assessment:
FDA agrees with the Applicant's position but highlights that the Applicant's use of the term "DLBCL" in the proposed indication and throughout the Applicant's sections in this document refers to LBCL and encompasses histologies distinct from DLBCL, including HGBL with *MYC* and *BCL2* and/or *BCL6* rearrangements (also referred to as double hit or triple hit lymphoma), HGBL NOS, T-cell/histiocyte-rich LBCL, and anaplastic lymphoma kinase (ALK) positive LBCL. The DLBCL subtypes eligible for POLARIX were de novo DLBCL NOS, EBV positive DLBCL, and HHV8 positive DLBCL. The study excluded patients with primary mediastinal large B-cell lymphoma, transformed lymphoma, or known CNS involvement by lymphoma.

Study Endpoints

The Applicant's Description: The primary and key secondary endpoints were discussed and agreed upon between the Applicant and the FDA prior to the conduct of the study.

Primary Efficacy Endpoint

- **PFS**: time from randomization to the first occurrence of disease progression or relapse as determined by the Investigator according to Lugano Response Criteria for Malignant Lymphoma, or death from any cause (whichever occurred first)

Key Secondary Efficacy Endpoints (included in the hierarchical testing procedure)

- **EFS_{eff}** defined as the time from randomization to disease progression or relapse; death from any cause; the efficacy reason determined by the investigator, other than disease progression/relapse, that leads to initiation of any non-protocol specified new anti-lymphoma therapy (NALT); if biopsy is obtained after treatment completion, and is positive for residual disease, regardless of NALT status
- **CR** rate at the end of treatment (EOT) by FDG-PET as determined by BICR
- **OS** defined as the period from the date of randomization until the date of death from any cause

Additional Secondary Efficacy Endpoints (not adjusted for testing multiplicity) included CR at EOT by FDG-PET by INV, ORR at EOT by INV and BICR, PFS24 by INV, disease-free survival (DFS) by INV, DOR by INV, and event-free survival-all causes (EFS_{all}) by INV and PRO endpoints including**:** Time to Deterioration (TTD) in physical functioning and fatigue as per EORTC QLQ-C30 and in lymphoma symptoms as per FACT-Lym LymS; Proportion of patients achieving meaningful improvement in EORTC QLQ-C30 physical functioning and fatigue scales and the FACT-Lym LymS; and EORTC QLQ-C30 rate of treatment-related symptoms and FACT/GOG-NTX PN rate.

The FDA's Assessment:
The FDA agrees with the Applicant's summary of the study design and endpoints.

Statistical Analysis Plan and Amendments

The Applicant's Description: All versions of the SAP were submitted under IND 109409. Version 3 of the SAP was submitted on 12 October 2020 (Serial No. 0805). The Agency confirmed via email on 23 October 2020 they found the proposed content of the SAP reasonable and had no additional comments. All

statistical analyses performed for the primary analysis are consistent with SAP v3. On 2 December 2021, SAP v4 was submitted and reviewed by the Agency.

The timing of the primary analysis in POLARIX was driven by the event requirements for the primary PFS analysis, which were met with 228 PFS events observed across both treatment arms and all patients were on study for at least 24 months.

An interim OS analysis was conducted at the same time as the primary PFS analysis, and a final OS analysis will be performed at approximately 36 months after the last patient is enrolled.

The primary analysis of the study tested the equality of investigator-assessed PFS distributions in pola+R-CHP versus R-CHOP:

$$H_0: PFS_{R\text{-}CHP+pola}=PFS_{R\text{-}CHOP} \text{ versus } H_1: PFS_{R\text{-}CHP+pola}>PFS_{R\text{-}CHOP}$$

Treatment comparisons were made using a one-sided level 0.025 stratified log-rank test.

Hierarchical Testing Procedure: To control the overall type I error rate at a one-sided 0.025 level of significance, the following hierarchical testing procedure including possible alpha recycling was used to adjust for multiple statistical testing of the primary and key secondary efficacy endpoints:

- (1) Test PFS assessed by investigator at a one-sided 0.025 level.
- (2) If (1) was significant, test EFS_{eff} by investigator at a one-sided 0.025 level
- If (2) was significant, the one-sided 0.025 alpha (a)was to be split between EOT CR rate by BICR (a = 0.005) and OS (a = 0.02). If either endpoint was significant at its corresponding a level, the corresponding a can then be recycled for the other endpoint so that the other endpoint can then be tested again at a one-sided 0.025 level.

Note that all p-values were reported as two-sided p-values in Section 8.1.1, and were compared to corresponding two-sided alpha values.

Overall Type I Error Control: The overall type I error rate was strongly controlled at a one-sided significance level of 0.025 by a hierarchical testing procedure including possible α splitting and recycling (Bretz et al 2009).

SAP v1 was dated 18 June 2020. The summary of the SAP amendments is provided below:

- SAP v2 (9 September 2020) was amended to incorporate the following major changes
  - The primary PFS analysis will be conducted after approximately 228 PFS events have occurred in the ITT population, and at least 24 months after the last patient is enrolled during the global enrollment phase, whichever occurs later.
  - Censoring tables have been added to clarify the efficacy analysis of PFS, OS, and EFS.
  - The boundary determination for the interim and final analysis of OS has been clarified.
  - Additional sensitivity analyses for PFS and OS have been added.
- SAP v3 (12 October 2020) amended the censoring tables to clarify the efficacy analysis of PFS and EFS_{eff}; updated the method for analyzing EFS_{all} to be consistent with the method for PFS; for time-to-event endpoints where median survival time will not expect to be reached, 1-year and 2-year rates will be reported; updated the immunogenicity analysis population to include all enrolled patients who have at least one serum ADA assessment.
- SAP v4 (1 December 2021) was amended to perform a 2nd formal interim OS analysis in the global cohort approximately 32 months after last patient is enrolled.

Table 11 Applicant: Analysis Populations

Population	Definition
ITT	All patients randomized during the global enrollment phase (including patients enrolled in mainland China during that phase), i.e., the global study, whether or not the patients received the assigned treatment. The global study is defined as the 879 patients randomized into the study on or before 27 June 2019.
PK-evaluable	All patients in the global study who have received at least one dose of polatuzumab vedotin and who have at least one evaluable PK sample post dose for at least one analyte.
Safety-evaluable	All patients in the global study who received at least one dose of study treatment (pola, rituximab, cyclophosphamide, doxorubicin, vincristine, or prednisone), with patients grouped according to the treatment regimen actually received. Specifically, a patient will be included in the pola+R-CHP arm in safety analyses if the patient receives any amount of pola, regardless of the initial treatment assignment by IxRS.
PRO-evaluable	All randomized patients in the global study who have a baseline and at least one post-baseline PRO assessment
Biomarker-evaluable	All randomized patients in the global study who have a valid baseline assessment for that specific biomarker (for each analyzed biomarker)

Planned Subgroup Analyses

The unstratified exploratory subgroup analysis evaluated treatment effect on the primary endpoint of INV-PFS without adjusting for multiplicity, includes patient demographic and patient characteristics, local histopathologic diagnosis, and centrally tested biologic subgroups.

The FDA's Assessment:

FDA agrees with the description of the statistical analysis plan. Additionally, FDA reviews and re-analyzes data as appropriate to evaluate the robustness of the results across various sensitivity analyses, which may differ from what was specified in the protocol or SAP.

Protocol Amendments

The Applicant's Description: Protocol v1 for Study GO39942 was dated 18 July 2017. This protocol had six amendments; the first patient was enrolled/dosed in November 2017, after the implementation of the protocol v2. Key protocol changes were as follows:

- Protocol v2 (18 October 2017): Amended according to Voluntary Harmonization Procedure (VHP) recommendations to include sexual abstinence for men (per vincristine and cyclophosphamide Summary of Product Characteristics), pregnancy testing for women of childbearing potential and clarification on the safety of immunization with live vaccines.
- Protocol v3 (3 August 2018): Inclusion criteria updates on tumor samples at patient enrollment and addition of the refraining from eggs donation to the previously presented contraceptive inclusion criteria for women. Exclusion criteria were updated to include dose and duration of allowed corticosteroids use, additional clarification regarding receiving curative treatment and study enrollment, clarification that the exclusion based on active infections is at the investigator's discretion.

- Protocol v4 (9 October 2018): Amended according to VHP recommendations to perform pregnancy testing for women of childbearing potential 7 days of the study treatment and on Day 1 of each therapy (clarification added on Cycle 1 and 8); removed text which was added on v3 that the exclusion based on active infections is at the investigator's discretion.
- Protocol v5 (3 December 2019): Adjusted sample size and analysis plan of the Asian subpopulation, removed planned futility analysis, updated rational for iDMC to reflect monitoring of only safety (efficacy is no longer included in iDMC monitoring).
- Protocol v6 (10 December 2020): Updates of the primary statistical considerations and the analysis plan were updated on the timing of the primary and secondary analyses and the overall survival (interim and final analyses):
  - The primary analysis to occur at approximately 228 PFS events and after all patients in the global study were enrolled for at least 24 months, whichever comes later.
  - The hierarchical testing procedure, including possible α recycling that was used to adjust for multiple statistical testing of the primary and key secondary efficacy endpoints was updated.
- Protocol v7 (18 December 2020): Primarily clarifications per VHP request were added regarding local lab sensitivity for hepatitis B DNA by PCR; changes pertaining to patients in China extension cohort were clarified; further context to the statistical considerations and analysis plan were included.

The FDA's Assessment:
FDA agrees with the description of protocol amendments. The amendments did not impact the interpretability of results.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant's Position: All studies included in this submission were conducted in accordance with the principles of Good Clinical Practice, the principles of the Declaration of Helsinki, and the local laws and regulations of the countries in which the studies were conducted. Ethics Committees and Institutional Review Boards reviewed and approved all studies. No critical audit findings were observed. The POLARIX audit certificate is provided in the Clinical Study Report (CSR) 1106275.

The FDA's Assessment:
The Applicant indicated that the study was conducted in accordance with good clinical practices.

Financial Disclosure

The Applicant's Position: There were 16 out of 2,427 (0.01%) reportable financial disclosures in the POLARIX study, and no reportable financial disclosures in Study GO29044. See Appendix for Financial Disclosure Information.

The FDA's Assessment:
Financial disclosure information was not disclosed for 9 subinvestigators in POLARIX. It was deemed that this would not affect the interpretation of the trial.

Patient Disposition

Data: A total of 1063 patients were screened for entry into POLARIX and 184 patients failed screening. Of the 879 patients enrolled at 211 sites in 22 countries, in 3 regions and randomized in a 1:1 ratio, 440 patients received pola+R-CHP and 439 patients received R-CHOP.

The top recruiting geographical regions presented in descending order were

- Western Europe/US/Canada/Australia (603 patients [Australia, Austria, Belgium, Canada, Switzerland, Germany, Spain, France, UK, Italy, US]).
- Asia (160 patients [China, Japan, South Korea and Taiwan]).
- Rest of the World (116 patients [Brazil, Czech Republic, New Zealand, Poland, Russian Federation, Turkey, Ukraine]).

Six patients (4 in pola+R-CHP arm and 2 in R-CHOP arm) did not receive any study treatment. The reasons were: physician decision (2 patients), subject withdrawal (1) and other (latent TB was found prior to randomization, (1) in the pola+R-CHP arm and subject withdrawal (1) and other (other malignancy identified, (1) in the R-CHOP arm.

At the time of clinical cut-off date ([CCOD] 28 June 2021) 142 patients (16.2%) had discontinued the study: 66 (15.0%) patients in the pola+R-CHP arm and 76 (17.3%) in the control arm. The main reason for discontinuation was death in 12.3% (108/879) patients.

A total of 879 patients were included in the ITT population (439 in R-CHOP and 440 in pola+R-CHP), 873 patients were included in the SE population (438 in R-CHOP and 435 in pola+R-CHP) and 434 patients in the PK-evaluable population.

The Applicant's Position: The global distribution of countries contributing patients to the POLARIX study is an adequate representation of the global incidence of DLBCL. Patient discontinuations from the study were balanced between arms and a low number of discontinuations for reasons other than deaths were observed.

The FDA's Assessment:
FDA agrees with the Applicant's presentation of patient disposition in POLARIX.

Protocol Violations/Deviations

Data: Major protocol deviations were reported under the following four categories: inclusion criteria, exclusion criteria, procedural and medication. The most frequently reported major protocol deviations were exclusion criteria not met (1.9%), non-compliance with study drug (treatment modification) or stoppage rules (either temporary or permanent) (0.9%), accidental unblinding of a subject or subjects (0.8%) and incorrect subject kit given/administered (0.7%) (**Table 12**).

Table 12 Applicant: Major Protocol Deviations of Interest (ITT population)

Category Description	Pola+R-CHP (N=440)	R-CHOP (N=439)	Total (N=879)
Total number of patients with at least one major protocol deviation	27 (6.1%)	23 (5.2%)	50 (5.7%)
Total number of major protocol deviations	29	26	55
Exclusion criteria: Exclusion criteria not met	12 (2.7%)	5 (1.1%)	17 (1.9%)
Inclusion criteria: Inclusion criteria not met	4 (0.9%)	1 (0.2%)	5 (0.6%)
Medication:			
Incorrect subject kit given/administered	2 (0.5%)	4 (0.9%)	6 (0.7%)
Non-compliance with study drug tx mod or stoppage rules (either temporary or permanent)	3 (0.7%)	5 (1.1%)	8 (0.9%)
Procedural:			
>2 Tumor assessments not performed (during post-treatment phase)	3 (0.7%)	2 (0.5%)	5 (0.6%)
Accidental unblinding of a site staff team member or member(s)	1 (0.2%)	2 (0.5%)	3 (0.3%)
Accidental unblinding of a subject or subject(s)	3 (0.7%)	4 (0.9%)	7 (0.8%)
Any tumor assessments not performed (during treatment phase)	0 (%)	1 (0.2%)	1 (0.1%)

Source: t_dv_PDINT_IT_28JUN2021_39942

The Applicant's Position: Protocol deviations were relatively balanced between arms, and were unlikely to bias the study results.

None of the major protocol deviations led to exclusion of data from the analysis, posed an increased safety risk to any patient continuing on study treatment, or were considered to have affected the integrity of the study findings.

The FDA's Assessment:
FDA agrees with the Applicant's position. The numbers of other reported major deviations were generally balanced between arms, with none involving randomization.

Table of Demographic Characteristics

Data: The study population included predominately white (471/879; 53.6%), male (473/879; 53.8%), with a median age of 65 years (range: 19-80 years). The majority of patients had IPI status 3-5 (62.0%), advanced Ann Arbor stage III and IV (88.7%) and baseline LDH > 1X ULN (65.4%) at diagnosis (**Table 13**).

Table 13 Applicant: Demographic and Baseline Characteristics

Parameters	Pola+R-CHP (N=440)	R-CHOP (N=439)	Total (N=879)
ITT population			
Demographics			
Age (years)			
mean (SD)	63.1 (11.36)	63.0 (11.87)	63.1 (11.61)
median (range)	65.00 (19.0-80.0)	66.00 (19.0-80.0)	65.00 (19.0-80.0)
< 65	209 (47.5%)	203 (46.2%)	412 (46.9%)
≥ 65	231 (52.5%)	236 (53.8%)	467 (53.1%)
Sex			
Male	239 (54.3%)	234 (53.3%)	473 (53.8%)
Female	201 (45.7%)	205 (46.7%)	406 (46.2%)
Geographic region (IxRS)			
Asia	81 (18.4%)	79 (18.0%)	160 (18.2%)
Rest of World	57 (13.0%)	59 (13.4%)	116 (13.2%)
Western Europe/ USA/Canada/Australia	302 (68.6%)	301 (68.6%)	603 (68.6%)
Race			
American Indian or Alaska Native	1 (0.2%)	2 (0.5%)	3 (0.3%)
Asian	85 (19.3%)	84 (19.1%)	169 (19.2%)
Black or African American	8 (1.8%)	8 (1.8%)	16 (1.8%)
Native Hawaiian or other Pacific Islander	0	3 (0.7%)	3 (0.3%)
White	235 (53.4%)	236 (53.8%)	471 (53.6%)
Other	6 (1.4%)	6 (1.4%)	12 (1.4%)
Unknown	105 (23.9%)	100 (22.8%)	205 (23.3%)
Baseline Disease Characteristics			
ECOG	440	438	878
0	175 (39.8%)	173 (39.4%)	348 (39.6%
1	199 (45.2%)	190(43.3%)	389 (44.3%)
2	66 (15.0%)	75 (17.1%)	141 (16.0%)
Ann Arbor Stage	440	439	879
I-II	47 (10.7%)	52 (11.9%)	99 (11.3%)
III-IV	393 (89.3%)	387 (88.2%)	780 (88.7%)
Stratification – IPI Score (IxRS)	440	439	879
2	167 (38.0%)	167 (38.0%)	334 (38.0%)
3-5	273 (62.0%)	272 (62.0%)	545 (62.0%)
Stratification – Bulky Disease (IxRS)	440	439	879
Present	193 (43.9%)	192 (43.7%)	385 (43.8%)
Baseline LDH	437	438	875
≤ 1xULN	146 (33.2%)	154 (35.1%)	300 (34.1%)
> 1x ULN	291 (66.1%)	284 (64.7%)	575 (65.4%)

Biomarker-Evaluable population			
Parameters	**Pola+R-CHP (N=440)**	**R-CHOP (N=439)**	**Total (N=879)**
Double-Expressor evaluable (Central Review)	362	366	728
DEL	139 (38.4%)	151 (41.3%)	290 (39.8%)
Double/Triple-Hit evaluable (Central Review)	331	334	665
DH/TH+	26 (7.9%)	19 (5.7%)	45 (6.8%)
Cell of Origin (Central Review)	330	338	668
ABC	102 (30.9%)	119 (35.2%)	221 (33.1%)
GCB	184 (55.8%)	168 (49.7%)	352 (52.7%)
Unclassified	44 (13.3%)	51 (15.1%)	95 (14.2%)

Source: t_dm_bsch_IT_28Jun2021_39942; t_bas_biom_IT_28Jun2021_39942

The Applicant's Position: Patient demographics and baseline characteristics between the treatment arms were generally balanced and representative of patients with previously untreated DLBCL.

The FDA's Assessment:

FDA agrees with the Applicant's presentation of patients' demographics and baseline characteristics but highlights the underrepresentation of ethnic and racial minorities in POLARIX, when considering the demographics of the general U.S. population with LBCL (source: SEER database). Of the 879 patients randomized, 19% were Asian, 1.8% were Black or African American, and 6% were Hispanic or Latino. Of note, the POLARIX study population may not be representative of the general population of patients with previously untreated LBCL given the eligibility requirements, such as the exclusion of patients with poor performance status, prohibitive comorbidities, end-organ dysfunction, or known CNS involvement by lymphoma. The latter may bias the HGBL outcomes in particular, since HGBL is a highly aggressive lymphoma with a heightened risk of CNS dissemination. Accordingly, more intensive frontline regimens for HGBL include systemic agents that penetrate the blood-brain barrier, such as methotrexate and cytarabine.

As noted previously, the Applicant's proposed indication for "DLBCL" includes a heterogeneous group of aggressive lymphomas, including HGBL which is itself heterogeneous. Importantly there is uncertainty to what extent use of R-CHOP is generalizable to the U.S. population with HGBL, given that other, generally more intensive frontline regimens tend to be preferred (Table 2).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data: Overall, in the SE population 93.6% (407/435) and 90.6% (397/438) of patients received at least 6 cycles of any study drug in the pola+R-CHP arm and the R-CHOP arm, respectively; 89.2% (388/435) in the pola+R-CHP arm and 86.3% (378/438) in the R-CHOP arm received all 8 cycles of rituximab. Most patients completed 6 cycles of pola/vincristine (91.7% (399/435) in pola+R-CHP arm and 88.5% (386/436) in R-CHOP arm). The primary reason for treatment discontinuation was progressive disease (3.3%), followed by AE (3.0%) and physician decision (2.3%).

As of the CCOD, a total of 737 patients (83.8%) were still on study, and 142 patients (16.2%) had discontinued the study. The most frequent reason for patients discontinuing the study was due to death (12.3%) (Section 8.1.1 Study Results, Patient Disposition).

Concomitant Medications:

During the study period, concomitant treatment including prophylactic treatment in pola+R-CHP vs R-CHOP was used in the following drug categories: G-CSF (92.9% vs 95.2%) and anti-infectives for prophylaxis use (61.6% vs 57.1%). The use of other permitted concomitant medications is not expected to affect the efficacy results.

The Applicant's Position: Overall, treatment exposure was comparable between both arms. Concomitant non-cancer therapies were consistent with preventing and treating chemotherapy associated toxicities possibly associated with either pola+R-CHP or R-CHOP.

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

Efficacy Results – Primary endpoint (including sensitivity analyses)

Data: The primary endpoint was met as the pre-specified primary analysis α boundary (one-sided α=0.025, or two-sided α=0.05) was crossed for INV-PFS in the 1L DLBCL population with a statistically significant benefit in the pola+R-CHP treatment arm. This occurred at a protocol-specified analysis of efficacy after 241/879 (27.4%) INV-assessed PFS events had occurred and after all patients had at least 24 months of follow-up. Treatment with pola+R-CHP resulted in a statistically significant reduction in the risk of progression/relapse as assessed by the investigator, or death, compared with the patients treated with R-CHOP (stratified hazard ratio [HR] 0.73 [95% CI: 0.57, 0.95]; stratified log-rank two-sided p=0.0177)(**Table 14**).

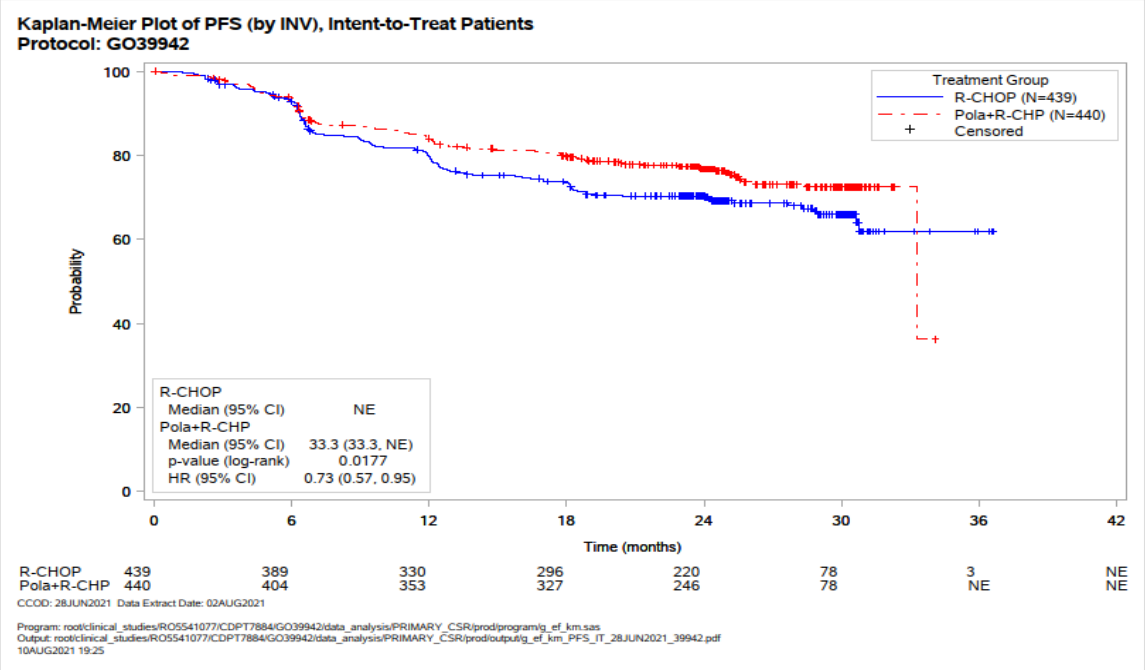
In the Kaplan-Meier analysis, a separation of the curves after 6 months after randomization favoring pola+R-CHP over R-CHOP treatment was observed; the separation was maintained and continued to widen during follow-up (Figure 2). These data were further supported by the PFS analyses at 1- and 2-year milestone, as described in **Table 14**.

Table 14 Applicant: Results of the Primary Efficacy Endpoint (INV-PFS) (ITT Population)

	Pola+R-CHP (N=440)	R-CHOP (N=439)
INV-Assessed PFS		
Patients with event (%)	107 (24.3%)	134 (30.5%)
Earliest contributing event		
Death	19	20
Disease progression	88	114
Patients without event (%)	333 (75.7%)	305 (69.5%)
Stratified HR (95% CI)	0.73 (0.57, 0.95)	
Stratified p-value (log-rank)	0.018	
Unstratified HR (95% CI)	0.76 (0.59, 0.98)	
Unstratified p-value (log-rank)	0.033	
12 Month Duration		
Patients remaining at risk	353	330
Event free rate (%)(95% CI)	83.91 (80.43, 87.39)	79.77 (75.92, 83.61)
Difference in event free rate 95% CI	4.14 (-1.05, 9.32)	
18 Month Duration		
Patients remaining at risk	327	296
Event free rate (%)(95% CI)	79.84 (76.03, 83.65)	73.45 (69.21, 77.69)
Difference in event free rate 95% CI	6.39 (0.69, 12.09)	
24 Month Duration		
Patients remaining at risk	246	220
Event free rate (%)(95% CI)	76.71 (72.65, 80.76)	70.20 (65.80, 74.61)
Difference in event free rate 95% CI	6.50 (0.52, 12.49)	

Source: t_ef_tte_PFS_IT_28Jun2021_39942.
Notes:
-With 24.3% patients experiencing PFS events, the median PFS time estimation in the pola+R-CHP arm was not considered mature at CCOD.
-All reported p-values are two-sided.
-Stratified p-value is nominal.

Figure 2 Applicant: Kaplan-Meier Plot of Time to Investigator-Assessed PFS (ITT Population)



Sensitivity Analyses: The results of pre-specified Investigator assessed PFS sensitivity analyses are presented in Table 15. The stratified HR obtained from the interval censoring method was 0.75 (95% CI: 0.58, 0.96) in favor of pola+R-CHP treatment. The results of the discount method (10% discount: stratified HR 0.73, 95%CI: 0.57-0.95; 30% discount: stratified HR 0.73, 95% CI: 0.57-0.95; 50% discount: stratified HR 0.73, 95% CI: 0.57-0.94) together with the results from the sensitivity analysis where PFS was censored at the last adequate tumor assessment before the initiation of NALT prior to progression or death (stratified HR 0.77, 95%: CI 0.59-1.01) suggested that there was little impact on the treatment effect of pola + R-CHP over R-CHOP when taking into account NALT in the PFS calculation. The difference in the average event-free survival time between treatment and control arm from randomization to 12 and 24 months after randomization was assessed using RMST method. The observed event-free survival time difference (in months) between the treatment arms were 0.2 months [95% CI: -0.1, 0.5] at 12 months; 1.0 month [95% CI: 0.1, 2.0] at 24 months; all in favor of pola+R-CHP. Overall, the results of all sensitivity analyses are consistent with results of the primary analysis of INV-PFS with the HR range from 0.73 to 0.77 in the ITT population.

Table 15 Applicant: Investigator Assessed PFS Sensitivity Analyses

	Pola-R-CHP (N = 440)	R-CHOP (N = 439)
Restricted Mean Survival Time (in month)		
12 months restricted mean survival time (95% CI)	11.1 (10.8, 11.3)	10.9 (10.6, 11.1)
Difference in restricted mean survival time (95% CI)	0.2 (-0.1, 0.5)	
24 months restricted mean survival time (95% CI)	20.6 (20.0, 21.3)	19.6 (18.9, 20.3)
Difference in restricted mean survival time (95% CI)	1.0 (0.1, 2.0)	
Interval Censoring:		
Stratified Hazard Ratio (95% CI)	0.75 (0.58, 0.96)	
Stratified P-value (Sun's test)	0.0144	
Censored at NALT:		
Patients with events	100 (22.7%)	118 (26.9%)
Stratified Hazard Ratio (95% CI)	0.77 (0.59, 1.01)	
Stratified P-value (Log-rank)	0.0567	
Discount Method for NALT (10% discount)		
Stratified Hazard Ratio (95% CI)	0.73 (0.57, 0.95)	
Stratified P-value (Log-rank)	0.0177	
Discount Method for NALT (30% discount)		
Stratified Hazard Ratio (95% CI)	0.73 (0.57, 0.95)	
Stratified P-value (Log-rank)	0.0168	
Discount Method for NALT (50% discount)		
Stratified Hazard Ratio (95% CI)	0.73 (0.57, 0.94)	
Stratified P-value (Log-rank)	0.0163	

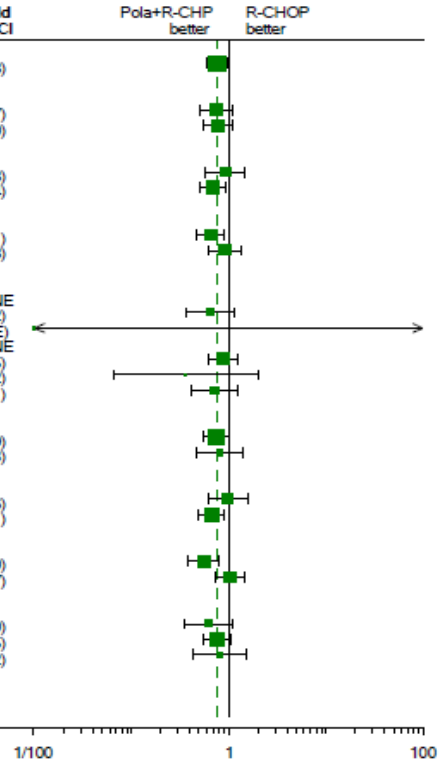
Source: t_ef_tte_rmst_PFS_IT_28JUN2021_39942, t_ef_tte_ic_PFSI_IT_28JUN2021_39942, t_ef_tte_PFSN_IT_28JUN2021_39942, t_ef_tte_DPFS10_IT_28JUN2021_39942, t_ef_tte_DPFS30_IT_28JUN2021_39942, t_ef_tte_DPFS50_IT_28JUN2021_39942.

Subgroup Analyses: The treatment effect on the primary endpoint of INV-PFS was explored in an unstratified exploratory subgroup analysis without adjusting for multiplicity including patient demographic and patient characteristics, local histopathologic diagnosis, and centrally tested biologic subgroups. A directionally consistent treatment effect (HR<1) supporting the PFS benefit of pola+R-CHP compared to R-CHOP was observed in the majority of subgroups. Given the known limitations of the subgroup analysis (Wang et al 2007, Alosh et al 2016), no formal statistical inference may be drawn for the treatment effect in any of the subgroups.

Figure 3 Applicant: Subgroup Analysis: Forest Plot of HR of INV-PFS by Baseline Risk Factors (Part 1)

Forest Plot of Hazard Ratio for PFS (by INV) by Baseline Characteristics Subgroup (part 1), Intent-to-Treat Patients
Protocol: GO39942

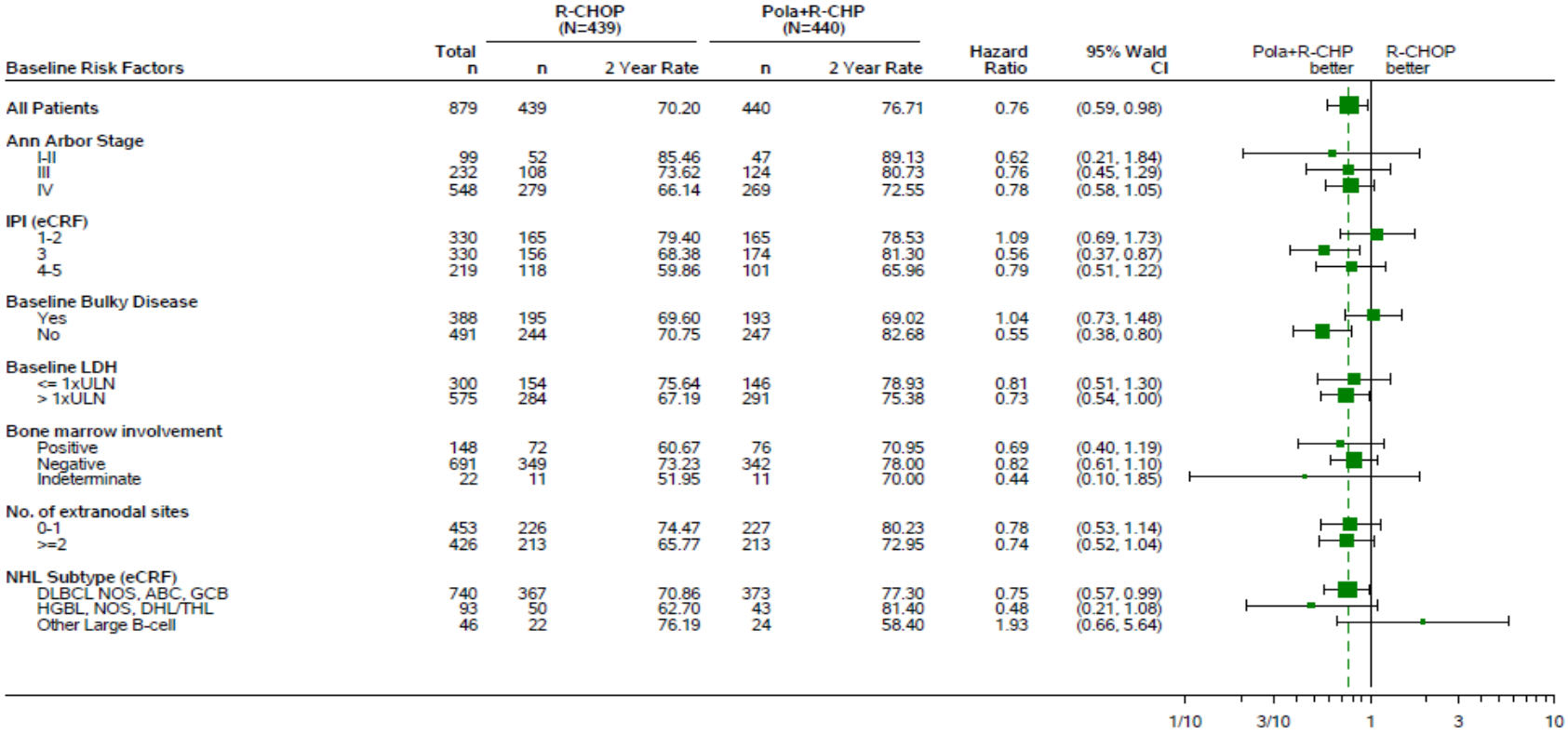
Baseline Risk Factors	Total n	R-CHOP (N=439) n	R-CHOP (N=439) 2 Year Rate	Pola+R-CHP (N=440) n	Pola+R-CHP (N=440) 2 Year Rate	Hazard Ratio	95% Wald CI
All Patients	879	439	70.20	440	76.71	0.76	(0.59, 0.98)
Age Group							
<= 65	444	219	72.20	225	77.89	0.74	(0.51, 1.07)
>65	435	220	68.21	215	75.38	0.78	(0.55, 1.10)
Age Group							
<= 60	271	131	71.85	140	74.12	0.93	(0.58, 1.48)
>60	608	308	69.50	300	77.87	0.69	(0.51, 0.94)
Sex							
Male	473	234	65.87	239	75.87	0.66	(0.47, 0.91)
Female	406	205	75.19	201	77.70	0.93	(0.62, 1.38)
Race							
American Indian or Alaska Native	3	2	100.00	1	NE	NE	NE
Asian	169	84	66.11	85	74.04	0.64	(0.36, 1.12)
Black or African American	16	8	46.88	8	100.00	<0.01	(0.00, NE)
Native Hawaiian or other Pacific Islander	3	3	100.00			NE	NE
White	471	236	72.03	235	76.62	0.88	(0.62, 1.25)
Other	12	6	33.33	6	66.67	0.36	(0.07, 2.02)
Unknown	205	100	71.69	105	77.84	0.71	(0.42, 1.21)
ECOG							
0-1	737	363	71.22	374	78.42	0.75	(0.56, 0.99)
2	141	75	64.99	66	67.24	0.81	(0.46, 1.43)
Stratification - IPI score (IxRS)							
IPI 2	334	167	78.46	167	79.32	0.99	(0.63, 1.56)
IPI 3-5	545	272	65.12	273	75.16	0.67	(0.49, 0.91)
Stratification - Bulky Disease (IxRS)							
Absent	494	247	70.68	247	82.68	0.55	(0.38, 0.80)
Present	385	192	69.68	193	69.03	1.03	(0.72, 1.47)
Stratification - Geographic Region (IxRS)							
Asia	160	79	65.55	81	74.24	0.62	(0.35, 1.10)
Western Europe/USA/Canada/Australia	603	301	71.93	302	78.57	0.76	(0.55, 1.05)
Rest of world	116	59	67.25	57	70.80	0.81	(0.43, 1.52)



Unstratified hazard ratio is displayed.
CCOD: 28JUN2021 Data Extract Date: 02AUG2021
Program: root/clinical_studies/RO5541077/CDPT7884/GO39942/data_analysis/PRIMARY_CSR/prod/program/g_ef_fp.sas
Output: root/clinical_studies/RO5541077/CDPT7884/GO39942/data_analysis/PRIMARY_CSR/prod/output/g_ef_fp_PFS_PART1_IT_28JUN2021_39942.pdf 10AUG2021 19:41

Figure 4 Applicant: Subgroup Analysis: Forest Plot of HR of INV-PFS by Baseline Risk Factors (Part 2)

Forest Plot of Hazard Ratio for PFS (by INV) by Baseline Characteristics Subgroup (part 2), Intent-to-Treat Patients
Protocol: GO39942



Baseline Risk Factors	Total n	R-CHOP (N=439) n	R-CHOP (N=439) 2 Year Rate	Pola+R-CHP (N=440) n	Pola+R-CHP (N=440) 2 Year Rate	Hazard Ratio	95% Wald CI
All Patients	879	439	70.20	440	76.71	0.76	(0.59, 0.98)
Ann Arbor Stage							
I-II	99	52	85.46	47	89.13	0.62	(0.21, 1.84)
III	232	108	73.62	124	80.73	0.76	(0.45, 1.29)
IV	548	279	66.14	269	72.55	0.78	(0.58, 1.05)
IPI (eCRF)							
1-2	330	165	79.40	165	78.53	1.09	(0.69, 1.73)
3	330	156	68.38	174	81.30	0.56	(0.37, 0.87)
4-5	219	118	59.86	101	65.96	0.79	(0.51, 1.22)
Baseline Bulky Disease							
Yes	388	195	69.60	193	69.02	1.04	(0.73, 1.48)
No	491	244	70.75	247	82.68	0.55	(0.38, 0.80)
Baseline LDH							
<= 1xULN	300	154	75.64	146	78.93	0.81	(0.51, 1.30)
> 1xULN	575	284	67.19	291	75.38	0.73	(0.54, 1.00)
Bone marrow involvement							
Positive	148	72	60.67	76	70.95	0.69	(0.40, 1.19)
Negative	691	349	73.23	342	78.00	0.82	(0.61, 1.10)
Indeterminate	22	11	51.95	11	70.00	0.44	(0.10, 1.85)
No. of extranodal sites							
0-1	453	226	74.47	227	80.23	0.78	(0.53, 1.14)
>=2	426	213	65.77	213	72.95	0.74	(0.52, 1.04)
NHL Subtype (eCRF)							
DLBCL NOS, ABC, GCB	740	367	70.86	373	77.30	0.75	(0.57, 0.99)
HGBL, NOS, DHL/THL	93	50	62.70	43	81.40	0.48	(0.21, 1.08)
Other Large B-cell	46	22	76.19	24	58.40	1.93	(0.66, 5.64)

Unstratified hazard ratio is displayed.
CCOD: 28JUN2021 Data Extract Date: 02AUG2021
Program: root/clinical_studies/RO5541077/CDPT7884/GO39942/data_analysis/PRIMARY_CSR/prod/program/g_ef_fp.sas
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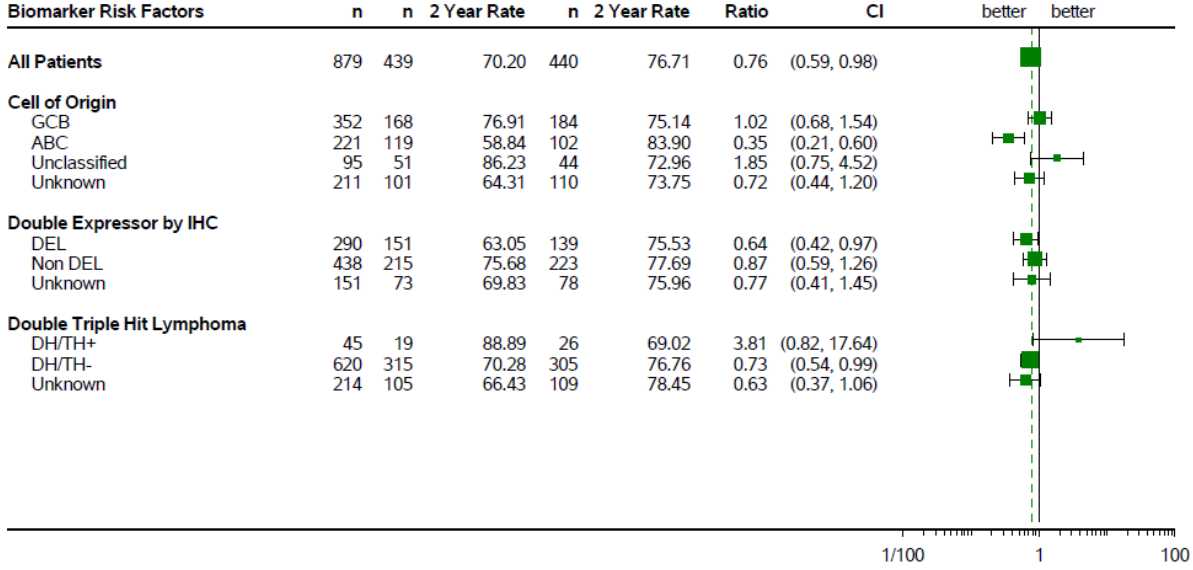
Point estimates for PFS with 95% CI (pola+R-CHP vs. R- CHOP) for COO, DEL, DHL/THL are shown in **Figure 5**. For the majority of molecular subgroups, the 95% CI of their HRs overlap with the 0.73 PFS HR in the ITT population, demonstrating consistency with the primary PFS results. The PFS in some of the more commonly represented high-risk patient subgroups are: for the ABC-DLBCL subgroup, the 2-year investigator-assessed PFS rate was 83.9% in the pola+R-CHP arm vs 58.8% in the R-CHOP arm (HR 0.35 [95% CI: 0.21, 0.60]); for the DEL subgroup, the 2-year investigator-assessed PFS rate was 75.5% in the pola+R-CHP arm vs. 63.1% in the R-CHOP arm (HR 0.64 [95% CI: 0.42, 0.97]). For the less commonly represented DH/TH+ subgroup, the PFS HR appears to favor R-CHOP, but the ability to draw conclusions is limited due to the small numbers of patients and PFS events should be interpreted with caution.

Figure 5 Applicant: Subgroup Analysis: Forest Plot of HR of INV-PFS by Biomarkers

Forest Plot of Hazard Ratio for PFS (by INV) by Biomarker Subgroup, Intent-to-Treat Patients
Protocol: GO39942

Biomarker Risk Factors	Total n	R-CHOP (N=439) n	R-CHOP (N=439) 2 Year Rate	Pola+R-CHP (N=440) n	Pola+R-CHP (N=440) 2 Year Rate	Hazard Ratio	95% Wald CI
All Patients	879	439	70.20	440	76.71	0.76	(0.59, 0.98)
Cell of Origin							
GCB	352	168	76.91	184	75.14	1.02	(0.68, 1.54)
ABC	221	119	58.84	102	83.90	0.35	(0.21, 0.60)
Unclassified	95	51	86.23	44	72.96	1.85	(0.75, 4.52)
Unknown	211	101	64.31	110	73.75	0.72	(0.44, 1.20)
Double Expressor by IHC							
DEL	290	151	63.05	139	75.53	0.64	(0.42, 0.97)
Non DEL	438	215	75.68	223	77.69	0.87	(0.59, 1.26)
Unknown	151	73	69.83	78	75.96	0.77	(0.41, 1.45)
Double Triple Hit Lymphoma							
DH/TH+	45	19	88.89	26	69.02	3.81	(0.82, 17.64)
DH/TH-	620	315	70.28	305	76.76	0.73	(0.54, 0.99)
Unknown	214	105	66.43	109	78.45	0.63	(0.37, 1.06)



Unstratified hazard ratio is displayed.
CCOD: 28JUN2021 Data Extract Date: 02AUG2021
Program: root/clinical_studies/RO5541077/CDPT7884/GO39942/data_analysis/PRIMARY_CSR/prod/program/g_ef_fp.sas
Output: root/clinical_studies/RO5541077/CDPT7884/GO39942/data_analysis/PRIMARY_CSR/prod/output/g_ef_fp_PFS_BIOM1_IT_28JUN2021_39942.pdf 10AUG2021 19:43

The Applicant's Position: The POLARIX study met its primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in PFS in the pola+R-CHP arm compared with the R-CHOP arm in the ITT population, inclusive of high-risk subpopulations with poor prognostic factors (stratified HR=0.73; 95% CI: 0.57, 0.95; two-sided p=0.0177). The observed PFS HR translated into a reduction of the risk of disease progression or death by 27% in the pola+R-CHP arm compared with the R-CHOP arm. The avoidance of PFS events represents curative outcomes for previously untreated patients with DLBCL: patients avoid experiencing all of disease relapse, disease progression, and death from any cause.

With less than 1/3 of patients with PFS events in both arms, the median PFS times were not reached for

either arm (the median PFS time estimation was not considered mature for either treatment arm at CCOD). As the pattern of having the majority of PFS events occurring within the first 24 months after starting therapy is known and expected for DLBCL (Maurer et al 2018), the 2 year PFS event rate is considered more clinically meaningful than median PFS as a measurement of treatment effect. Treatment with pola+R-CHP resulted in a higher proportion of patients alive and progression free at 1 and 2 year milestones compared to the R-CHOP regimen, and the observed treatment difference in PFS event-free rate increased from the 1 year milestone (4.14 [95% CI: -1.05, 9.32]) to the 2 year milestone (6.5 [95% CI: 0.52,12.49]).

PFS results were considered robust due to a consistent treatment effect observed across a panel of pre-specified sensitivity analyses for PFS (i.e. effect of NALT treatment, missing tumor assessments, and RMST as an alternative measure for HR). Furthermore, the PFS results are generalizable to patients with DLBCL who have a variety of baseline clinical features and various tumor subtypes, including high-risk subgroups, given that the exploratory subgroup analyses showed a directionally consistent treatment effect supporting the PFS benefit of pola+R-CHP in the majority of subgroups (HR <1).

The totality of the pola+R-CHP treatment data demonstrate clinically meaningful treatment benefit for patients with previously untreated DLBCL.

The FDA's Assessment:
Although FDA confirmed the calculations presented above, FDA has a different interpretation regarding the robustness of the PFS results.

1. Magnitude of the PFS Benefit of Pola+R-CHP

Although the primary analysis of PFS was statistically significant, the effect size with pola+R-CHP was modest. The point estimates in 1-year and 2-year PFS rates differed by 4.1% and 6.5%, respectively, and it is questionable whether this rate of difference is clinically meaningful. Additionally, there was heterogeneity in the observed treatment effect by lymphoma subgroups, as detailed in sections below. Although the modest PFS difference is in the setting of a substitution trial, these results must be considered along with the other efficacy results, OS results, and toxicity when considering the overall benefit-risk of polatuzumab in combination with R-CHP.

2. Sensitivity analyses of PFS

FDA conducted various sensitivity analyses to evaluate the robustness of the PFS result (Table 16). Regardless of the statistical approach, the upper bounds of the confidence intervals for the HR approached or exceeded 1, and the largest calculated difference in 2-year PFS was 6.5%, which is modest for a critical timepoint given that most DLBCL treatment failures occur within the first 2 years from diagnosis or treatment initiation.

Table 16: PFS Results by Censoring Rules

PFS Analyses by Censoring Rules	Difference in 2-year PFS	HR (95% CI)	p-value
Original Data (Sponsor's primary analysis)			
NALT: Not Censored ≥2 Missed Assessments: Not Censored	6.5%	0.73 (0.57, 0.95)	0.0177 [a]
Sensitivity Analyses on Original Data (nominal p-values)			
NALT: Censor ≥2 Missed Assessments: Not Censored	4.9%	0.77 (0.59, 1.01)	0.0567 [b]
NALT: Censor ≥2 Missed Assessments: Censored	4.9%	0.77 (0.59, 1.01)	0.0541
Sensitivity Analyses on New Data (nominal p-values)			
NALT: Censored ≥2 Missed Assessments: Not Censored	6.1%	0.74 (0.57, 0.96)	0.0251
NALT: Censor ≥2 Missed Assessments: Censored	5.9%	0.75 (0.57, 0.97)	0.0308

Note: Median follow-up time for PFS was 24.7 months
[a] Prespecified by Applicant with two-sided alpha 0.05
[b] Prespecified sensitivity analysis by Applicant
Source: FDA analysis

The Applicant's prespecified sensitivity analysis, censoring for NALT, had a PFS HR of 0.77 with a nominal p-value of 0.0567. Based on the original data, the number of PFS events when censoring for NALT was only 23 fewer, compared to the number of PFS events observed if NALT were not censored. The fact that a small change in the number of events changed the statistical significance (nominal p-value = 0.0177 vs. 0.0567) suggests that the PFS benefit is modest and lacks robustness. Additionally, for lymphoma products, the Division typically censors both for NALT and ≥2 consecutive missed disease assessments; this approach evaluates the sole effect of experimental treatment in absence of subsequent therapy, which results in a nominal p-value of 0.0541 and a confidence interval for the HR that does not exclude 1.

FDA noticed some discrepancies in the Applicant's NALT categorization and recategorized some NALT variables (a post-hoc change). Therapies that were not censored represent either continuation of standard therapy or prophylactic therapies (e.g., methotrexate, radiation) that are not uniformly administered to patients Table 17. Sensitivity analyses were conducted based on the new data (after recategorization). FDA considers assessment of the both the original and the new data to be important sensitivity analyses to assess the robustness of the treatment effect.

Table 17: Scenarios for Recategorization of NALT Censoring Before a PFS Event

	Scenario	Censoring
NALT scenario, will not be censored		
1	IV or IT methotrexate administered in the absence of efficacy findings.	No
2	Standard of care R-CHOP or R-CHOP-like therapy in the absence of efficacy findings, including the presence of toxicity. Only includes dose modifications or discontinuations of R-CHOP components. May also include IV or IT methotrexate.	No
3	Preplanned radiation therapy, irrespective of any response at treatment completion.	No
4	Therapy that is given for a second malignancy unlikely to affect LBCL outcomes.	No
5	Therapy that is administered within 3 days of confirming disease progression.	No
NALT scenarios, will be censored		
6	Any unplanned radiation therapy.	Yes
7	Consolidation with chemotherapy and/or stem cell transplantation in the setting of a complete metabolic response.	Yes
8	Receipt of NALT therapy that is different from R-CHOP (e.g. R-ICE, R-GemOx) in the presence of efficacy reasons or not, including therapy that would be for an unrelated lymphoma that could impact LBCL outcome	Yes
NALT scenario, after event, not applicable in censoring		
9	Therapy after disease progression/disease relapse	N/A

IV=intravenous; IT=intrathecal; LBCL=large B-cell lymphoma; NALT=non-protocol anti-lymphoma therapy; R-CHOP rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-ICE=rituximab plus ifosfamide, carboplatin, and etoposide; R-GemOx=rituximab plus gemcitabine and oxaliplatin.
Source: Applicant's table

Data Quality and Integrity

Data: Information requested by the OSI for pivotal Study GO39942 is provided in Module 5.3.5.4 as part of this sBLA.

The Applicant's Position: No issues were identified that could potentially impact data integrity, prevent an adequate assessment of the data and change the conclusions drawn.

The FDA's Assessment:
Data integrity appeared acceptable. Issues with the quality of datasets and CRFs were addressed through multiple IRs.

Efficacy Results – Secondary and other relevant endpoints

Data:
Investigator-Assessed Event-Free Survival for Efficacy Reasons (INV-EFS_{eff})
The statistically significant reduction by 25% in the risk of an EFS_{eff} event (disease progression, relapse, death, biopsy that is positive for residual disease after treatment completion, or start of a NALT due to

efficacy reasons) was observed in the pola+R-CHP arm compared with the R-CHOP arm (stratified HR=0.75 [95% CI: 0.58, 0.96], two-sided p-value=0.0244, two-sided α=0.05, Table 18). At the time of CCOD, 138 (31.4%) patients in R-CHOP arm and 112 (25.5%) of patients in pola+R-CHP arm had an EFS_{eff} event. On the basis of Kaplan-Meier estimates, treatment with pola+R-CHP resulted in a higher proportion of patients alive and event-free compared to R-CHOP at 1 year (82.5% vs 78.7%) and 2 years (75.6% vs 69.4%). KM curves for EFS_{eff} began to separate at approximately 6 months after randomization in favor of pola+R-CHP and the separation was maintained for the duration of follow up (Figure 6).

BICR-Assessed Complete Response (CR) Rate at End of Treatment (by PET-CT)

BICR-assessed CR rates at EOT (by PET-CT), were not statistically significant, but numerically favored pola+R-CHP treatment compared to R-CHOP treatment (treatment difference: 3.92 [95% CI: -1.89, 9.70], two-sided p-value=0.16, two-sided α boundary of 0.01), Table 18. The INV-CR rates at EOT were comparable to BICR-assessed CR rates in both arms. At the end of treatment, CR concordance between investigator and BICR was 88.9% in the pola + R-CHP arm, and 88.6% in the R-CHOP arm.

Overall Survival

First interim analysis of OS (CCOD: 28 June 2021): Per protocol, a formal interim analysis of OS was performed at the time of primary PFS analysis, however these results are still immature beyond 24 months, and the event patient ratio is low. As of the CCOD, a total of 110 events had been reported: 53 (12%) in pola+R-CHP arm and 57 (13%) in R-CHOP arm. The median duration of survival follow-up was 28.1 months in the pola+R-CHP arm (range: 0-43 months) and 28.2 months in the R-CHOP arm (range: 0-42 months) with a minimum follow up of 24 months (duration from last patient randomized date to CCOD) in both arms. The observed stratified HR 0.94 (95% CI [0.65,1.37]) did not meet the pre-specified threshold for statistical significance (stratified log-rank two-sided p-value=0.7524, two-sided α boundary=0.002). Milestone OS results for the pola + R-CHP arm and R-CHOP arm were 92.2% and 94.6% at 1 year and 88.7%, and 88.6% at 2 years, respectively (Table 18).

Second interim analysis of OS (CCOD: 25 February 2022): At the updated CCOD, 125 randomized patients had died, 61/440 patients (13.9%) in the pola+R-CHP arm and 64/439 patients (14.6%) in the R-CHOP arm. With the additional follow-up, the effect estimate was consistent with the primary analysis and remained in favor of the pola+R-CHP arm compared with the R-CHOP arm and there was no evidence of detriment with the observed stratified HR (stratified HR 0.95 [95% CI: 0.67, 1.35], stratified two-sided log-rank p =0.7696, two-sided α boundary=0.002) (Table 18).

On the basis of Kaplan-Meier estimates, the estimated probabilities of being alive at 12, 18, 24, 30, and 36 months are presented in Table 18.

The final OS analysis (two-sided α boundary = 0.04) is planned with a CCOD in June 2022.

The results of additional (not α controlled) secondary endpoints (DFS, DOR, BOR) are presented in Table 18.

Table 18 Applicant: Overview of Key Secondary Efficacy Endpoints (ITT Population)

	Pola+R-CHP (N=440)	R-CHOP (N=439)
INV-Assessed Event-Free Survival for Efficacy Reasons (EFS_{eff})*		
Patients with event (%)	112 (25.5%)	138 (31.4%)
Earliest contributing event		
Death	18	20
Disease Progression	86	106
NALT due to efficacy reasons or positive biopsy	8	12
Patients without event (%)	328 (74.5%)	301 (68.6%)
Stratified HR (95% CI)	0.75 (0.58, 0.96)	
Stratified p-value (log-rank)	0.02	
1 year EFS_{eff} rate (95% CI)	82.52 (78.93, 86.12)	78.67 (74.76, 82.58)
2 year EFS_{eff} rate (95% CI)	75.57 (71.46, 79.69)	69.39 (64.96, 73.81)
BICR-Assessed Complete Response (CR) Rate at End of Treatment (by PET-CT)		
Complete Responders (95% CI)	343 (78.0%) (73.79, 81.74)	325 (74.0%) (69.66, 78.07)
Difference in response rate (95% CI)	3.92 (-1.89, 9.70)	
Stratified p-value (CMH)	0.16	
Overall Survival (First Interim Analysis, CCOD 28 June 2021)		
Patients with event (%)	53 (12.0%)	57 (13.0%)
Stratified HR (95% CI)	0.94 (0.65, 1.37)	
Stratified p-value (log-rank)	0.75	
Unstratified HR (95% CI)	0.92 (0.63, 1.34)	
Unstratified p-value (log-rank)	0.67	
1 year OS rate (95% CI)	92.17 (89.64, 94.70)	94.62 (92.48, 96.76)
2 year OS rate (95% CI)	88.66 (85.67, 91.65)	88.61 (85.57, 91.64)
3 year OS rate (95% CI)	86.46 (82.79, 90.13)	85.58 (81.90, 89.26)
Overall Survival (Second Interim Analysis, CCOD 25 February 2022)		
Patients with event (%)	61 (13.9%)	64 (14.6%)
Stratified HR (95% CI)	0.95 (0.67, 1.35)	
Stratified p-value (log-rank)	0.7696	
Unstratified HR (95% CI)	0.95 (0.67, 1.34)	
Unstratified p-value (log-rank)	0.7525	
1 year OS rate (95% CI)	92.2 (89.6, 94.7)	94.6 (92.5, 96.8)
2 year OS rate (95% CI)	88.7 (85.7, 91.7)	88.7 (85.7, 91.7)
3 year OS rate (95% CI)	86.0 (82.8, 89.3)	85.8 (82.4, 89.1)

Note: all reported p-values are two-sided.
* EFS_{eff} boundary: one-sided a = 0.025 or equivalently a two-sided a = 0.05; EOT BICR-CR rate boundary: one-sided a = 0.005 or equivalently a two-sided a = 0.01.
Source: t_ef_tte_EFSEFF_IT_28JUN2021_39942, t_ef_rsp_EOTCRBICR_IT_28JUN2021_39942, t_ef_tte_OS_IT_28JUN2021_39942; t_ef_tte_OS_IT_25FEB2022_39942.

Figure 6 Applicant: Kaplan-Meier Plot of Investigator-Assessed EFS_{eff} (ITT Population)

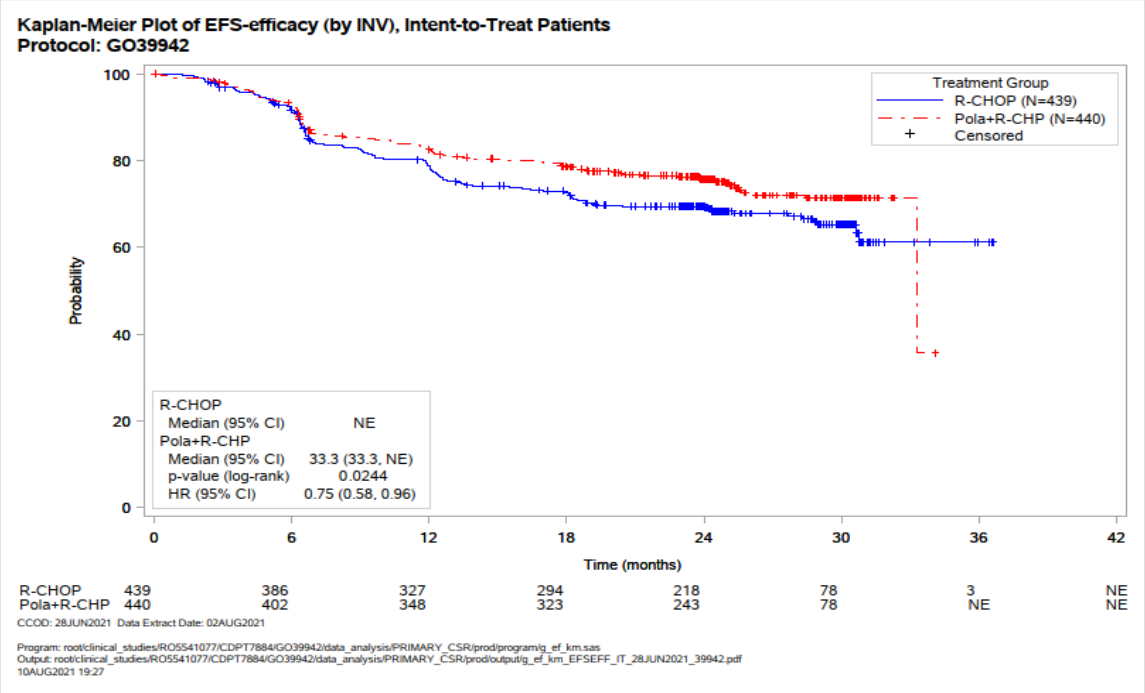
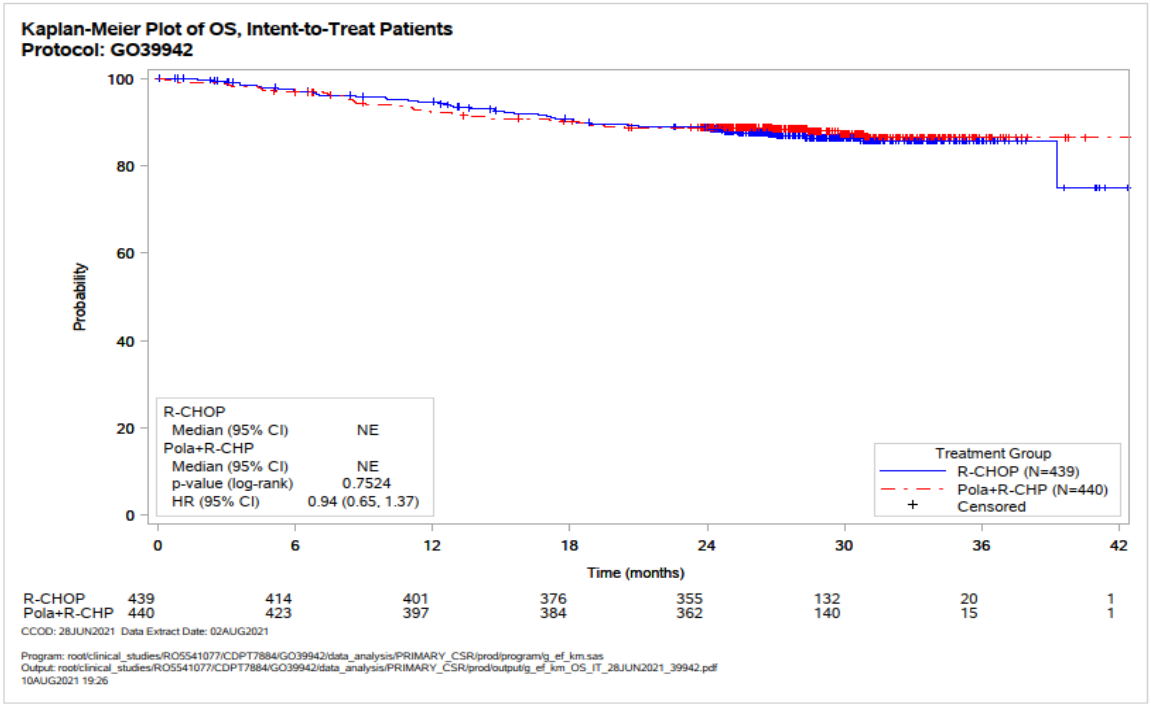
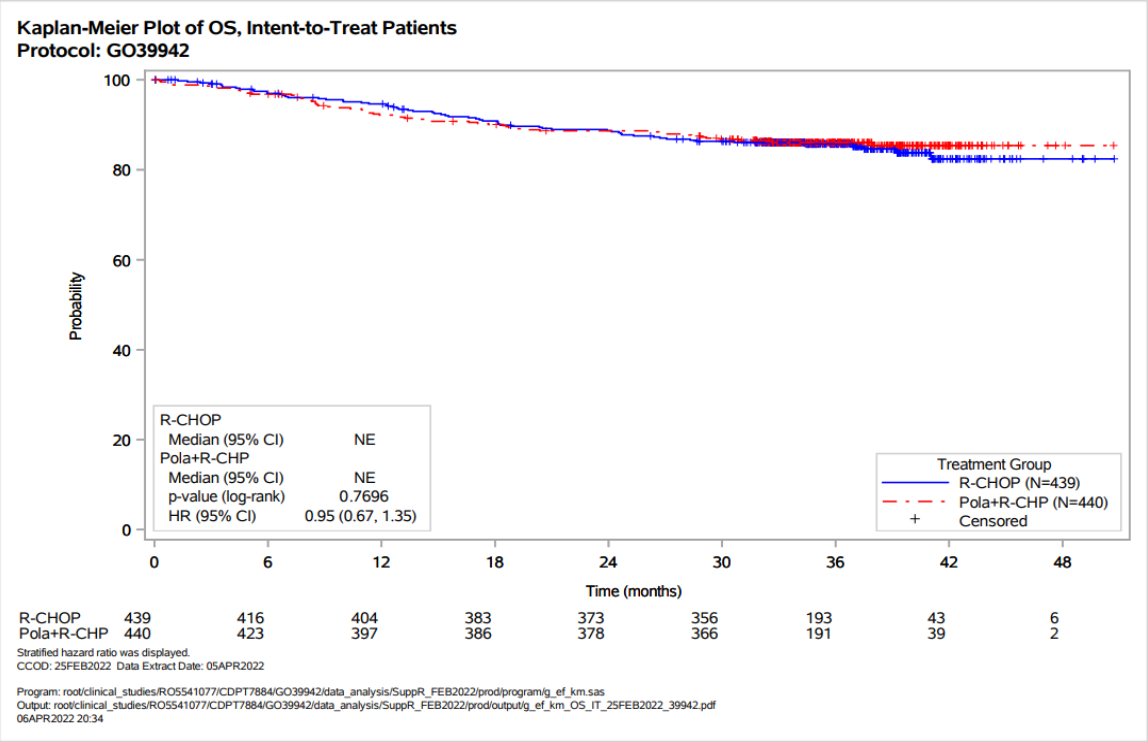


Figure 7 Applicant: Kaplan-Meier Plot of Time to OS (ITT Population; CCOD: 28 June 2021)



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

Figure 8 Applicant: Kaplan-Meier Plot of Time to OS (ITT Population; CCOD: 25 February 2022)



Additional Secondary Efficacy Endpoints (not formally tested)

INV-BOR showed high response rates (i.e. best response of CR or PR while on study) in both the pola+R-CHP arm (95.9% [95% CI: 93.61, 97.56]) and the R-CHOP arm (94.1% [95% CI: 91.44, 96.10]). Treatment difference was 1.83% (95% CI: -1.27, 5.00) in favor of pola+R-CHP.

INV-DOR: In patients who achieve partial or complete response (PR or CR), DOR favors pola+R-CHP compared to R-CHOP (stratified HR 0.74 [95% CI: 0.56, 0.98]). Treatment with pola+R-CHP reduced the risk of progression or death in patients with a CR or PR by 26% compared to patients with a CR or PR who received treatment with R- CHOP.

INV-DFS: In patients who achieve CR, the favorability of the pola+R-CHP arm compared to the R-CHOP arm in DFS suggests that even though CR was high in both treatment arms, remission status was more durable in the pola+R-CHP arm; treatment with pola+R-CHP reduced the risk of progression or death by 30% compared to treatment with R-CHOP (stratified HR 0.70 [95% CI: 0.50, 0.98]).

INV-ORR (i.e. CR or PR) at the end of treatment a high proportion of patients achieved INV-ORR in both arms (84.5% [95% CI: 80.82, 87.79] vs. 80.9% [95% CI: 76.87, 84.44]), with patients in the pola+R-CHP arm achieving a better response in terms of ORR, compared to patients in the R-CHOP arm (treatment difference of 3.68% [95% CI: -1.49, 8.84]). The results of BICR-assessed ORR were similar to that of Investigator-assessed ORR.

The Applicant's Position: Results of the key (α-controlled) secondary endpoint EFS_{eff} were highly

consistent with the PFS results and supportive of clinical benefit for pola+R-CHP compared with R-CHOP. Other key secondary endpoints such as BICR-Assessed CR rates at EOT (by PET-CT) although not statistically significant, numerically favor pola+R-CHP compared to R-CHOP. The favorability of the pola+R-CHP arm compared to R-CHOP arm in DOR and DFS suggests that even though CR was high in both treatment arms, remission status was more durable in the pola+R-CHP arm, further supporting the PFS findings. Interim OS data (CCOD: 28 June 2021) were still immature beyond 24 months, and the event patient ratio was low at the time of the CCOD (the median OS follow up was 28.2 months). Nevertheless, there is no evidence of detriment with stratified HR 0.94 [95% CI: 0.65, 1.37]. The updated OS data (CCOD: 25 February 2022) represents more mature OS data and with the appearance of the Kaplan-Meier curve, an evolving trend of benefit was observed in milestone OS at later time points favoring pola+R-CHP arm. The results of additional (non α-controlled) secondary endpoints (BOR, DOR, DFS and ORR) further support pola's positive treatment effect observed on INV-PFS.

The FDA's Assessment

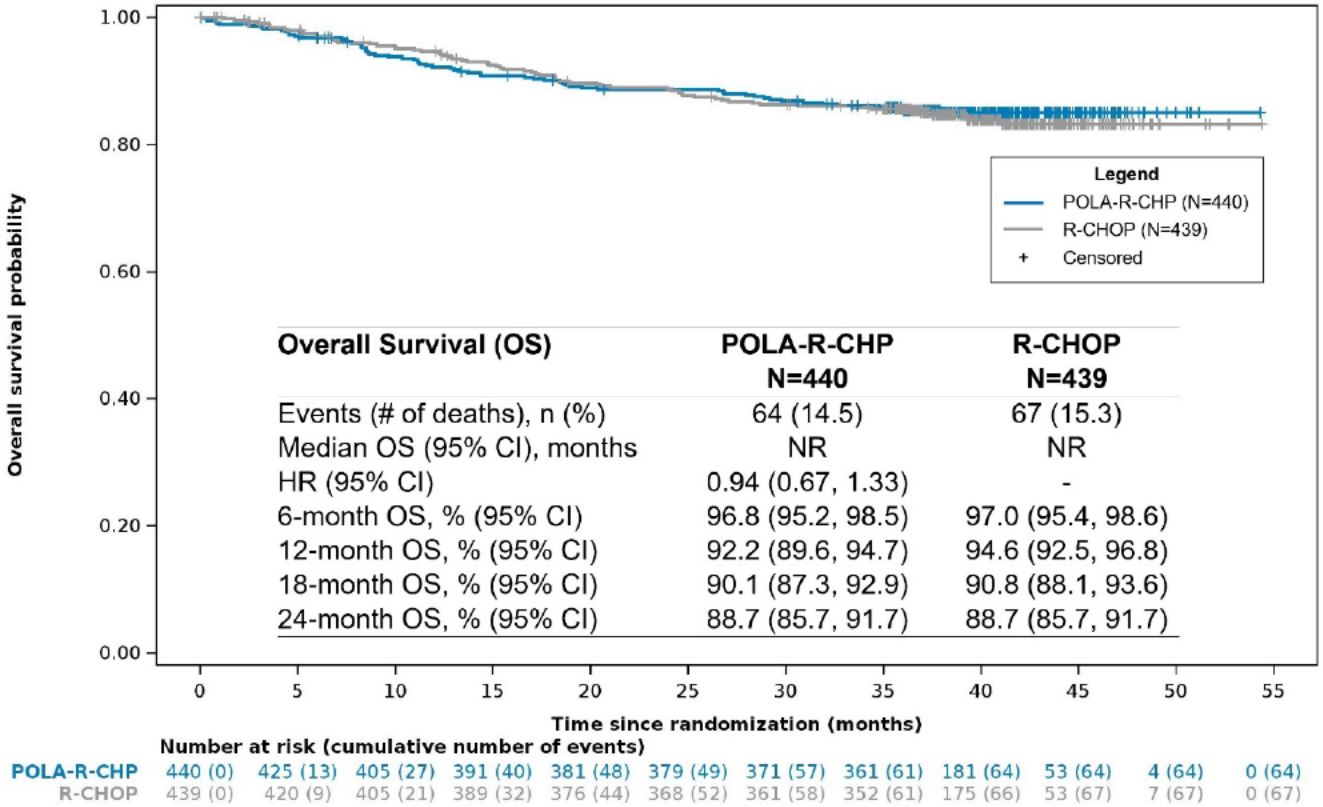
Although FDA confirmed most calculations as presented above, FDA has a different interpretation of the study results. Several issues with the outcomes require additional consideration:

1. **OS Results with Pola+R-CHP**

FDA disagrees with the Applicant's contention of an evolving trend of OS benefit favoring pola+R-CHP arm at later time points. As shown in the Kaplan-Meier plot of the final OS analysis (Figure 9), the PFS benefit of pola+R-CHP did not translate into an improvement in OS. With an estimated median follow-up of 3.3 years, the OS HR was 0.94 with an upper limit of the 95% confidence interval of 1.33. The OS curves appeared to be similar. The OS rates were numerically lower in the pola+R-CHP arm at some early time points (1-year estimate: 92.2% vs. 94.6% in the R-CHOP arm), but similar at the 2-year time point. As detailed later in Section 8.1.2 ("Additional Analyses Conducted on the Individual Trial"), the OS HR for DLBCL NOS, the largest lymphoma subgroup in POLARIX, exceeded 1 (**Figure 11**).

OS is an important metric of both efficacy and safety. POLARIX was not adequately powered to detect improvements in OS, and there is uncertainty due to the low event rates. However, a trial need not be powered for OS to provide important information, and the OS analysis, even if descriptive, informs the benefit-risk determination.

Figure 9: Final OS Analysis and Estimated Early Survival Rates in the ITT Population



Overall Survival (OS)	POLA-R-CHP N=440	R-CHOP N=439
Events (# of deaths), n (%)	64 (14.5)	67 (15.3)
Median OS (95% CI), months	NR	NR
HR (95% CI)	0.94 (0.67, 1.33)	-
6-month OS, % (95% CI)	96.8 (95.2, 98.5)	97.0 (95.4, 98.6)
12-month OS, % (95% CI)	92.2 (89.6, 94.7)	94.6 (92.5, 96.8)
18-month OS, % (95% CI)	90.1 (87.3, 92.9)	90.8 (88.1, 93.6)
24-month OS, % (95% CI)	88.7 (85.7, 91.7)	88.7 (85.7, 91.7)

2. Other Secondary Endpoints

Analyses of other efficacy endpoints, although supportive, have limitations.

Modified EFS (EFS eff)

Modified EFS per investigator, an alpha-allocated secondary endpoint, was statistically significant in the pola+R-CHP arm, with a HR of 0.75 (95% CI: 0.58, 0.96; p-value = 0.0244). However, the treatment effect on this endpoint was modest, with the 1-year point estimate differing by 3.8% and the 2-year point estimate differing by 6.2% (Table 19).

CR rate

FDA does not agree with the Applicant's efficacy claims based on a numerically, but not statistically significant, higher CR rate in the pola+R-CHP arm. The difference in BICR-assessed CR rate at the EOT, an alpha allocated endpoint, did not achieve statistical significance. Moreover, the observed difference was small (3.9%), with a 95% CI that crossed zero (95% CI: -1.9, 9.7). Thus, the PFS benefit observed with pola+R-CHP was not coupled by a significant improvement in the depth of response, raising further uncertainty about the treatment effect of polatuzumab vedotin.

Disease-free survival and duration of response

The differences in DFS and DOR were modest (Table 19). DFS and DOR are not validated, established regulatory endpoints for approval of a drug product. DFS is defined as the time from the date of the first

occurrence of a documented CR to the date of relapse or death from any cause for the subgroup of patients achieving CR and is equivalent to duration of CR. FDA considers results of these endpoints to be exploratory. Given that these endpoints are based on non-randomized subsets of patients and Type I error rate was not controlled, caution should be taken in comparing these outcomes between treatment arms. No statistical significance or comparative efficacy claims should be inferred. Furthermore, the Applicant's analyses of these two endpoints do not censor for NALT, making it difficult to separate the effect of the investigational drug from the effect of NALT.

Table 19: Modified EFS, Duration of Response, and Disease-Free Survival in the ITT Population

Secondary Endpoint	Outcome	Pola + R-CHP	R-CHOP
Modified EFS per investigator [a]	N	440	439
	Patients with event, n	112 (25.5%)	138 (31.4%)
	Death	18	20
	Progression	86	106
	Positive biopsy or NALT due to efficacy reasons [a]	8	12
	HR (95% CI)	0.75 (0.58, 0.96)	
	Stratified log-rank p-value	0.0244[c]	
	1-year rate (95% CI)	82.5% (78.9, 86.1)	78.7% (74.8, 82.6)
	difference (95% CI)	3.8% (-1.5, 9.2)	
	2-year rate (95% CI)	75.6% (71.5, 79.7)	69.4% (65.0, 73.8)
	difference (95% CI)	6.2% (0.1, 12.2)	
DOR per investigator [b]	N	422	413
	2-year rate (95% CI)	75.7% (71.0, 80.3)	71.7% (67.1, 76.2)
	difference (95% CI)	4.0% (-2.5, 10.5)	
DFS per investigator [b]	N	381	363
	2-year rate (95% CI)	81.8% (77.4, 86.2)	77.4% (72.7, 82.0)
	difference (95% CI)	4.4% (-1.9, 10.8)	

[a] Modified EFS includes four events: disease progression, death, initiation of NALT due to an efficacy reason, and positive biopsy for residual disease after treatment completion. NALT initiated for safety reasons was not censored in this analysis.
[b] not censored for NALT
[c] two-sided $\alpha = 0.05$
Source: FDA analysis of originally submitted data

Dose/Dose Response

Data: The exposure-efficacy analysis based on POLARIX study at one dose level of 1.8 mg/kg Q3W up to 6 cycles (N=429 for patients with PK data) was performed. Exposure-efficacy analysis indicated that increased acMMAE AUC may be associated with longer PFS and EFS_{eff} (see section 6.2.2 for details).

The Applicant's Position: The positive efficacy findings and manageable toxicity profile seen in POLARIX study confirm the clinical benefit of pola+R-CHP combination therapy in patients with 1L DLBCL receiving 1.8 mg/kg Q3W pola when administered in combination with R-CHP.

The FDA's Assessment:
FDA agrees with proposed pola dosing regimen 1.8 mg/kg Q3W with R-CHP in previously untreated DLBCL. E-R analysis for efficacy did not identify any clear associations between acMMAE AUC and overall survival or probability of complete response. The E-R analysis for safety identified that both acMMAE and MMAE were associated with multiple treatment-emergent adverse events (TEAEs) and TEAEs leading to dose modifications of pola. See Section 6.2.2.1,6.3.2.2,18.3.3.2, and 18.3.3.4 for details.

Persistence of Effect

Data: Discussed under Efficacy Results – Primary Endpoint

The Applicant's Position: Although OS endpoint is still immature, the 27% risk reduction in INV-PFS shows that patients with 1L DLBCL treated with pola+R-CHP continue to derive benefit. Persistence of effect are supported by landmark analyses of PFS at 1 year and 2 years, with an increase in the PFS rate over time (Section 8.1.1).

The FDA's Assessment:
The results indicate a modest PFS benefit compared to R-CHOP without a clear conclusion regarding relative persistence of effect at later time points.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data: A summary of the key PRO results is presented below.

- The overall completion rates were ≥ 96% at baseline and ≥ 80% throughout the study of the psychometrically valid questionnaires EORTC QLQ-C30, FACT-Lym LymS and FACT GOG-Ntx
- Physical functioning (EORTC QLQ-C30)
  42.4% [95% CI: 37.56, 47.30] of patients in the pola+R-CHP arm experienced a clinically meaningful improvement in physical functioning compared to 39.6% [95% CI: 34.81, 44.47] of patients in the R-CHOP arm.

  Patients in both arms experienced similar rates of deterioration in physical functioning (pola+R-CHP: 41.6% vs. R-CHOP: 42.6%).

Fatigue (EORTC QLQ-C30)
  74.8% of patients in the pola+R-CHP arm had experienced a clinically meaningful improvement in fatigue compared to 68.2% in the R-CHOP arm.

  Treatment with pola+R-CHP resulted in median 6.7 months time to deterioration of the fatigue scores compared to 3.0 months for R-CHOP. There was no overall difference (HR=0.94).

- Lymphoma symptoms (FACT-Lym LymS)
  The proportion of patients with a clinically meaningful improvement in lymphoma symptoms was pola+R-CHP: 82.3% [95% CI: 78.30, 85.88] vs. R-CHOP: 81.3% [95% CI: 77.20, 84.96].

Treatment with pola+R-CHP reduced the risk of deterioration of night sweat score by 22% compared to R-CHOP (stratified HR: 0.78 [0.60, 1.02]).

- PN (FACT/GOG-Ntx)

  Both arms showed low levels of PN at baseline (baseline mean [SE]: 39.81 [0.221] vs. 39.49 [0.248]). The questionnaire scoring ranges from 0 to 44, with higher scores reflective of lower levels of PN.

  Patients in the R-CHOP arm experienced increases in PN (i.e. decrease in mean score) in Cycle 4 vs patients in the pola arm in Cycle 6. While on treatment, PN increases baseline-adjusted mean range: 0.22 to -2.71 in the pola +R-CHP arm and baseline-adjusted mean range: 0.01 to -3.51 in the R-CHOP arm.

The Applicant's Position: Psychometrically valid questionnaires – the EORTC QLQ-C30, FACT-Lym LymS and FACT/GOG-Ntx, were used to regularly collect information from patients over the course of the study; completion rates for these questionnaires were high, further supporting the validity of the data. Treatment with pola+R-CHP resulted in a clinically meaningful delay in deterioration of pre-specified secondary endpoints of patient-reported physical functioning and fatigue compared with R-CHOP. All of these results are substantiated by additional pre-specified exploratory PRO analyses, which showed consistent treatment benefits in favor of pola+R-CHP. Overall, patients on pola+R-CHP were able to maintain aspects of their baseline HRQoL and experienced an improvement in disease-related symptoms after starting treatment.

The FDA's Assessment:
The PRO completion rate was high enough to examine PRO results through follow-up month 12. FDA disagrees with the Applicant's assessment that the results demonstrate consistent treatment benefits in favor of pola+R-CHP including a clinically meaningful delay in deterioration in physical functioning and fatigue. The Applicant's assessment focused on proportions of patients who experienced improvement and time to deterioration, whereas FDA also examined mean scores over time and mean change from baseline. Overall, there were no observed differences between arms in terms of physical function, fatigue, lymphoma symptoms, or peripheral neuropathy. A formal comparison could not be conducted as these were not prespecified, multiplicity-adjusted endpoints. Furthermore, the sparse assessment frequency may obscure changes in physical function and fatigue, particularly early during the treatment period. See Section 8.2.6 for further description of patient-reported symptoms and tolerability.

Additional Analyses Conducted on the Individual Trial

New Anti-Lymphoma Therapy (NALT)

Data: A lower number of patients (75 [17.0%]) in pola+R-CHP arm received post-treatment lymphoma therapy, collected as NALT, compared to the control R-CHOP arm (103 [23.5%]). Among pola + R-CHP arm, 9 (2.0%) received chimeric antigen receptor T-cell (CAR-T), 17 (3.9%) received autologous transplantation, no patients received allogeneic transplantation; within the R-CHOP arm, 16 (3.6%) received CAR-T, 30 (6.8%) received autologous transplantation, 1 (0.2%) received allogeneic transplantation. Hematopoietic stem-cell transplantation (HSCT) data reflect HSCT as subsequent therapy at any point. Among the patients who received HSCT, two (0.5%) patients in the pola + R-CHP arm and one (0.2%) patient in the R-CHOP arm received the HSCT as consolidation without prior disease progression or residual disease after completion of study treatment. Forty-one (9.3%) patients in

pola + R-CHP arm and 57 (13.0%) patients in the control arm received pre-planned post-treatment radiotherapy, which was permitted per protocol and not included in the EFS_{eff} or the EFS_{all} analysis. Thirty (6.8%) patients in pola + R-CHP arm and 39 (8.9%) patients in the control arm received unplanned post-treatment radiotherapy.

The Applicant's Position: The goal of treatment for previously untreated patients with DLBCL is cure. While PFS has surrogacy to OS, and PFS at 24 months (2-years) corresponds to survival outcomes consistent with age, sex, matched populations, another metric of improved efficacy of pola+R-CHP in previously untreated patients with DLBCL is reduced need for NALT. Patients who experience disease progression or relapse (meaning that they were not cured by the standard of care treatment) typically are treated with NALT, and often require multiple NALTs. NALT is particularly burdensome to patients, families, and health care systems and the majority of patients who require NALT for R/R DLBCL still die of their disease. In addition to the PFS improvement in pola+R-CHP, results of the NALT demonstrate that fewer patients treated with pola+R-CHP compared to R-CHOP need subsequent therapy and specifically, some intensive/high cost/high risk therapies.

The number of patients receiving stem cell transplants and CAR-T, each, was also lower in the pola+R-CHP arm compared to the R-CHOP arm. While the number of NALT may reflect added burden to patients and poor efficacy, subsequent treatment options may be confounded by treatment-related toxicities from the previous line of therapy. In the case of POLARIX, the overall safety profile was comparable between the two treatment arms, and cumulative toxicity did not appear to impact one arm more than the other. Resolution of toxicities was similar between the two arms and other factors, such as dose reductions and discontinuation of study treatment due to AE was similar between the treatment arms and numerically lower in the pola+R-CHP arm compared to the R-CHOP arm. These data indicate that overall, the health status of patients who experience disease relapse in the study would not impact the ability to receive subsequent treatment for lymphoma.

The FDA's Assessment:
FDA disagrees with the contention that less NALT in the pola arm necessarily indicates better efficacy. The finding of less NALT in the pola+R-CHP arm, should not be used as evidence of superiority compared to R-CHOP, since NALT can be given for various reasons and has a component of subjectivity. The number of patients receiving NALT was not a prespecified endpoint due to these reasons. We are cautious in assessment of the amount of NALT given these considerations.

Subpopulations

Data: The potential impact of molecular DLBCL subtypes on the treatment effect was assessed under unstratified exploratory subgroup analysis **Figure 5**.

The FDA's Assessment:
Although FDA agrees with the Applicant's PFS subgroup results shown in **Figure 3**, **Figure 4**, and **Figure 5**, there are important considerations based on descriptive subgroup analyses of outcomes in POLARIX, including the OS outcomes. In particular, the heterogeneity of lymphoma subtypes and the observed treatment effect has the potential to impact the interpretability and generalizability of the overall study findings.

Heterogeneity of the Study Population and Treatment Effect

In the ITT population, 84% of the study population had DLBCL NOS, 11% had either HGBL NOS (which itself is a heterogenous entity) or HGBL with *MYC* and *BCL2* and/or *BCL6* translocations, and 5% had other LGBLs based on local diagnosis. The treatment effect of pola+R-CHP appeared heterogeneous across lymphoma subgroups, as summarized in Table 20. The Appendix provides forest plots of PFS and OS by lymphoma subgroup (Figure 43 and Figure 44, respectively) and estimates at landmark timepoints (Table 55).

Table 20: Summary of Outcomes by NHL Subgroup

Outcome	Pola+R-CHP	R-CHOP
ITT Population	n=440	n=439
PFS HR (95% CI)	0.73 (0.57, 0.95)	
OS HR (95% CI)	0.94 (0.67, 1.33)	
CR rate (95% CI)[a]	78.0% (73.8%, 81.7%)	74.0% (69.7, 78.1)
Difference (95% CI)	3.9% (-1.9, 9.7)	
DLBCL NOS	n= 373	n= 367
PFS HR (95% CI)	0.75 (0.57, 0.99)	
OS HR (95% CI)	1.02 (0.70, 1.49)	
CR rate (95% CI)	76.7% (72.0, 80.9)	74.9% (70.2, 79.3)
Difference (95% CI)	1.7% (-4.7, 8.2)	
HGBL NOS, DH/TH	n= 43	n= 50
PFS HR (95% CI)	0.48 (0.21, 1.08)	
OS HR (95% CI)	0.42 (0.15, 1.19)	
CR rate (95% CI)	88.4% (74.9, 96.1)	64.0% (49.2,77.1)
Difference (95% CI)	24.4% (5.8, 42.9)	
Other LBCL [b]	n= 24	n= 22
PFS HR (95% CI)	1.93 (0.66, 5.64)	
OS HR (95% CI)	1.89 (0.35, 10.33)	
CR rate (95% CI)	79.2% (57.8, 92.9)	81.8% (59.7,94.8)
Difference (95% CI)	-2.7% (-28.2, 22.9)	

[a] CR rate per BICR at the end of therapy
[b] T-cell/histiocyte-rich LBCL (n=28) and EBV+ DLBCL (n=18)
Source: FDA analysis. OS based on CCOD of 6/15/2022.

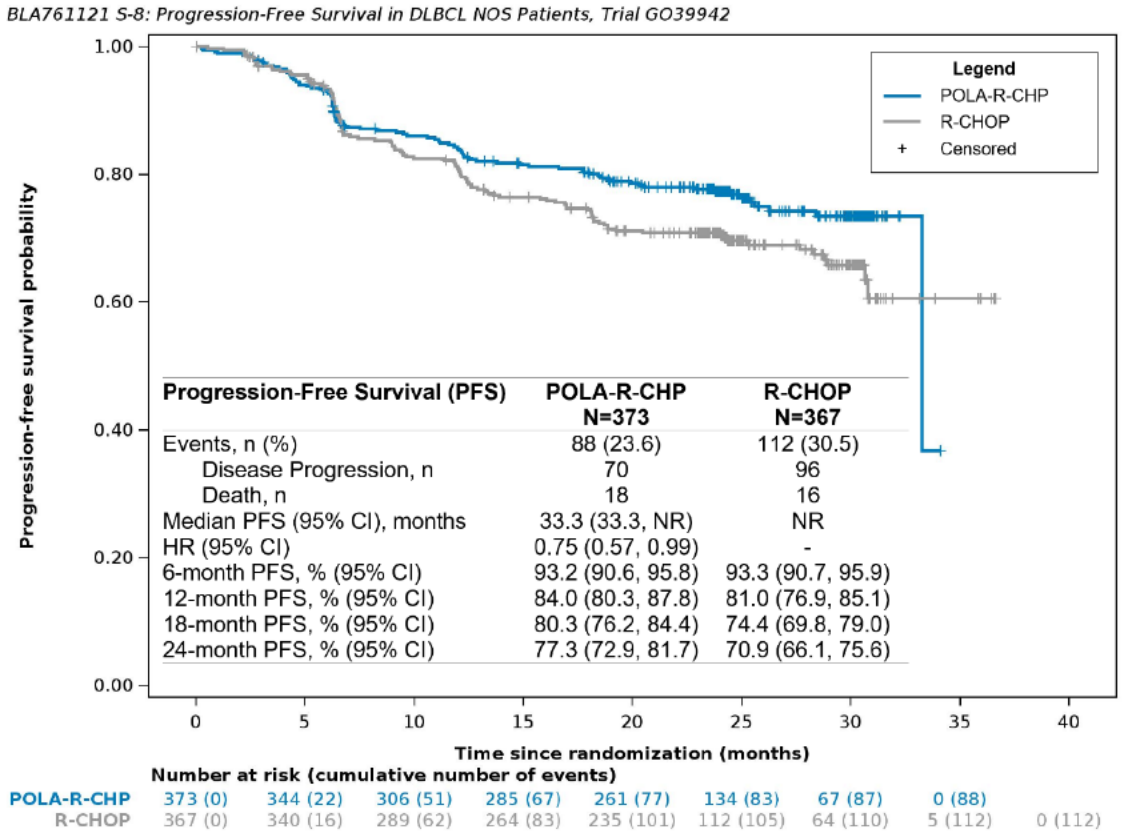
Acknowledging that this is an exploratory post hoc evaluation with sample size limitations, the results tended to favor pola+R-CHP for the HGBL subgroup, had variable results in DLBCL NOS, and favored the control arm for the minority of other LBCLs combined. When considering CR rates (Table 20), pola+R-CHP appeared to benefit the HGBL subgroup.

For DLBCL NOS, the largest subgroup (n=740), the results were either marginal or not indicative of a positive treatment effect. The Kaplan-Meier curves of PFS and OS in DLBCL NOS are shown in **Figure 10**

and **Figure 11**, respectively. Among those with DLBCL NOS, the OS HR was 1.02, with an estimated 1-year OS of 91.8% in the pola+R-CHP arm and 95.5% in the R-CHOP arm (**Figure 11**).

However, for the subgroup analyses, there is high uncertainty in the point estimates as evidenced by the wide confidence intervals, and the findings are hypothesis-generating.

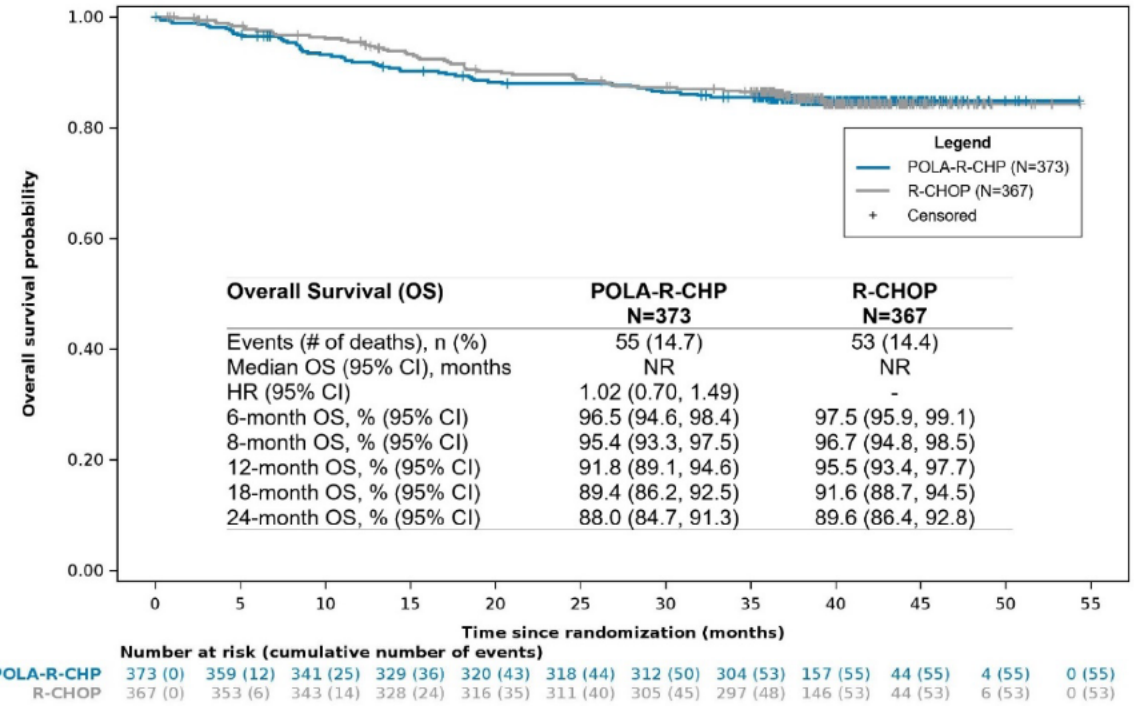
Figure 10: Kaplan-Meier Plot of PFS in Patients with DLBCL NOS



Progression-Free Survival (PFS)	POLA-R-CHP N=373	R-CHOP N=367
Events, n (%)	88 (23.6)	112 (30.5)
Disease Progression, n	70	96
Death, n	18	16
Median PFS (95% CI), months	33.3 (33.3, NR)	NR
HR (95% CI)	0.75 (0.57, 0.99)	-
6-month PFS, % (95% CI)	93.2 (90.6, 95.8)	93.3 (90.7, 95.9)
12-month PFS, % (95% CI)	84.0 (80.3, 87.8)	81.0 (76.9, 85.1)
18-month PFS, % (95% CI)	80.3 (76.2, 84.4)	74.4 (69.8, 79.0)
24-month PFS, % (95% CI)	77.3 (72.9, 81.7)	70.9 (66.1, 75.6)

Source: FDA analysis

Figure 11: Kaplan-Meier Plot of OS in Patients with DLBCL NOS



Overall Survival (OS)	POLA-R-CHP N=373	R-CHOP N=367
Events (# of deaths), n (%)	55 (14.7)	53 (14.4)
Median OS (95% CI), months	NR	NR
HR (95% CI)	1.02 (0.70, 1.49)	-
6-month OS, % (95% CI)	96.5 (94.6, 98.4)	97.5 (95.9, 99.1)
8-month OS, % (95% CI)	95.4 (93.3, 97.5)	96.7 (94.8, 98.5)
12-month OS, % (95% CI)	91.8 (89.1, 94.6)	95.5 (93.4, 97.7)
18-month OS, % (95% CI)	89.4 (86.2, 92.5)	91.6 (88.7, 94.5)
24-month OS, % (95% CI)	88.0 (84.7, 91.3)	89.6 (86.4, 92.8)

Source: FDA analysis. CCOD 6/15/2022.

IPI score

There also appeared to be a heterogenous effect across the strata of IPI scores. IPI score was a stratification factor for randomization (2 vs. 3-5). On FDA analysis, the PFS HRs were 0.99 (95% CI: 0.63, 1.56) and 0.67 (95% CI: 0.49, 0.91) for patients with IPI 2 vs. IPI 3-5, respectively. The OS HRs on final analysis were 1.08 (95% CI: 0.53, 2.18) and 0.90 (95% CI: 0.61, 1.33) for patients with IPI 2 vs. IPI 3-5, respectively. As evidenced by the point estimates and upper confidence limits, there is uncertainty regarding the evidence of efficacy in patients with an IPI score of 2. However, these results are also based on a post hoc exploratory evaluation with sample size limitations and are considered hypothesis-generating.

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:

The primary evaluation of efficacy is based on the single pivotal study POLARIX. Further discussion is provided in the Integrated Assessment of Effectiveness.

8.1.4. Assessment of Efficacy Across Trials

The Applicant's Position: This application is based primarily on efficacy data from the primary analysis of the pivotal Study POLARIX. Supportive efficacy data from patients with previously untreated DLBCL are provided from Phase Ib/II Study GO29044 and were consistent with the results from POLARIX (Module 2.7.3 SCE, Section 2).

The FDA's Assessment:
The basis of FDA's efficacy determination in the first-line setting is the POLARIX study.

8.1.5. Integrated Assessment of Effectiveness

The Applicant's Position:
POLARIX met its primary endpoint and demonstrated a statistically significant and clinically meaningful INV-PFS improvement with the combination of pola+R-CHP over R-CHOP in the ITT population, inclusive of high-risk subpopulations with poor prognostic factors. The observed HR of 0.73 represents a 27% decrease in relative risk of disease progression, relapse, or death; or, in other words, pola+R-CHP spares approximately 1 out of 4 patients who would otherwise have a PFS event with R-CHOP from having that event. The avoidance of PFS events represents curative outcomes for previously untreated patients with DLBCL.

The study design stipulated that all patients be followed for at least 24 months after treatment initiation, which covers the period when most of the disease relapses occur, thus ensuring that the observed treatment benefits of pola are reliable. At the 2-year mark, treatment with pola+R-CHP resulted in a higher proportion of patients alive and progression-free compared to R-CHOP (76.7% vs 70.2%, respectively). The PFS results from the POLARIX study are considered sufficiently mature and are not likely to change appreciably with longer follow-up based on the magnitude of treatment effect observed with pola+R-CHP over R-CHOP, and the stability of HR estimates. PFS results were considered robust due to a consistent treatment effect observed across a panel of pre-specified sensitivity analyses for PFS.

Results of the secondary endpoint EFS_{eff} were statistically significant, clinically meaningful and highly consistent with the primary endpoint of INV-PFS results and supportive of clinical benefit for pola + R-CHP compared with R-CHOP. Furthermore, fewer patients in the pola+R-CHP than in the R-CHOP arm received subsequent NALT. The total number of NALT and the intensity of these treatments (such as autologous transplantation and CAR-T) are associated with high treatment burden and additional health care utilization. Thus, the observed benefit for pola + R-CHP also suggest a curative effect in the 1L DLBCL patients. Although not statistically significant, BICR-Assessed CR rates by PET-CT at EOT were numerically higher in the pola+R-CHP arm compared with R-CHOP. While response rates were similar between arms, the significance of a response endpoint is measured by both its magnitude and duration. DOR and DFS analyses (HR 0.74 and 0.70, respectively) show that there are quantitative differences in durability, with more durable responses in patients in the pola+R-CHP arm compared to the R-CHOP arm. These observations are of particular importance because the lack of durability translates to death or relapse, which more patients can avoid with pola+R-CHP treatment, and correlates the DOR and DFS findings with the PFS results.

Interim OS data were still immature beyond 24 months, and the event patient ratio was low at the time of the CCOD (28 June 2021). Nevertheless, there is no evidence of detriment with stratified HR 0.94 [95% CI: 0.65, 1.37]. Moreover, the distribution of subsequent therapies in the study is not controlled and may confound OS analysis, as there have been some patients in the R-CHOP arm who have received pola as NALT, and there are more patients in the R-CHOP arm who have received more intensive therapies such as stem cell transplantation and CAR-T therapy. Overall, results of a second interim OS analysis based on the CCOD 25 February 2022 were consistent with the results of the first interim OS analysis and continue to show no evidence of detriment with longer follow up. Furthermore, evolving

trend of benefit is observed at a later part of the curve with longer follow up favoring pola-R-CHP (Module 5.3.5.1 Supplemental OS Update Report).

Treatment with pola+R-CHP resulted in a clinically meaningful delay in deterioration of patient-reported physical functioning and fatigue compared with R-CHOP. Overall, patients on pola+R-CHP were able to maintain aspects of their baseline HRQoL and experienced an improvement in disease-related symptoms after starting treatment.

The totality of efficacy data from POLARIX show that pola+R-CHP represents a significant advancement for the treatment of patients with previously untreated DLBCL. Additionally, the efficacy results from the supportive Study GO29044 are consistent with the results from POLARIX in a similar population. Overall, the Applicant concludes that clinical benefit was observed with pola in combination with R-CHP in patients with previously untreated DLBCL, inclusive of higher risk subgroups.

The FDA's Assessment:

FDA deemed that there were residual uncertainties based on the results of POLARIX. For this reason, the FDA took this application to an ODAC meeting, as summarized in Section 9.1. FDA does not agree with the Applicant's claims related to health-related QoL (refer to Sections 8.1.2 and 8.2.6).

FDA's overall assessment of efficacy is that the primary PFS analysis and various sensitivity analyses demonstrated a modest benefit for pola+R-CHP. The largest difference in the 2-year PFS rate was 6.5%. Additionally, the PFS benefit was not explained by a benefit in CR rate, and there was lack of an OS benefit and substantial uncertainty in the estimated OS. The utility of other secondary efficacy endpoints such as modified EFS, DFS, and DOR is limited and the results were modest. The latter two endpoints are not ITT-based analyses, and these endpoints can only serve as supportive evidence. The finding of less NALT in the pola+R-CHP arm, should not be used as evidence of superiority compared to R-CHOP, since NALT can be given for various reasons and has a component of subjectivity. The number of patients receiving NALT was not a prespecified endpoint due to these reasons.

Additionally, the heterogeneity of the POLARIX study population and outcomes with respect to histologic subgroups impacts the interpretability and generalizability of the study findings. Outcomes consistently favored pola+R-CHP in the minority of patients with HGBL, where the adequacy of R-CHOP is questionable and more intensive regimens are generally preferred. In the largest subgroup (DLBCL NOS, comprising 84% of the study population), the PFS effect was modest, there were similar CR rates and notably, the OS HR was 1.02 (95% CI: 0.70, 1.49) on the final prespecified analysis. At some landmark timepoints, the OS rates were either similar or numerically lower in the pola+R-CHP arm. Longer follow-up may be needed to inform the impact of pola+R-CHP on OS, and this is the basis of the recommended PMR described in Section 13.

Of note, in the CHOP regimen, the specific contribution of vincristine is unknown, as the efficacy of CHOP vs. CHP has not been directly compared. Because POLARIX was a substitution trial, substituting polatuzumab vedotin for vincristine, there are challenges in understanding the contribution of polatuzumab vedotin to the overall regimen. However, based on the ODAC meeting and other discussions, the review team determined that the treatment effect on PFS observed with pola+R-CHP, compared to R-CHOP in the ITT population, while modest, is clinically meaningful and indicative of clinical benefit.

8.2. Review of Safety

The Applicant's Position: The safety assessment of the pola 1.8 mg/kg in combination with R-CHP in patients with previously untreated DLBCL is based primarily on data (CCOD: 28 June 2021) from 435 patients in the pola+R-CHP arm of the POLARIX study in comparison with 438 patients from the R-CHOP control arm (Section 7).

Additional supportive data from a cohort of patients with previously untreated DLBCL (n=66) who received pola 1.8 mg/kg in combination with R-CHP (n=45) or obinutuzumab (G)-CHP (n=21) in the GO29044 study was assessed. As requested by the Agency (Reference ID: 4679238), safety analysis in the pooled population from POLARIX and Study GO29044, in addition to the side-by-side comparison, is discussed in the Summary of Clinical Safety (SCS). A comparison of the safety profile of pola+R-CHP/G-CHP in 1L DLBCL (506 patients pool [POLARIX +GO29044]) against the safety profile of pola+BR/BG in R/R DLBCL and R/R FL (247 patients) is also discussed in the SCS as requested by the FDA.

The safety profile of pola+R-CHP regimen was comparable to R-CHOP and in line with the known safety profiles of each individual component and the underlying disease.

The FDA's Assessment:
FDA agrees that the overall safety profile of pola+R-CHP was comparable to R-CHOP; however, the incidences of infection, febrile neutropenia, nausea, and diarrhea were at least 5% higher in recipients of pola+R-CHP. Refer to Sections 8.2.4 and 8.2.5 for FDA's analysis of safety.

8.2.1. Safety Review Approach

The Applicant's Position: The safety and tolerability assessment was based on the frequency of AEs, serious adverse events (SAEs), fatal AEs, AEs leading to discontinuation, AEs leading to dose reduction or interruption, AESIs/Selected AEs, clinical laboratory assessments and vital sign measurements.

The FDA's Assessment:
FDA agrees with the Applicant's position. The FDA reviewed data from POLARIX in addition to the final OS analysis report. The safety population consists of patients who received pola+R-CHP (n=435) and R-CHOP (n=438). AE reporting period was defined as new or worsening AE from the first dose of any study drug through 90 days after the last dose of any study drug or prior to NALT, whichever is earlier. Toxicity was graded using NCI CTCAE version 4.0.

The safety and tolerability evaluation included an assessment of:

- Incidence and severity of all-cause treatment-emergent adverse events (TEAEs)
- Grade 3-5 TEAEs
- Serious adverse events
- TEAEs leading to treatment modification or discontinuation
- Adverse events of special Interest

AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.0. To inform the safety review, FDA used grouped preferred terms for more sensitive and informative safety analyses. The FDA preferred terms are listed in the Appendix, Table 54.

8.2.2. Review of the Safety Database

Overall Exposure

Data:

Table 21 Applicant: Safety Population, Size, and Denominators

Safety Database* for the Study Drug[1] Individuals exposed to the study drug in this development program for the indication under review N=435		
	POLARIX	
Clinical Trial Groups	Pola+R-CHP (n=435)	R-CHOP (n=438)
Controlled trials conducted for this indication[2]	1 study (n=435)	1 study (n=438)

[1] *study drug* means the drug being considered for approval.

[2] to be used in product's labeling

* Safety data was evaluated from the 66 patients with 1L DLBCL treated with pola 1.8 mg/kg with R-CHP or G-CHP in the supportive Study GO29044 as a part of the dossier.

Table 22 Applicant: Summary of Extent of Exposure to Pola, Vincristine, Rituximab, Cyclophosphamide, Doxorubicin and Prednisone

POLARIX				
	Pola+R-CHP (N=435)		R-CHOP (N=438)	
Treatment	Median treatment duration, months (range)	Median number of cycles (range)	Median treatment duration, months (range)	Median number of cycles (range)
Pola / Vincristine	3.5 (0-5)/ NA	6 (1-6)/ NA	NA/3.5 (0-8)	NA/6 (1-6)
Rituximab	4.9 (0-8)	8 (1-8)	4.9 (0-11)	8 (1-8)
Cyclophosphamide	3.5 (0-5)	6 (1-6)	3.5 (0-8)	6 (1-6)
Doxorubicin	3.5 (0-5)	6 (1-6)	3.5 (0-8)	6(1-6)
Prednisone	3.6 (0-5)	6 (1-6)	3.6 (0-6)	6 (1-6)

Source: t_ex_SE_28JUN2021.

The Applicant's Position: Most of the patients completed the planned study treatment. The median duration of treatment in the pola+R-CHP arm (3.5 months) was comparable with the R-CHOP arm (3.5 months). For the investigational agents that were administered in a blinded fashion, a higher number of patients (91.7%) received all six planned doses of pola in the pola+R-CHP arm compared to the number of patients who received all six planned doses of vincristine in the R-CHOP arm (88.5%).

The FDA's Assessment:
FDA agrees with the Applicant's position. Most patients in both arms received the planned doses of polatuzumab vedotin and vincristine.

Relevant Characteristics of the Safety Population

The Applicant's Position: The characteristics of the SE population were generally balanced between treatment arms, and are described in Section 8.1.2.

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

Adequacy of the Safety Database

The Applicant's Position: The POLARIX study safety database (sufficiently large, includes the most common subgroups of DLBCL and enrolled patients from 22 countries spanning 3 geographic regions) is considered adequate to support the benefit-risk assessment for the proposed indication in 1L DLBCL. Based on the design of POLARIX, the 435 previously untreated DLBCL patients from the pola+R-CHP arm adequately characterize the safety profile in the intended indication (DLBCL) and the combination treatment regimen (pola+R-CHP). Safety analysis from the previously untreated patients with DLBCL who received pola 1.8 mg/kg from the supportive Study GO29044 further demonstrates the consistency of the safety profile of pola+R-CHP.

The FDA's Assessment:
FDA agrees that the POLARIX safety database is adequate to support the benefit-risk assessment for the proposed indication. FDA did not verify the safety analysis from Study GO29044.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position: No issues relating to data integrity or quality were identified for the studies included in this submission.

The FDA's Assessment:
No issues were identified regarding data integrity or submission quality that had an effect on the clinical safety review. Revised datasets were submitted upon request.

Categorization of Adverse Event

The Applicant's Position: Verbatim description of AEs were mapped to MedDRA thesaurus. All AEs were coded using MedDRA v24.0. AEs were graded by the investigator in accordance with the National Cancer Institute-Common Terminology Criteria for Adverse Event (NCI CTCAE version 4.0), and laboratory values were graded according to these criteria by the Applicant based on the reported results. Summaries of treatment-emergent AEs that occurred from the first dose of any study drug through 90 days after the last dose of any study drug or prior to NALT, whichever is earlier, were included in the safety analysis. Serious AEs, Grade 3–4 AEs, fatal AEs, AEs leading to study drug discontinuation, interruption, or dose reduction were summarized accordingly.

Adverse Events of Particular Interest (AEPIs) including PN, neutropenia (including febrile neutropenia), anemia, thrombocytopenia, infections, hepatic toxicity, tumor lysis syndrome (TLS), pulmonary toxicity, secondary malignancy/carcinogenicity, hyperglycemia, cardiac arrhythmias and infusion-related reactions (IRR) were also summarized. A set of comprehensive definitions using Standardized MedDRA Queries was used for the purpose of AEPIs identification and analysis from the AE clinical database by medical concept. The medical concepts correspond to the identified risks and potential risks for pola.

The FDA's Assessment:
FDA agrees with the Applicant's position. FDA used a combination of individual MedDRA PTs and custom groupings of PTs as defined in Table 54.

Routine Clinical Tests

The Applicant's Position: The safety assessment methods and time points that were described in the POLARIX protocol were adequate for the previously untreated DLBCL patients. In the POLARIX study, safety was evaluated through the monitoring of the following:

- SAEs that were attributed to protocol-mandated interventions from the time of signing informed consent until the first dose of study treatment on Cycle 1, Day 1.
- All AEs, including SAEs, from Cycle 1, Day 1 regardless of the relationship to the study drug, were reported until 90 days after the last dose of study drug. After this period, the Sponsor was notified of only SAEs believed to be related to prior study drug treatment, for an indefinite period of time, or adverse events of special interest considered to be related to study drug until 12 months after the last dose of study drug.
- Measurements of protocol-specified hematology and clinical chemistry laboratory values.
- Measurements of protocol-specified vital signs.
- Assessment of ECGs and physical findings on clinical physical examinations.

The detailed schedule of assessments (activities) is provided in Appendix 1 of the POLARIX Protocol (v7); the summary is presented in Table 10.

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

8.2.4. Safety Results

Deaths

Data: At the time of CCOD, a total of 111 patients (12.7%) had died due to any cause. The proportion of patients who died was 12.0% [52 patients] in the pola+R-CHP arm and 13.5% [59 patients] the R-CHOP arm; see Table 23.

The most common cause of death during the entire study period in both treatment arms was disease progression (6.4% [28 patients] in the pola+R-CHP arm and 7.1% [31 patients] in the R-CHOP arm). Almost all deaths due to disease progression occurred during the follow-up period.

Table 23 Applicant: Summary of Deaths

	Pola+R-CHP (n=435)	R-CHOP (n=438)	Total (n=873)
Total number of deaths	52 (12.0%)	59 (13.5%)	111 (12.7%)
Primary Cause of Death			
Disease progression	28 (6.4%)	31 (7.1%)	59 (6.8%)
Adverse event	13 (3.0%)	11 (2.5%)	24 (2.7%)
Other	11 (2.5%)	17 (3.9%)	28 (3.2%)
DLBCL was a contributing factor	3 (0.7%)	2 (0.5%)	5 (0.6%)
DLBCL not known to be a contributing factor	8 (1.8%)	15 (3.4%)	23 (2.6%)
Deaths during AE reporting period	13 (3.0%)	12 (2.7%)	25 (2.9%)
Primary Cause of Death			
Disease progression	0	2 (0.5%)	2 (0.2%)
Adverse event	13 (3.0%)	10 (2.3%)	23 (2.6%)
Deaths during follow-up	39 (9.0%)	46 (10.5%)	85 (9.7%)
Primary Cause of Death			
Disease progression	28 (6.4%)	29 (6.6%)	57 (6.5%)
Adverse event	0	1 (0.2%)	1 (0.1%)
Other	11 (2.5%)	16 (3.7%)	27 (3.1%)
DLBCL was a contributing factor	3 (0.7%)	2 (0.5%)	5 (0.6%)
DLBCL not known to be a contributing factor	8 (1.8%)	14 (3.2%)	22 (2.5%)

Source: t_dd_SE.
Note: One patient in the R-CHOP arm with a partially missing death date (unknown month, day) obtained from the public record was included in the 'Total number of deaths' row but excluded from the subtotal row of 'Deaths during AE reporting period' or 'Deaths during follow-up' as the reporting period during which the death occurred could not be determined.

The proportion of patients with Grade 5 AEs during the AE reporting period was 3.0% [13 patients] in the pola+R-CHP arm and 2.3% [10 patients] in the R-CHOP arm, see Table 24. One additional patient in the R-CHOP arm experienced a Grade 5 AE (acute myeloid leukemia) during the follow up period.

See Table 24 for the most frequent Grade 5 AEs (by preferred term [PT]). Details of all Grade 5 AEs reported in the SE population are provided in the patient narratives within the POLARIX CSR.

Table 24 Applicant: Grade 5 Adverse Events

Adverse Event	Pola+R-CHP (n=435)	R-CHOP (n=438)
Total number of patients with at least one AE	13 (3.0%)	10 (2.3%)
Pneumonia	4 (0.9%)	3 (0.7%)
Sepsis	1 (0.2%)	1 (0.2%)
Septic shock	0	2 (0.5%)
Death	4 (0.9%)	1 (0.2%)
Cardiac death	1 (0.2%)	0
Multiple organ dysfunction syndrome	0	1 (0.2%)
Atrioventricular block complete	0	1 (0.2%)
Intestinal perforation	1 (0.2%)	0
Injury	0	1 (0.2%)
Acute kidney injury	1 (0.2%)	0
Respiratory failure	1 (0.2%)	0

Source: t_ae_SOC_pt_G5 SE.

The Applicant's Position: The incidence of Grade 5 AEs was comparable between patients treated with pola+R-CHP and R-CHOP. Most of the fatal AEs in both the treatment arms were due to infections or complications of infection. The Grade 5 AE in the R-CHOP arm due to multiple organ dysfunction and the Grade 5 AEs in the pola+R-CHP arm due to acute kidney failure and respiratory failure occurred in the setting of infections. Grade 5 AEs reported as Death were unexplained death and limited details were available regarding the cause of death.

The FDA's Assessment:
FDA agrees with the Applicant on the rate of fatal AEs in the safety reporting period (within 90 days of the last dose).

Given that the pola+R-CHP OS curve lies below that of the R-CHOP curve at some early time points (Figure 9), FDA conducted additional interrogation of deaths within and beyond the safety reporting period. Limited information was available for some deaths occurring beyond 90 days, precluding confirmation of the cause of death (i.e., adverse event versus progression) in those cases. In summary, the number and patterns of deaths in the safety reporting period were similar between both arms with AEs, mostly infection, being the leading cause of death, followed by progressive disease. The FDA also interrogated deaths in the first 18 months from randomization in 6-month time periods but did not identify a safety signal (Table 25).

Table 25: Deaths Within and Beyond the Safety Reporting Period

Deaths by Time Period	Pola+R-CHP (N=435)	R-CHOP (N=438)
Death ≤ 90 days after last dose , n	13 (3.0%)	12 (2.7%)
Progressive disease	0	2 (0.5%)
Adverse event	13 (3.0%*) • infection (6) • kidney injury (1) • intestinal perforation (1) • sudden death (1) • unknown (4)	10 (2.3%) • infection 7) • cardiac (1) • unknown (1) • other (1)
Deaths 8 to 18 months from randomization, n	25 (6%)	22 (5%)
Progressive disease	16 (64%)	14 (64%)
Infections	5	3
Unknown	4	2
Cardiac arrest	0	1
Stroke	0	1
Second primary malignancy	0	1

*2.8% if a case of fatal infection after PD is excluded
Source: FDA analysis. CCOD 6/15/2022.

Serious Adverse Events

Data: The proportion of patients with at least one SAE was 34.0% [148 patients] in the pola+R-CHP arm and 30.6% [134 patients] in the R-CHOP arm. SAEs were most commonly reported (≥ 5% of patients in either arm) in the following SOCs (pola+R-CHP arm and R-CHOP arm, respectively): Infections and infestations (14.0% [61 patients] and 10.3% [45 patients]), Blood and lymphatic system disorders (11.5% [50 patients] and 9.1% [40 patients]), Gastrointestinal disorders (7.1% [31 patients] and 5.9% [26 patients]) and General disorders and administration site conditions (6.0% [26 patients] and 4.6% [20 patients]). A summary of the most common SAEs (≥ 1% of patients in either arm) by PT is shown in Table 26.

Table 26 Applicant: Serious Adverse Events (incidence ≥ 1%), Safety-Evaluable Population

System Organ Class (SOC) Grouped Preferred Terms / Medical Concept	Pola+R-CHP (435)	R-CHOP (n=438)
	Patients with SAEs	
Infections and infestations		
Pneumonia	23 (5.3%)	20 (4.6%)
Sepsis	9 (2.1%)	13 (3%)
Urinary tract infection	9 (2.1%)	3 (0.7%)
Skin infection	5 (1.1%)	2 (0.5%)
Blood and lymphatic system disorders		
Febrile neutropenia	46 (10.6%)	30 (6.8%)
Neutropenia	7 (1.6%)	9 (2.1%)
Anemia	4 (0.9%)	6 (1.4%)
Gastrointestinal disorders		
Diarrhea*	11 (2.5%)	2 (0.5%)
Vomiting	5 (1.1%)	2 (0.5%)
Small intestinal obstruction*[a]	0	5 (1.1%)
General disorders and administration site conditions		
Pyrexia*	8 (1.8%)	8 (1.8%)
Mucositis	5 (1.1%)	1 (0.2%)

Source: t_ae_adr_SER_SE_28JUN2021_39942; t_ae_soc_pt_p1_SER_SE_28JUN2021_39942.
Incidence (%) is presented for the grouped preferred term/medical concept which includes one or more clinically similar MedDRA PTs.
*Medical Concept represented by single reported MedDRA PT.
[a] Serious AE identified from t_ae_soc_pt_p1_SER_SE_28JUN2021_39942.

The Applicant's Position: The incidence of SAEs was comparable between patients treated with pola+R-CHP and R-CHOP. The frequency and nature of SAEs observed in the pola+R-CHP arm was generally consistent with the known safety profile of the individual treatment components and the underlying disease.

The FDA's Assessment:
In general, FDA agrees with the overall incidence of SAEs and Applicant's overall description of SAEs. However, the incidence of sepsis is higher in the FDA analysis, because of FDA's expanded grouping of preferred terms (PTs) to include cases of neutropenic sepsis and bacteremia. All FDA safety analyses presented in this review use a custom grouping of PTs, as defined in Table 54 and consider all-cause treatment-emergent events. Table 27 summarizes SAEs by category and by specific cause and by age group. In both arms, by system organ class, infection was the leading cause of SAEs. SAEs in ≥ 2 % of the pola+R-CHP group included febrile neutropenia, pneumonia, sepsis and diarrhea. SAEs in ≥ 2 % of R-CHOP group were febrile neutropenia, pneumonia and sepsis.

Table 27: Serious Adverse Events in POLARIX

Event	Pola+R-CHP (N=435) n (%)	R-CHOP (N=438) n (%)
Any SAE	148 (34)	134 (31)
SAEs in ≥ 5% by System Organ Class		
Infections and infestations	62 (14)	45 (10)
Blood and lymphatic system disorders	50 (11.5)	40 (9)
Gastrointestinal disorders	30 (7)	26 (6)
General disorders, admin. site conditions	25 (6)	
SAEs in > 2% by Preferred Term or Grouped Preferred Term		
Febrile neutropenia	46 (11)	30 (7)
Pneumonia	23 (5)	19 (4.3)
Sepsis*	12 (2.8)	13 (3)
Diarrhea	10 (2.3)	
*Include cases of neutropenic sepsis Source: FDA analysis SOC: system organ class		

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

Table 28 Applicant: Incidence of Adverse Events Leading to Discontinuation, Drug Interruption or Dose Modification of Study Drugs

	Pola+R-CHP (n=435)	R-CHOP (n=438)
Patients with AEs leading to any study drug		
Discontinuation	27 (6.2%)	29 (6.6%)
Dose reduction	40 (9.2%)	57 (13.0%)
Drug interruption (delay/withholding dose)	103 (23.7%)	111 (25.3%)
Patients with AEs leading to Pola/Vincristine		
Discontinuation	19 (4.4%)	22 (5.0%)
Dose reduction	24 (5.5%)	45 (10.3%)
Drug interruption (delay/withholding dose)	61 (14.0%)	60 (13.7%)

Source: t_ae_soc_pt_DSCANY_SE, t_ae_soc_pt_DSCPL_SE, t_ae_soc_pt_REDANY_SE, t_ae_soc_pt_REDPL_SE, t_ae_soc_pt_INRANY_SE, t_ae_soc_pt_INRPL_SE, t_ae_soc_pt_INRVC_SE, t_ae_soc_pt_REDVC.

The FDA's Assessment:

FDA agrees with the Applicant's overall assessment and incidence of AEs leading to polatuzumab vedotin/vincristine dose discontinuation and reduction in both arms. On FDA analysis, the incidence of AEs leading to dose interruption of polatuzumab vedotin and vincristine were 17 (18%) and 68 (16%), respectively.

Dose Interruption/Reduction Due to Adverse Effects

Data: The most common AEs by PT (≥ 1% of patients in either arm) that led to any study treatment dose reduction were (pola+R-CHP arm and R-CHOP arm, respectively): PN (2.1% [9 patients] and 5.0% [22 patients]); peripheral sensory neuropathy (1.8% [8 patients and 2.3% [10 patients]) and febrile neutropenia (1.1% [5 patients] and 0.5% [2 patients]). The most common AEs by PT (≥ 1% of patients in either arm) that led to any study treatment dose interruption were (pola+R-CHP arm and R-CHOP arm, respectively): pneumonia (2.1% [9 patients]) and 1.6% [7 patients]); neutropenia (3.7% [16 patients] and 5.3% [23 patients]); dyspnea (1.8% [8 patients] and 1.8% [8 patients]); chills (1.1% [5 patients] and 2.3% [10 patients]); pyrexia (0.9% [4 patients] and 1.4% [6 patients]); throat irritation (0.5% [2 patients] and 1.1% [5 patients]) and urticaria (0.2% [1 patients] and 1.1% [5 patients]).

The Applicant's Position: The proportion of patients who experienced AEs leading to any study treatment dose reduction was lower in the pola+R-CHP arm (9.2% [40 patients]) compared to the R-CHOP arm (13.0% [57 patients]). In particular, the proportion of patients who experienced AEs leading to pola dose reduction in the pola+R-CHP arm (5.5% [24 patients]) was lower than the proportion of patients who experienced AEs leading to vincristine dose reduction in the R-CHOP arm (10.3% [45 patients]). This difference was primarily driven by the higher incidence of AEs related to PN resulting in dose reduction in the R-CHOP arm.

The FDA's Assessment:
In the pola+R-CHP arm, AEs led to dose reduction of polatuzumab vedotin in 6% of patients, mainly from peripheral neuropathy. AEs led to dose interruption of polatuzumab vedotin in 18% of patients, most commonly from pneumonia and neutropenia, and permanent discontinuation of polatuzumab vedotin in 4.4% of patients, mostly due to pneumonia and PN.

In the R-CHOP arm, adverse events led to dose reduction of vincristine in 10% of patients, mainly from peripheral neuropathy (8%). AEs led to dose interruption of vincristine in 16% of patients, most commonly from neutropenia and pneumonia, and permanent discontinuation of vincristine in 5% of patients, mostly from PN and pneumonia.

The FDA agrees with the Applicant's statement that the incidence of AE-driven dose reduction of polatuzumab vedotin/vincristine was lower in the R-CHOP arm, primarily driven by actions due to PN.

Significant Adverse Events

Data: The incidence of Grade 3–4 AEs was 57.7% [251 patients] in the pola+R-CHP arm and 57.5% [252 patients] in the R-CHOP arm, and the majority were associated with myelosuppression. The summary of the most common Grade 3-4 AEs by highest grade is presented in Table 29.

Table 29 Applicant: Most Common Grade 3-4 AEs (≥2% incidence), SE population

Grouped Preferred Terms / Medical Concepts	Pola+R-CHP (n=435)	R-CHOP (n=438)
Neutropenia	150 (34.5%)	160 (36.5%)
Febrile Neutropenia	63 (14.5%)	38 (8.7%)
Anaemia	52 (12.0%)	38 (8.7%)
Leukopenia	42 (9.7%)	43 (9.8%)
Lymphopenia	20 (4.6%)	25 (5.7%)
Thrombocytopenia	23 (5.3%)	22 (5.0%)
Pneumonia	18 (4.1%)	21 (4.8%)
Diarrhoea*	17 (3.9%)	8 (1.8%)
Fatigue*	4 (0.9%)	11 (2.5%)
Syncope	9 (2.1.%)	10 (2.3%)
Hypertension	7 (1.6%)	10 (2.3%)
Hyponatraemia*	6 (1.4%)	9 (2.1%)

Source: t_ae_pt_ctc34_pi2_SE_28JUN2021_39942; t_ae_soc_pt_grd_SE_28JUN2021_39942; t_ae_adr_grd_v2_SE_28JUN2021_39942.
Incidence (%) is presented for the grouped preferred term/medical concept which includes one or more clinically similar MedDRA PTs.
*Medical Concept represented by single reported MedDRA PT

The Applicant's Position: The incidence of Grade 3-4 AEs was comparable between patients treated with pola+R-CHP and R-CHOP. The Grade 3-4 AEs observed with pola+R-CHP are consistent with the known safety profile and/or underlying disease.

The FDA's Assessment:
Refer to the section below for the incidence of AEs including G3-4 AEs.

Adverse Reactions

Data: In the current application, the proposed US prescribing information (USPI) was updated to include clinically significant ADRs of pola+R-CHP in comparison to the R-CHOP control in the previously untreated DLBCL patients from the POLARIX study (CCOD: 28 June 2021) (Section 6.1 of the USPI). The ADR identification methodology in the front-line setting is described in the ADR rationale document (Module 2.7.4 SCS Appendix) and includes the following 3 qualifying categories: **(1)** Known ADRs identified from the R/R DLBCL safety population; **(2)** AEs with an incidence difference of ≥2% between pola+R-CHP (N=435) and the control arm R-CHOP (N=438) in POLARIX and medically relevant. **(3)** Medically relevant AEs with an incidence difference of <2% between pola+R-CHP (N=435) and the control arm R-CHOP (N=438) in POLARIX.

In recipients of pola+R-CHP, ADRs in ≥20% of patients included PN, nausea, diarrhea, constipation, neutropenia, anemia, fatigue, mucositis and alopecia.

A summary of the comprehensive safety analysis of ADRs based on the 435 1L DLBCL patients treated with pola, [redacted] (b) (4) is presented in Table **30**.

Table 30 Applicant: Summary of Adverse Drug Reactions in >5% of Patients with Previously Untreated DLBCL in the POLIVY Plus R-CHP Group in POLARIX

Adverse Reactions by Body System	POLIVY + R-CHP n = 435		R-CHOP n = 438	
	All Grades, %	Grade 3 or Higher, %	All Grades, %	Grade 3 or Higher, %
Nervous System Disorders				
Peripheral Neuropathy	53	1.6	54	1.1
Dizziness	9	0.2	8	0.2
Gastrointestinal Disorders				
Nausea	42	1.1	37	0.5
Diarrhea	31	3.9	20	1.8
Constipation	29	1.1	29	0.2
Abdominal Pain	16	1.1	14	1.6
Vomiting	15	1.1	14	0.7
Blood and Lymphatic System Disorders				
Neutropenia	38	35	39	37
Anemia	29	12	27	9
Febrile Neutropenia	15	15	9	9
Leukopenia	14	10	13	10
Thrombocytopenia	13	5	13	5
Lymphopenia	7	4.6	9	6
General Disorders and Administration Site Conditions				
Fatigue	26	0.9	27	2.5
Mucositis	22	1.4	19	0.5
Pyrexia	16	1.4	13	0
Asthenia	12	1.6	12	0.5
Peripheral Edema	11	0.2	9	0.2
Skin and Subcutaneous Tissue Disorders				
Alopecia	24	0	24	0.2
Rash	13	0.9	11	0
Pruritus	8	0	6	0.2
Skin infections	7	1.1	3.0	0.7
Dry skin	6	0	2.7	0
Musculoskeletal Disorders				
Myalgia	9	0.2	7	0.2
Arthralgia	6	0	8	0

Adverse Reactions by Body System	POLIVY + R-CHP n = 435		R-CHOP n = 438	
	All Grades, %	Grade 3 or Higher, %	All Grades, %	Grade 3 or Higher, %
Infections and Infestations				
Upper respiratory tract infection	17	0.5	16	0.5
Pneumonia	9	5[a]	7	6
Urinary tract infection	8	1.8	7	1.1
Metabolism and Nutrition Disorders				
Decreased appetite	17	1.1	14	0.7
Hypokalaemia	8	1.8	9	1.8
Respiratory, Thoracic and Mediastinal Disorders				
Cough	15	0	14	0
Dyspnoea	13	0.9	10	0.9
Injury, Poisoning, and Procedural				
Infusion related reaction[b]	13	1.1	16	1.6
Investigations				
Weight decreased	13	0.9	12	0.2
Transaminases increased	7	0.7	6	0.2

MedDRA version 24.0.

Clinical safety data from study GO39942; CCOD: 28JUN2021.

The table includes a combination of grouped and ungrouped terms. ADR grouped terms are listed in the SCS Appendix, Table 2. Events were graded using NCI CTCAE version 4.

[a] Includes 4 events with fatal outcome

[b] Infusion related reaction ADR is reflective of the combination regimen POLIVY + R-CHP due to same day administration.

Source: t_ae_adr_grd_SE; t_ae_adr_G35_SE.

The Applicant's Position: Overall, pola+R-CHP was well tolerated when compared to R-CHOP and the toxicities were manageable. No new safety signals were identified.

The FDA's Assessment:

Because of differences in grouping of PTs, FDA's characterization of common TEAEs differs slightly from the Applicant's. Table 31 presents select TEAEs by SOC and PT. The overall incidence of TEAEs was comparable between the two arms. In the pola+R-CHP arm, the most common TEAEs (incidence ≥ 20%), excluding laboratory abnormalities were peripheral neuropathy, nausea, fatigue, diarrhea, constipation, alopecia, and mucositis. New or worsening Grade 3 to 4 laboratory abnormalities in ≥10% of patients were lymphopenia, neutropenia, hyperuricemia, and anemia. Alignment on grouping of PTs was reached during labeling negotiations.

Table 31: Select Adverse Reactions Occurring in ≥10% of Patients Treated with Pola+R-CHP in POLARIX

Adverse Reactions by Body System	Pola+R-CHP n = 435		R-CHOP n = 438	
	All Grades, %	Grade 3 or 4, %	All Grades, %	Grade 3 or 4, %
Blood and Lymphatic System Disorders*				
Lymphopenia	80	44	77	44
Anemia	68	14	67	11
Neutropenia	60	39	60	42
Thrombocytopenia	32	8	33	6
Febrile neutropenia[a]	15	15	9	9
Nervous System Disorders				
Peripheral neuropathy[b]	53	1.6	54	1.1
Altered taste	14	0	16	0
Headache	13	0.2	14	0.9
Gastrointestinal Disorders				
Nausea	42	1.1	37	0.5
Diarrhea	31	3.7	20	1.8
Constipation	29	1.1	29	0.2
Abdominal pain	15	1.1	14	1.6
Vomiting	15	1.1	14	0.7
Mucositis	22	1.4	19	0.5
General Disorders				
Fatigue[c]	37	2.5	38	3
Pyrexia	15	1.1	13	0
Edema[d]	14	0.5	11	0.2
Infusion-related reaction[h]	13	1.1	16	1.6
Investigations, excluding electrolytes				
Creatinine increased	66	0.7	64	0.9
ALT increased*	25	1.4	27	0.5
AST increased*	26	0.7	23	1.1
Alkaline phosphatase increased*	23	0	22	0.5
Uric acid increased*	19	18	17	16
Weight decreased	13	0.9	12	0.2
Skin and Subcutaneous Tissue Disorders				
Alopecia	24	0	24	0.2
Rash[e]	12	0.7	11	0

Adverse Reactions by Body System	Pola+R-CHP n = 435		R-CHOP n = 438	
	All Grades, %	Grade 3 or 4, %	All Grades, %	Grade 3 or 4, %
Musculoskeletal Disorders				
Musculoskeletal pain[f]	19	0.5	21	1.8
Infections				
Upper respiratory tract infection[g]	17	0.5	16	0.5
Metabolism and Nutrition Disorders				
Decreased appetite	17	1.1	14	0.7
Respiratory Disorders				
Cough	15	0	14	0
Dyspnea	13	0.9	10	0.9

The table includes a combination of grouped and ungrouped terms.
* Values are based on integrated analysis of laboratory and adverse reaction data.
[a] Febrile neutropenia includes febrile neutropenia, febrile bone marrow aplasia and neutropenic sepsis
[b] Peripheral neuropathy includes all terms containing "neuropathy", neuralgia, dysesthesia, paresthesia, hypoesthesia, peroneal nerve palsy, hypotonia, hyporeflexia, neuromyopathy and hyperesthesia
[c] Fatigue includes fatigue and asthenia
[d] Edema includes edema, face edema, swelling face, edema peripheral, fluid overload, fluid retention, pulmonary edema, peripheral swelling and swelling
[e] Rash includes rash, dermatitis, and related terms
[f] Musculoskeletal pain includes musculoskeletal pain, back pain, musculoskeletal chest pain, neck pain, myalgia, and bone pain
[g] Upper respiratory tract infection incudes sinusitis, laryngitis, pharyngitis, nasopharyngitis, rhinitis, and specific infections
[h] Infusion related reaction is reflective of the combination regimen due to same-day administration.
Source: FDA and Applicant's analysis.

Other clinically relevant adverse reactions in <10% of recipients of pola+R-CHP included:

- **Infections**: pneumonia (9%), herpesvirus infection (3.7%), sepsis (2.9%), cytomegalovirus infection (0.7%)
- **Metabolic**: tumor lysis syndrome (0.5%)
- **Investigations**: renal insufficiency (3.9%)
- **Respiratory disorders**: pneumonitis (1.1%)

Tumor lysis syndrome may be underestimated in this analysis, particularly given the contrast in incidences of tumor lysis syndrome by AE analysis (0.5% in the pola+R-CHP arm) and uric acid elevation (19% in the pola+R-CHP arm, with the majority of these cases being detected by AE rather than lab-shift analysis).

Laboratory Findings

(b) (4)

Table 32 Applicant: Selected Laboratory Abnormalities New and Worsening from Baseline in Patients with Previously Untreated DLBCL in POLARIX

Laboratory Parameter[a]	POLIVY + R-CHP n=435			R-CHOP n=438		
	All Grades, (%)	Grade 3–4, (%)	Grade 4, (%)	All Grades, (%)	Grade 3–4, (%)	Grade 4, (%)
Hematologic						
Neutrophil count decreased	56	35	23	57	37	22
Lymphocyte count decreased	79	43	9	77	43	10
Platelet count decreased	31	7	3.0	30	6	2.3
Hemoglobin decreased	62	10	0	63	8	0
Chemistry						
Phosphorus decreased	19	3.7	0	14	2.1	0
SGPT/ALT increased	24	0.9	0	26	0.5	0
SGOT/AST increased	24	0.5	0	22	1.1	0.2
Calcium decreased	26	1.4	0.2	21	0.9	0.7
Albumin decreased	21	0.7	0	18	0.2	0
Potassium decreased	17	2.5	0	11	1.8	0

[a] Includes laboratory abnormalities that are new or worsening in grade or with worsening from baseline unknown.
Source: t_lb_abn_v2_WORSEN_SE_28JUN2021_39942.

The Applicant's Position: Overall, the incidence of the selected laboratory abnormalities was comparable between the study arms. The clinical laboratory results showed no unexpected safety findings.

The FDA's Assessment:
See Table 33 for an integrated analysis of treatment-emergent laboratory abnormalities. Values are based on an integrated analysis of laboratory and adverse reaction data, given that analysis of the ADLB.xpt dataset in isolation would have resulted in underreporting of treatment-emergent laboratory abnormalities. Of note, myelosuppression is likely underestimated in the POLARIX trial, given that labs were mandated only at the start of each cycle, thus not capturing the blood count nadir.

Table 33: Integrated Analysis of Treatment-Emergent Laboratory Abnormalities (≥15% of Patients Treated with Pola+R-CHP)

Laboratory Parameter[a]	Pola+R-CHP (N=435) n (%)		R-CHOP (N=438) n (%)	
	All Grades, (%)	Grade 3–4, (%)	All Grades, (%)	Grade 3–4, (%)
Hematologic				
Lymphocyte count decreased	80	44	77	44
Hemoglobin decreased	68	14	67	11
Neutrophil count decreased	60	39	60	42
Platelet count decreased	32	8	33	6
Chemistry				
Creatinine increased	66	0.7	64	0.9
Calcium decreased	26	1.6	23	1.4
AST increased	26	0.7	23	1.1
ALT increased	25	1.4	27	1.5
Alkaline phosphatase increased	23	0	22	0.5
Potassium decreased	21	2.8	15	3.4
Uric acid increased	19	18	17	16
Sodium decreased	18	2.5	15	3.0

[a] Values are based on integrated analysis of laboratory and adverse reaction data.
Source: Applicant's analysis

Vital Signs

The Applicant's Position: Vital signs parameters in both treatment arms were consistent throughout treatment and no clinically meaningful difference from baseline to any time post-baseline was observed between the pola+R-CHP and R-CHOP treatment arms.

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

Electrocardiograms (ECGs)

The Applicant's Position: The overall incidence of clinically significant ECG abnormalities at baseline and post-baseline was low and comparable between both the treatment arms.

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

QT

The Applicant's Position: No new information is provided in the current submission.

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

Immunogenicity

Data: For all ADA-evaluable patients, the baseline prevalence of ADAs was 2.4% (20 of 849). Post-baseline, ADAs were detected in 6 of 427 (1.4%) ADA evaluable patients treated with pola. All 6 ADA-positive patients had treatment-induced ADA (i.e. ADA negative at baseline or missing a baseline sample for ADA analysis and at least one positive post−baseline ADA result) with persistent responses(i.e. ADA positive result detected at the last post−baseline sampling time point or at ≥2 time points during treatment where the first and last ADA positive samples are separated by a period ≥16 weeks). None of the 6 ADA-positive patients tested positive for neutralizing antibodies.

The Applicant's Position: The incidence of treatment-emergent ADAs in the pola treatment group was low (1.4%) and the presence of ADA did not appear to impact exposure, safety, or efficacy. The low incidence of ADAs in patients receiving pola suggests that the immunogenicity potential is low.

The FDA's Assessment:
FDA agrees with the Applicant's position. Refer to Clinical Pharmacology section 6.2.

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1 Adverse Events of Particular Interest

Data:
AEPIs are identified or potential risks of pola for which additional analysis are presented.

- **PN:** The overall incidence of PN was 52.9% in the pola+R-CHP and 53.9% in the R-CHOP arms. Among the patients who developed PN, 26.1% [60/230] of patients in the pola+R-CHP arm experienced Grade ≥2 PN events compared to 30.9% [73/236] in the R-CHOP arm. PN-related AEs led to study treatment discontinuation and dose reduction in 0.7% and 4.6% patients in the pola+R-CHP vs. 2.3% and 8.2% patients in R-CHOP arm respectively.

- **Neutropenia including Febrile Neutropenia:** The overall incidence of neutropenia (including febrile neutropenia) was 46.0% in the pola+R-CHP and 42.7% in the R-CHOP arms. The incidence of Grade 3-4 neutropenia was 41.8% and 40.2%, respectively. No Grade 5 neutropenia events were reported. The incidence of serious neutropenia AEs was 11.5% in the pola+R-CHP arm and 8.4% in the R-CHOP arm (8.4%); the difference was mainly due to a higher incidence of serious febrile neutropenia in the pola+R-CHP arm than in the R-CHOP arm (9.9% vs. 6.4%). The incidence of prophylactic G-CSF use was 90.1% in the pola+R-CHP arm vs. 93.2% in the R-CHOP arm.
- **Infections:** The overall incidence of infections was 49.7% and 42.7% in the pola+R-CHP arm and the R-CHOP arm, respectively. The majority of events were Grade 1 or 2. Grade $\geq$ 3 infections incidence was 15.2% in the pola+R-CHP arm and 12.6% in the R-CHOP arm.
- **Hepatotoxicity or Hepatic Toxicity:** The incidence of hepatic toxicity was 10.6% in the pola+R-CHP arm and 7.3% in the R-CHOP arm. The majority of hepatic toxicity events were Grade 1-2 liver enzyme elevations in both the treatment arms.

Analyses for anemia, thrombocytopenia, TLS, pulmonary toxicity, secondary malignancy/carcinogenicity, hyperglycemia, cardiac arrhythmias, and IRR are also presented in the sBLA.

The Applicant's Position: With respect to the AEs of particular interest for pola+R-CHP and R-CHOP, there were some numerical differences in certain AEPI categories but the overall AEPI of pola+R-CHP was generally consistent with its known safety profile and with the underlying disease. No new safety signals were identified.

The FDA's Assessment:

- **Peripheral neuropathy:** The FDA agrees with the overall analysis of PN by the Applicant. The treatment arms had similar rates and grades of peripheral neuropathy, and similar rates of peripheral neuropathy- driven dose modifications and discontinuations. However, FDA notes that fewer patients in the pola+R-CHP arm had resolution of peripheral neuropathy, with or without sequelae, by the clinical cutoff date: 58%, versus 67% in the R-CHOP arm (Table 34).

Table 34: Peripheral Neuropathy in POLARIX

	Pola+R-CHP (n=435) n (%)	R-CHOP (n=438) n (%)
Baseline PN history, %	14 (3.2)	11 (2.5)
Treatment-emergent PN, %		
Any grade	230 (53)	236 (54)
Grade 2	55 (13)	70 (16)
Grade 3	7 (1.6)	5 (1.2)
Grade 4	0	0
Time to PN onset, months		
Median	2.3	1.9
Min, max	0-6.7	0-8.1
Outcome, %		
Recovered with or without sequalae	58	67
Time to resolution, months		
Median	4	4.6
Min, Max	0-36	0-35
Source: FDA and Applicant's analysis		

- **Neutropenia, febrile neutropenia and infections:** FDA generally agrees with the Applicant's assessment of infection rates and febrile neutropenia. However, myelosuppression is likely underestimated in the POLARIX trial, given that hematology labs were mandated only at the start of each cycle, thus not capturing the blood count nadir. Mandated prophylactic G-CSF was administered in 90% of patients in the pola+R-CHP arm and 93% in R-CHOP; 10% of patients in the pola+R-CHP arm and 6% of patients in the R-CHOP arm developed febrile neutropenia despite G-CSF prophylaxis.

Table 35: Neutropenia, Febrile neutropenia, and Infections in POLARIX

	Pola+R-CHP (n=435) n (%)	R-CHOP (n=438) n (%)
Neutropenia		
All Grade*	262 (60)	264 (60)
Grade 3-4*	171 (39)	184 (42)
Febrile Neutropenia		
All Grade	65 (15)	38 (9)
Grade 3-4	65 (15)	38 (9)
Serious Febrile Neutropenia	46 (11)	30 (7)
Infections		
All Grade	216 (50)	187 (43)
Grade 3-4	61 (14)	49 (11)
Grade 5^	5 (1.1)	6 (1.4)
Serious	62 (14)	45 (10)
Opportunistic infections	8 (1.8)	13 (2.9)

*Based on integrated laboratory analysis of ADAE.xpt and ADLB.xpt datasets
^ Grade 5 infections: pola+R-CHP: pneumonia (4 patients), sepsis (1 patient); R-CHOP: pneumonia (3 patients), sepsis (3 patients).
Source: FDA and Applicant's analysis

- **Hepatotoxicity:** The FDA disagrees with the Applicant on the reporting of hepatotoxicity. Based on the integrated analysis that combined laboratory measurements of transaminase elevation with the corresponding AE PTs of ALT and AST increased, in the pola+R-CHP arm, ALT elevation was reported in 25% of patients, with Grade 3–4 cases in 1.4%; and AST elevation was reported in 26% of the patients, with Grade 3–4 cases in 0.7%. In the R-CHOP arm, ALT elevation was reported in 27% of patients, with Grade 3–4 cases in 0.5%; and AST elevation was reported in 23% of the patients, with Grade 3–4 cases in 1.1%.

  Hy's law assessment: The drug-induced liver injury (DILI) team was consulted to evaluate whether there were any Hy's law cases in POLARIX and study GO29365, in addition to provide comments on labeling in the Warnings and Precautions on hepatotoxicity. Ten cases were adjudicated. None of the liver injury cases were attributable to polatuzumab vedotin (Causality scores all = 5). Although these 10 subjects met minimum biochemical characteristics of Hy's Law, there was no confirmed Hy's law case.

8.2.5.2 Analysis of Safety from 1L DLBCL R-CHP/G-CHP population and R/R DLBCL Expanded Safety Population

Data: As requested by the FDA (FDA Type C Written Responses dated October 1, 2020; Reference ID:

4679238), the Applicant provides the comprehensive safety analysis of the expanded safety population (n=247, R/R DLBCL and R/R FL patients treated with pola+BR and pola+BG) from Study GO29365 in comparison to the pola+R-CHP/G-CHP treated 1L DLBCL patients (n=501, pooled POLARIX+GO29044).

- The proportion of patients with at least one AE in the pooled 1L DLBCL safety population who received pola+R-CHP/G-CHP was 98.2% and the proportion of R/R DLBCL/FL patients with at least one AE in Study GO29365 who received pola+BR/BG treatment was 99.6%.
- Grade 3–4 AEs were reported in 58.5% of patients in the pooled 1L DLBCL safety population treated with pola+R-CHP/G-CHP and 69.2% of patients with R/R DLBCL/FL treated with pola+BR/BG treatment in Study GO29365. Grade 3–4 AEs were most frequently reported in the SOCs of Blood and lymphatic system disorders, Infections and infestations, and Investigations.
- Overall, AEs leading to death were reported in 3.0% of patients in the pooled 1L DLBCL safety population treated with pola+R-CHP/G-CHP and 12.6% of patients with R/R DLBCL/FL treated with pola+BR/BG treatment in Study GO29365. Most of the fatal AEs were due to infections or complications of infection.
- The overall incidence of SAEs was 34.9% among patients in the pooled 1L DLBCL safety population treated with pola+R-CHP/G-CHP and 57.9% in R/R DLBCL/FL patients treated with pola+BR/BG treatment in Study GO29365. The most frequently reported SAEs by SOC were Infections and infestations, Blood and lymphatic disorders, which included febrile neutropenia, Gastrointestinal disorders, and General disorders and administration site conditions.

An updated analysis of the safety profile of the pola+BR treatment regimen in patients with R/R DLBCL patients from Study GO29365 (N=247) with a CCOD of 11 March 2021 is included in the sBLA (Module 2.7.4 SCS, Appendix 2).

The Applicant's Position: Overall, the safety profile of both treatment regimens was in line with the known safety profiles of each individual treatment component and the stage of underlying disease. The higher rate of AEs in patients with R/R DLBCL was likely contributed to by increased susceptibility in these heavily pre-treated patients, as well as disease progression and subsequent anti-lymphoma therapy in this high-risk population. No new safety signals were identified with pola in combination with chemoimmunotherapy based on the assessment comparing the safety of previously untreated DLBCL patients treated with pola+R-CHP/G-CHP with R/R DLBCL/FL patients treated with pola+BR/BG.

The FDA's Assessment:
FDA did not verify the safety analysis of the population mentioned by the Applicant in this section.

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

The Applicant's Position: Overall, the COA results suggest that, with regard to the patient-relevant concepts assessed, pola+R-CHP is tolerable from the patients' perspective.

Patients in the R-CHOP arm experienced increases in PN earlier (Cycle 4) than patients in the pola arm (Cycle 6). Increase in PN in the R-CHOP arm were also larger than those in the pola arm.

Overall, the COA results suggest that patients maintained baseline level of physical functioning through the treatment. Patients treated with R-CHOP experienced deterioration in fatigue earlier than patients on pola+R-CHP. More patients in the pola+R-CHP arm experienced a clinically meaningful improvement in fatigue; Patients in both arms showed moderate levels of lymphoma symptoms at baseline with scores improving over time.

The FDA's Assessment:
See section in 8.1.2 for FDA's assessment of patient-reported fatigue, physical functioning, lymphoma symptoms. FDA disagrees with the applicant that pola+R-CHP is tolerable from the patients' perspective relative to R-CHOP. Based on the collected patient-reported neuropathy results, there was a later onset of neuropathy in the pola+R-CHP arm compared to R-CHOP. But in terms of severity and resolution after treatment completion, both arms were comparable. FDA did note that there were slightly higher proportions of patients who reported diarrhea, nausea, and decreased appetite in the pola+R-CHP arm during treatment. However, tolerability analysis is hampered by infrequent assessment of patient-reported treatment related symptoms, as these were collected only at baseline, C2D1, C3D1, C5D1 and treatment completion during the treatment period.

8.2.7. Safety Analyses by Demographic Subgroups

The Applicant's Position: Results of the safety analysis in POLARIX by baseline demographic factors demonstrated generally comparable safety profile of pola across subgroups by gender, age, race and body weight. The safety profile in patients with mild hepatic impairment was generally comparable with that observed in patients with normal hepatic function and the safety data for moderate to severe hepatic impairment was too limited to draw any meaningful conclusions. The safety profile in patients with mild or moderate renal impairment was generally comparable with that observed in patients with normal renal function and the safety data for severe renal impairment was too limited to draw any meaningful conclusions. No new safety signals were identified in any of the subgroups.

The FDA's Assessment:
FDA agrees with the Applicant's assessment. Rates of SAEs, grade 3 or higher AEs, and fatal AEs among histologic groups were similar between treatment arms (Table 36).

Table 36: Safety Overview by NHL Subgroup

	Pola+R-CHP, %	R-CHOP, %
Total safety population	n=435	n=438
SAEs [a]	34	32
Grade ≥3 AE	61	60
Fatal TEAEs	2.8	2.3
DLBCL NOS	n= 368	n= 367
SAEs	33	32
Grade ≥3 AE	60	60
Fatal TEAEs	3.2	2.5
Completed treatment	89	86
HGBL	n= 43	n= 49
SAEs	44	35
Grade ≥3 AE	65	69
Fatal TEAEs	0	4
Completed treatment	88%	80%
Other LBCL	n= 24	n= 22
SAEs	25	23
Grade ≥3 AE	63	59
Fatal TEAEs	4.2	0
Completed treatment	96	95%

[a] SAEs in both arms were primarily driven by infections (14% and 10% with pola+R-CHP and R-CHOP, respectively) and blood system disorders (11% and 9%, respectively).
Source: FDA analysis

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position: No studies were conducted to evaluate a specific safety concern.

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

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position: As of the CCOD (28 June 2021), the proportion of patients who experienced a carcinogenicity/secondary malignancy during the treatment-emergent AE interval (90 days after last dose of study drug or prior to NALT, whichever is earlier) in the pola+R-CHP arm (0.9% [4 patients]) was comparable with the R-CHOP arm (1.1% [5 patients]). Carcinogenicity events reported over the entire study period (which included the treatment emergent AE interval and up until CCOD) were reported in an additional 1 patient in the pola+R-CHP arm (colorectal cancer) and 4 patients in the R-CHOP arm.

The FDA's Assessment:
FDA agrees with the Applicant's analysis of second primary malignancies in the safety reporting period.

Human Reproduction and Pregnancy
The Applicant's Position: No pregnancies were reported during the study period. No new information is provided in the current submission.

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

Pediatrics and Assessment of Effects on Growth
The Applicant's Position: Not Applicable (please refer to Section 10).

The FDA's Assessment:
Not Applicable

Overdose, Drug Abuse Potential, Withdrawal, and Rebound
The Applicant's Position: No new information is provided in the current submission.

The FDA's Assessment:
Not Applicable

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience
Data: Since the initial market approval for the treatment of R/R DLBCL in the U.S. on 10 June 2019 through 9 June 2021, an estimated cumulative total of 10,529 patients have received pola from marketing experience worldwide (of these, 3,693 patients were in the US).

The Applicant's Position: No new or unexpected safety findings were identified in the post marketing setting for pola+BR regimen in R/R DLBCL.

The FDA's Assessment:
FDA has not verified these statements.

Expectations on Safety in the Postmarket Setting
The Applicant's Position: Not Applicable.

The FDA's Assessment:
In general, because of differences in the trial population and those who receive the product after approval, AEs may occur with higher incidence and severity in the postmarket setting. New safety signals might also emerge with larger numbers of patients exposed.

8.2.11. Integrated Assessment of Safety

The Applicant's Position: Pola+R-CHP in 1L DLBCL was generally well tolerated and toxicities were manageable. The safety profile of pola+R-CHP combination was comparable to that of R-CHOP, and in line with the known safety profiles of the individual components and the underlying disease. No new signals were identified.

Incidences of any grade AEs, Grade 3–4 AEs, Grade 5 AEs and SAEs were comparable between the treatment arms. Most of the fatal AEs in both arms were due to infections or complications of infection. The incidence of Grade 5 AEs observed in POLARIX was similar to that observed in other randomized Phase III studies involving R-CHOP in 1L DLBCL (e.g. GOYA, PHOENIX and ROBUST [Vitolo et al 2017; Younes at al 2019 and Nowakowski et al 2021, respectively]).

The incidence of AEs leading to discontinuation of any study treatment in the pola+R-CHP arm was comparable to the R-CHOP arm. The incidence of AEs leading to dose reduction of any study treatment in the pola+R-CHP arm was lower than that in the R-CHOP arm.

AEPIs were generally comparable between the POLARIX study arms, although some numerical differences were observed.

- The proportion of patients who experienced PN in the pola+R-CHP arm was comparable with the R-CHOP arm and the majority of patients experienced low grade PN. Among the patients who developed PN, a lower proportion of patients in the pola+R-CHP arm experienced Grade ≥2 PN events compared to the R-CHOP arm. A lower proportion of patients in the pola+R-CHP arm experienced any study treatment discontinuation and any study treatment dose reduction due to PN compared to the R-CHOP arm.
- The proportion of patients who experienced the AEPI neutropenia (including febrile neutropenia) in the pola+R-CHP arm was generally comparable with the R-CHOP arm. The proportion of patients who experienced a serious neutropenia event in the pola+R-CHP arm was higher than in the R-CHOP arm and was mainly due to a higher incidence of serious febrile neutropenia in the pola+R-CHP arm than in the R-CHOP arm. Neutropenia is an identified risk and an adverse drug reaction of pola, which partially explains the higher incidence of febrile neutropenia in the pola+R-CHP arm. The relatively lower incidence of prophylactic G-CSF use in the pola+R-CHP arm compared to the R-CHOP arm may partially contribute to the higher incidence of febrile neutropenia in pola+R-CHP arm. The higher incidence of febrile neutropenia in the pola+R-CHP arm did not lead to an increase in study treatment discontinuations, dose reductions or study treatment interruptions compared with the R-CHOP arm. The majority of myelosuppression AEs were resolved at the time of CCOD.
- The proportion of patients who experienced the AEPI of infections in the pola+R- CHP arm was higher than the R-CHOP arm and the incidence of Grade ≥3 infections was numerically higher in the pola+R-CHP arm compared with the R-CHOP arm. The higher incidence of serious neutropenia events observed in the pola+R-CHP arm may have partially contributed to the higher incidence of infection in the pola+R-CHP arm as compared with the R-CHOP arm. However, the incidence of Grade 5 AEs associated with infections was comparable in both the treatment arms and the increased incidence of infections in the pola+R-CHP arm did not lead to an increase in study treatment discontinuations, dose reductions or treatment interruptions compared with the R-CHOP arm.
- The proportion of patients who experienced the AEPI hepatic toxicity in the pola+R-CHP arm was slightly higher than the R-CHOP arm. The majority of hepatic toxicity events were Grade 1-2 liver enzyme elevations in both the treatment arms. The increased incidence in the pola+R-CHP arm did not lead to an increase in study treatment discontinuations, dose reductions or treatment interruptions compared with the R-CHOP arm. The majority of hepatic toxicity AEs were resolved at the time of CCOD.

A comparable incidence of AEs leading to any treatment discontinuations between the treatment arms was noted and a lower incidence of AEs leading to any dose reductions in the pola+R-CHP arm driven by fewer dose reductions due to PN was noted, demonstrating that tolerability of pola+R-CHP was comparable and descriptively better than that of R-CHOP.

Overall, pola+R-CHP was well tolerated and the toxicities were manageable. No new safety signals were identified. No additional pharmacovigilance or risk minimization activities are proposed.

Furthermore, based on an update of POLARIX safety data with approximately 8 months of additional follow up (CCOD 25 February 2022), pola+R-CHP remained safe and tolerable with no new safety signals. Safety profile is consistent with that observed in primary analysis (28 June 2021 CCOD), comparable to R-CHOP and in line with safety profile (Module 5.3.5.1 Supplemental Safety Update Report).

Safety data from the Phase Ib/II Study GO29044 are consistent with the findings observed in POLARIX. The overall safety profile of pola (1.8 mg/kg)+R/G-CHP administered to patients with previously untreated DLBCL was well tolerated and manageable and no new safety signals were identified.

The FDA's Assessment:

Refer to Section 8.2.4 for the detailed safety analysis. FDA agrees with the Applicant's position on the generally comparable safety profile between pola+R-CHP and R-CHOP arms but underscores the increased incidence of febrile neutropenia and infections in the pola+R-CHP arm. Patient-report outcomes are another important metric of tolerability, as discussed in Sections 8.1.2 and 8.2.6.

SUMMARY AND CONCLUSIONS – Section 8

8.3. Statistical Issues

The FDA's Assessment:

While the Applicant did specify a primary PFS analysis without censoring for NALT, for lymphoma products the Division typically censors both for NALT and ≥2 consecutive missed disease assessments. This censoring approach evaluates the sole effect of experimental treatment in the hypothetical absence of subsequent therapy and represents a way of handling the confounding effect from subsequent therapy assuming non-informative censoring (which may be a strong assumption). A sensitivity analysis conducted with these censoring rules results in a nominal p-value of 0.0541 and a confidence interval for the HR that does not exclude 1. Regardless of the statistical approach, the upper bounds of the confidence intervals for the HR were near or greater than 1, and the largest calculated difference in 2-year PFS was 6.5%. Considering all analyses performed, the treatment effect for PFS appears to be modest and the statistical results are sensitive to the choice of censoring rules.

Analyses of other efficacy endpoints have limitations as summarized below, with particular concern related to the OS information:

- The final analysis of OS did not demonstrate an improvement in OS. At some landmark time points, the OS estimate was lower in the pola+R-CHP arm. However, there is uncertainty in the point estimates due to low event rates.

- Modified EFS results were modest.
- The difference in CR rate by BICR was not statistically significant and raises further uncertainty about the treatment effect.
- Analyses of disease-free survival and duration of response also suggested a modest treatment effect, but these are exploratory results based on non-randomized comparisons and not controlled for Type I error.
- Considering results from evaluation of multiple endpoints (PFS, OS and CR rate), the treatment effect appeared to be heterogenous across subgroups of patients with different non-Hodgkin lymphoma (NHL) subtypes. The treatment effect also appeared to be heterogenous across subgroups of patients by IPI score (2 versus 3-5). However, the evaluation of these subgroups is exploratory, and some subgroups had very few patient numbers.

8.4. Conclusions and Recommendations

The FDA's Assessment:

The review team recommend regular approval for polatuzumab vedotin + R-CHP for the treatment of adult patients who have previously untreated DLBCL, NOS or HGBL and who have an IPI score of 2 or greater.

DLBCL is a serious and life-threatening condition for which pola+R-CHP demonstrated meaningful clinical activity in POLARIX, compared to R-CHOP. In this substitution trial, the primary analysis of PFS, demonstrated a modest but statistically significant improvement with pola+R-CHP compared to R-CHOP in the ITT population (HR = 0.73; 95% CI: [0.57, 0.95]; p-value = 0.0177). The point estimates of 1-year and 2-year PFS rates differed by 4.1% and 6.5%, respectively. The difference in modified EFS, an alpha-allocated secondary endpoint, was statistically significant, with a HR of 0.75 (95% CI: 0.58, 0.96; p-value = 0.0244). However, the treatment effect was modest, with the 2-year point estimate differing by 6.2%. There was no improvement in CR rate or OS (HR 0.94; 95% CI: 0.67, 1.33). The safety profile of pola+R-CHP was acceptable and comparable to that of the R-CHOP arm.

In a descriptive analysis of the largest lymphoma subgroup, DLBCL NOS, the PFS HR was 0.75 (95% CI: 0.57, 0.99), and the OS HR on final analysis was 1.02 (95% CI: 0.70, 1.49). The OS outcomes in this subgroup were concerning but have large uncertainty. In patients with HGBL, the PFS HR was 0.48 (95% CI: 0.21, 1.08), and the OS HR was 0.42 (95% CI: 0.15, 1.19). There were insufficient data to evaluate efficacy in other LBCLs.

A number of issues raised uncertainty about the benefit-risk of polatuzumab vedotin in this frontline, curative-intent setting including the modest PFS benefit of pola+R-CHP, the OS results, results of other efficacy endpoints, and the heterogeneity of study population. Despite the uncertainties, the efficacy results indicate that pola+R-CHP has clinically meaningful activity in patients with previously untreated DLBCL, NOS or HGBL and who have an IPI score of 2 or greater.

The Applicant seeks regular approval of polatuzumab vedotin in the frontline, curative-intent setting based on the results of a single, but large and well-controlled randomized trial Given the uncertainties with the PFS and OS results in POLARIX, the question arose whether, based on the totality of data, the benefit-risk for polatuzumab vedotin is favorable in patients with LBCL in the frontline setting, including patients with DLBCL NOS. Ultimately, and after consideration of the ODAC meeting proceedings, the review team determined the benefit-risk profile of pola+R-CHP to be favorable for the recommended

indication. Notably, the indication was limited to those with previously untreated DLBCL, NOS or HGBL and who have an IPI score of 2 or greater given the paucity of data in patients with other LBCLs or an IPI score of less than 2. A PMR will be issued for extended follow-up, including an OS assessment of the POLARIX trial.

The review team concluded that the POLARIX trial results confirmed the clinical benefit of polatuzumab vedotin in the recommended population. The review team decided that the trial results warranted regular approval on the basis of PFS, because PFS was deemed to be a clinically meaningful endpoint in this context with appropriate supportive data.

X	X
Primary Statistical Reviewer	Statistical Team Leader
X	X
Primary Clinical Reviewer	Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

9.1. Advisory Committee Meeting

The FDA's Assessment:

FDA convened an Oncologic Drugs Advisory Committee (ODAC) meeting on 3/9/2023 to discuss concerns arising from POLARIX, a confirmatory trial intended to verify the clinical benefit of polatuzumab vedotin. The primary issues that were discussed included:

1. Modest PFS benefit of polatuzumab vedotin + R-CHP
2. Overall survival results
3. Other efficacy endpoints
4. Heterogeneity of the study population.

The purpose of this meeting was to obtain the Advisory Committee's input regarding the benefit-risk of polatuzumab vedotin + R-CHP for patients with previously untreated LBCL, including DLBCL NOS, based on the POLARIX data.

Questions to the Committee:

1. **DISCUSSION:** Discuss the benefit-risk profile of polatuzumab vedotin-piiq in combination with a rituximab product, cyclophosphamide, doxorubicin, and prednisone (R-CHP) for the proposed patient population with large B-cell lymphoma (LBCL), including patients with diffused large B-cell lymphoma (DLBCL) not otherwise specified (NOS), considering the results of the POLARIX trial.

   Committee Discussion: *The majority of the Committee members agreed that progression-free survival (PFS) was an appropriate primary endpoint in this setting and patient population and that the difference was clinically meaningful. Some Committee members noted that the likelihood of minimizing subsequent lines of therapy was a benefit for this patient population. Some Committee members questioned the meaningfulness of the PFS difference and noted the lack of adequate patient-reported outcomes. Some Committee members shared concerns related to the lack of central pathology review and the heterogeneity of the patients treated in this trial. Please see the ODAC transcript for details of the Committee's discussion.*

2. **DISCUSSION:** Based on the results of the POLARIX trial, specifically the overall survival results, discuss whether additional follow-up data from POLARIX should be required to inform the benefit-risk of polatuzumab vedotin-piiq in patients with LBCL in the frontline setting.

   Committee Discussion: *Committee members agreed that it would be beneficial to have additional overall survival data. The majority of the Committee members acknowledged that it might not be feasible or practical to demonstrate an improvement in overall survival in this patient population and setting. Please see the ODAC transcript for details of the Committee's discussion.*

3. **VOTE:** Given the results of the POLARIX trial, does polatuzumab vedotin-piiq have a favorable benefit-risk profile in patients with previously untreated LBCL, including DLBCL NOS?

Vote Result: **Yes: 11** **No: 2** **Abstain: 0**

Committee Discussion: *The majority of the Committee members voted "Yes", indicating that polatuzumab vedotin-piiq has a favorable benefit-risk profile in patients with previously untreated LBCL, including DLBCL NOS given the results of the POLARIX trial. These Committee members generally agreed that the difference in the primary endpoint, PFS, was considered clinically meaningful. Some Committee members voted "No", sharing concerns related to the lack of central pathology review and the heterogeneity of the patients treated in this trial. Please see the ODAC transcript for details of the Committee's discussion.*

10 Pediatrics

The Applicant's Position: Not Applicable as the applicant has not proposed any pediatric sections in the proposed labeling.

The FDA's Assessment:
The application is exempt from PREA requirements due to orphan designation.

11 Labeling Recommendations

Data: The table below provides a high-level summary of the changes made to the US Prescribing Information (USPI) for Polivy (polatuzumab) BLA 761121/supplement 008.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's Proposed Labeling**
1 Indications and Usage	Extended the indication to include the use of POLIVY in combination with a rituximab product, cyclophosphamide, doxorubicin, and prednisone (R-CHP) for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL).	POLIVY is indicated in combination with a rituximab product, cyclophosphamide, doxorubicin, and prednisone (R-CHP) for the treatment of adult patients who have previously untreated diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS) or high-grade B-cell lymphoma (HGBL) and who have an International Prognostic Index score of 2 or greater. Accelerated approval language removed from the original indication.
2 Dosage and administration	This section has been updated to include the dosing recommendations for patients with previously untreated DLBCL.	FDA revised management recommendations for adverse reactions in previously untreated LBCL based on the POLARIX protocol and for clarity. FDA disagreed with the Applicant's proposal to (b) (4) and revised peripheral neuropathy guidelines to be more conservative. FDA added mandated G-CSF prophylaxis for neutropenia for the pola + R-CHP regimen, (b) (4).
5 Warnings and Precautions	No new warnings added. Updated to reflect the safety data in 435 patients with previously untreated DLBCL from POLARIX.	FDA generally agreed but modified to: • remove statements (b) (4) throughout section 5.

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.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's Proposed Labeling**
		• base myelosuppression and hepatoxicity incidences on integrated adverse reaction and lab analysis. • remove (b) (4) the hepatotoxicity warning
6 Adverse Reactions	Updated to reflect the safety data in 873 patients (435 of whom received POLIVY) with previously untreated DLBCL from POLARIX.	FDA based laboratory data on integrated analysis of laboratory and adverse event data. FDA removed the Applicant's proposed (b) (4), and added peripheral neuropathy resolution data for both arms of POLARIX.
6.2 Immunogenicity	Updated to reflect the number of patients tested positive for antibodies against polatuzumab vedotin-piiq from POLARIX (n=427).	FDA moved the current subsection 6.3 to a new subsection **12.6 Immunogenicity** and made changes based on recommendations in the Immunogenicity in Human Prescription Therapeutic and Select Drug Product labeling draft guidance for Industry.
8.3 Females and Males of Reproductive Potential, and 13 Nonclinical Toxicology	No change	FDA added text on potential impairment of female fertility, based on recent data on MMAE-related ovarian toxicity
8.5 Geriatric Use	Updated to reflect the data from POLARIX.	FDA generally agreed.
12 Clinical Pharmacology	Updated to reflect the population from POLARIX and added new information for drug interaction studies.	FDA modified as follows: Subsection 12.2: • Added clarification that higher incidence of adverse reactions was associated with both antibody-conjugated MMAE (acMMAE) and unconjugated MMAE while lower efficacy was associated with was associated with lower antibody-conjugated MMAE. Subsection 12.3 (high-level summary): • Updated the exposure summary table to report geometric mean and geometric coefficient of variation of Cycle 1 Cmax and Cycle 1 AUC for both acMMAE and MMAE according to indication. • Population PK analysis updated throughout. • Specific Populations section updated to include specific race category details and a new hepatic impairment subheading.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's Proposed Labeling**
		• Other edits throughout this section to align with current labeling practice.
14 Clinical Studies	The efficacy data has been added for POLARIX.	FDA modified section 14.1 to: • add overall survival data • remove (b) (4) analyses • add descriptive data for DLBCL NOS and HGBL • note there was not enough data to evaluate efficacy in other LBCLs.

The Applicant's Position:

The results presented in the dossier from the pivotal study POLARIX demonstrate substantial evidence of safety and effectiveness of POLIVY in combination with R-CHP for the 1L treatment of patients with DLBCL. The magnitude of clinical benefit combined with the well tolerated and comparable safety profile of pola+R-CHP support this regimen as an important new treatment option for patients with previously untreated DLBCL, representing a substantive improvement over the R-CHOP regimen. The existing risk management measures in the POLIVY product label include adequate information to ensure safe use of pola in combination with R-CHP. Accordingly, based on the positive benefit risk of POLIVY for patients with previously untreated DLBCL, the following indication is proposed:

> *"POLIVY® in combination with a rituximab product, cyclophosphamide, doxorubicin, and prednisone is indicated for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma."*

The FDA's Assessment:

The FDA modified sections of the label as described in the table above.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:
The clinical review team does not recommend a REMS. Based on the risk/benefit profile of polatuzumab vedotin, safety issues can be adequately managed through appropriate labeling and routine post-marketing surveillance.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

PMR 3630-1: The POLARIX trial verified clinical benefit and as such, PMR 3630-1 is considered fulfilled. Therefore, PMR 3630-2 (POLARGO) is no longer required and can be released.

The review team recommends one PMR under FDAAA (Food and Drug Administration Amendments Act) and one postmarketing commitment (PMC).

PMR: Conduct an analysis of patients enrolled in Study GO39942 (POLARIX) to further characterize the serious risks, including infections and fatal adverse events, with extended follow-up in patients receiving polatuzumab vedotin in combination with R-CHP (rituximab, cyclophosphamide, doxorubicin, and prednisone) as first-line treatment for large B-cell lymphoma. Include evaluation of overall survival in each treatment arm in POLARIX, with a minimum of 2 additional years of follow-up, and include causes of death and narratives for death in the absence of treated disease progression.

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

PMC: Complete Study MO40598 (POLARGO), a randomized clinical trial evaluating polatuzumab vedotin in combination with rituximab, gemcitabine, and oxaliplatin (R-GemOx) versus R-GemOx alone in patients with relapsed or refractory large B-cell lymphoma, with a primary endpoint of overall survival.

Final Protocol Submission (Analysis Plan):	11/2024
Trial Completion:	12/2024
Final Report Submission:	06/2025

14 Division Director (OCP)

X

15 Division Director (OB)

X

16 Division Director (Clinical)

X _____

17 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 _____

18 Appendices

18.1. References

The Applicant's References:

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Applicant List of Referenced Studies

Primary Clinical Study Report – GO39942 (POLARIX): A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial Comparing the Efficacy and Safety of Polatuzumab Vedotin in Combination with Rituximab and CHP (R-CHP) versus Rituximab and CHOP (R-CHOP) in Previously Untreated Patients with Diffuse Large B-Cell Lymphoma. - Report No. 1106275 – October, 2021.

Final Clinical Study Report - GO29044: A Phase Ib/II Study Evaluating the Safety, Tolerability and Anti-Tumor Activity of Polatuzumab Vedotin (DCDS4501A) in Combination With Rituximab or Obinutuzumab, Cyclophosphamide, Doxorubicin, and Prednisone in Patients With B-Cell Non-Hodgkin's Lymphoma. Report No. 1109685, July 2021. (Legacy Report No.1095535 October 2019).

Exposure-Respone Report: Analysis of Exposure-Safety and Exposure-Efficacy Relationships for Polatuzumab Vedotin in Combination with R-CHP in Patients with Previously Untreated DLBCL. Report No. 1111193. October 2021.

Population Pharmacokinetic Report: DCS4968g, GO27834, GO29044, GO29365, BO29561 GO29833, GO29834. Population Pharmacokinetic Analysis for Polatuzumab Vedotin in Patients with Non Hodgkin's Lymphoma. Report No. 1090510. November 2018.

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The FDA's References:

Zelenetz AD, Gordon LI, Abramson JS, et al. NCCN Guidelines: B-Cell Lymphomas, Version 2.2023. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed February 12, 2023.

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18.2. Financial Disclosure

The Applicant's Position:

Summary of Findings:

Study GO39942 (POLARIX)

A total of 2,427 principal investigators and sub-investigators participated in pivotal Study POLARIX. Disclosable financial interests were recorded by 16 out of 2,427 (0.01%) investigators in POLARIX. No disclosable interests were recorded in 2,402 out of 2,424 (98.9%) investigators. Despite due diligence to obtain the information, a signed financial disclosure was not obtained for nine sub-investigators. The reason the information could not be collected, as well as the Applicant's due diligence efforts in attempting to obtain the information are provided in Section 1.3.4 of the sBLA.

Study GO29044

Financial disclosure information for supportive Study GO29044 was previously included in the original BLA 761121 (Sequence No. 0001), and minor changes have been made to the financial disclosures for the study since the original application. Specifically, the List of Investigators was updated to remove a small number of investigators because they did not participate in the conduct of the study. A total of 95 principal investigators and sub-investigators participated in Study GO29044. No disclosable interests were recorded in 95 out of 95 (100%) of investigators.

For further information for financial disclosures please see Module 1.3.4.

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

Covered Clinical Study (Name and/or Number):* GO39942 (POLARIX) & GO29044

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 2522		
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): 16		
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: 16 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) 2		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

18.3. OCP Appendices (Technical documents supporting OCP recommendations)

18.3.1. Bioanalytical Methods

The Applicant's Position:

Table 37: Summary Method Performance of a Bioanalytical Method to Measure Antibody-Conjugated MMAE from Polatuzumab Vedotin in Human Plasma

Bioanalytical method validation report name, amendments, and hyperlinks	The Validation History of the Method for the Determination of Antibody-Conjugated MMAE from Polatuzumab Vedotin (DCDS4501A) in Human Plasma (Report P290) Consists of the following reports: LCMSC 553, Project JVW2 LCMSC 553 Addendum 1, Project JVW4 LCMSC 553 Addendum 2, Project GEX LCMSC 553 Addendum 3, Project JVW5 S377-4 (LCMSC 553 Addendum 4, Project JVW5)
Method description	The method for the determination of antibody-conjugated monomethyl auristatin E (acMMAE) from polatuzumab vedotin (also known as DCDS4501A, DCDS4501S, and RO5541077) in human plasma by LC-MS/MS was developed by Genentech (South San Francisco, CA) and transferred to and validated at (b) (4) by 13 June 2018. A hybrid immunoaffinity capture LC-MS/MS assay was validated to quantify the concentration of acMMAE from polatuzumab vedotin. A matrix aliquot (50 mL) is fortified with 200 mL of 100 ng/mL internal standard (ADC-IS, IS, Tmab-vc-MMAF). The conjugated polatuzumab vedotin and ADC-IS are isolated through a solid phase immunoprecipitation extraction using MabSelect protein A resin (GE Healthcare; Piscataway, NJ) to enrich for IgG isotype antibodies in a 96-well filter plate. The immobilized antibody-drug conjugates (ADCs) are then digested with papain, releasing the MMAE and MMAF analytes, which are subsequently eluted with 500 mL of 70:30 ethanol:water, volume to volume (v/v). The eluate is evaporated under a nitrogen stream at approximately 50°C and the remaining residue is reconstituted with 50 mL of water. The sample then undergoes a protein precipitation using 500 mL of 70:30 acetonitrile:methanol, v/v. The supernatant is evaporated under a nitrogen stream at approximately 50°C and the remaining residue is reconstituted with 250 mL of 50:50:0.1 methanol:water:formic acid, v/v/v. The final extract is analyzed via HPLC with column-switching and MS/MS detection using positive ion electrospray. The lower limit of quantitation is 0.500 nM acMMAE.

Materials used for calibration curve & concentration	Anti-CD79b-vc-MMAE: Source: Genentech; Lot 870729; Concentration: 10.2 mg/mL; DAR: 3.7; Expiry: 31 Aug 2011 DCDS4501A (Anti-CD79b-vc-MMAE): Source: Genentech; Lot 79bvcMMAE809-2; Concentration: 10.3 mg/mL; DAR: 3.7; Expiry: 18 May 2016 aCD79b ADC Ph III Drug Product Stock I: Source: Genentech; Lot vup1-07Sep17-193C; Concentration: 10.5 mg/mL; DAR: 3.5; Expiry: 7 Sep 2021 DCDS4501S: Source: Genentech; Lot 608785; Concentration: 19.7 mg/mL; DAR: 3.6; Expiry: 25 Apr 2021 Tmab-vc-MMAF: Source: Genentech; Lot P08305; DAR: 2.43; Protein Concentration: 5.02 mg/mL; Expiry: 15 Dec 2011 Herceptin-MC-vc-PABMMAF (IS): Source: Genentech; Lot 929; Concentration: 20.5 mg/mL; DAR: 2.3; Expiry: 15 Dec 2019		
Validated assay range	MMAE nominal range of 0.500-50.0 nM, from ADC levels within a nominal range of 19.6-1960 ng/mL		
Material used for QCs & concentration	Same as above for calibration curve and concentration		
Minimum required dilutions (MRDs)	NA		
Source & lot of reagents (LBA)	NA for LC-MS/MS		
Regression model & weighting	Linear, 1/concentration squared weighted, least-squares regression algorithm		
Validation parameters	**Method validation summary**		**Acceptability**
Standard calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	8	Yes
	Cumulative accuracy (% bias) from LLOQ to ULOQ Validation Addendum 1	 -1.44% to 1.95% -5.47% to 5.28%	Yes
	Cumulative precision (% CV) from LLOQ to ULOQ Validation Addendum 1	 3.19% to 8.41% 1.68% to 5.87%	Yes
QCs performance during accuracy & precision	**Cumulative accuracy (%bias) in 5 QCs** QCs: 1.00, 2.00, 5.00, 12.0, and 39.0 nM Validation Addendum 1	 -5.26% to -2.27% 2.13% to 12.5%	Yes

	Inter-batch %CV QCs: 1.00, 2.00, 5.00, 12.0, and 39.0 nM Validation Addendum 1	 2.97% to 8.51% 2.93% to 14.7%	 Yes
	Total error: not calculated for LC-MS/MS	NA	**NA**
Selectivity & matrix effect	Validation Unfortified Specificity Six individual normal human plasma lots containing lithium heparin were analyzed for antibody-conjugated MMAE and its internal standard. Samples were analyzed unfortified and fortified with internal standard. • No significant chromatographic peaks were detected Fortified Specificity Six individual normal human plasma lots containing lithium heparin were analyzed fortified with antibody-conjugated MMAE at the LLOQ (0.500 nM). • % CV: 1.85% to 10.6% • % difference from theoretical range: -16.7% to -12.9% Matrix Factor Six individual normal human plasma lots were fortified with antibody-conjugated MMAE at high QC (39.0 nM) • % CV of analyte matrix factor: 8.03% • % CV of internal standard matrix factor: 7.72%		 Yes Yes Yes
	Addendum Unfortified Specificity Six individual normal human plasma lots containing lithium heparin were analyzed for antibody-conjugated MMAE and its internal standard. Samples were analyzed unfortified and fortified with internal standard. • No significant chromatographic peaks were detected Fortified Specificity Six individual normal human plasma lots containing lithium heparin were analyzed fortified with antibody-conjugated MMAE at the LLOQ (0.500 nM). • % CV: 1.23% to 15.1% • % difference from theoretical range: -12.8% to -1.40%		Yes Yes

Interference & specificity	Concomitant medications interference
	
	Validation:
	One human plasma blank with antibody-conjugated MMAE at low QC (0.500 nM) and high QC (39.0 nM) levels was fortified with the following compounds and analyzed:
	• 50.0 mg/mL acetaminophen, 20.0 mg/mL caffeine, and 500 ng/mL pseudoephedrine
	  o Low QC, % difference from theoretical: -0.233%
	  o High QC, % difference from theoretical: -3.68%
	• 1.00 ng/mL ethinyl estradiol, 100 ng/mL norgestrel, and 100 ng/mL norethindrone
	  o Low QC, % difference from theoretical: 3.60%
	  o High QC, % difference from theoretical: -3.33%
	• 10.0 mg/mL acetylsalicylic acid and 50.0 mg/mL salicylic acid
	  o Low QC, % difference from theoretical: -5.47%
	  o High QC, % difference from theoretical: -6.75%
	• 50.0 mg/mL ibuprofen, 100 mg/mL naproxen, and 100 ng/mL chlorpheniramine
	  o Low QC, % difference from theoretical: 1.70%
	  o High QC, % difference from theoretical: -5.98%
	
	Concomitant medications interference
	
	Addendum 3:
	One human plasma blank with antibody-conjugated MMAE at low QC (1.00 nM) and high QC (39.0 nM) levels was fortified with the following compounds and analyzed:
	• 10.0 mg/mL bendamustine
	  o Low QC, % difference from theoretical: -4.14%
	  o High QC, % difference from theoretical: -1.55%
	• 100 mg/mL ABT 199 (venetoclax), 1.50 mg/mL lenalidomide, 1000 mg/mL MPDL3280A, and 0.600 mg/mL rituximab
	  o Low QC, % difference from theoretical: 5.27%
	  o High QC, % difference from theoretical: -3.84%
	• 28.0 mg/mL cyclophosphamide, 0.300 mg/mL doxorubicin, and 0.800 mg/mL prednisone
	  o Low QC, % difference from theoretical: -5.40%
	  o High QC, % difference from theoretical: -7.18%
	• 1.55 mg/mL obinutuzumab/GA101 and 0.588 mg/mL rituximab
	  o Low QC, % difference from theoretical: 2.64%
	  o High QC, % difference from theoretical: -3.34%
		Yes
		
		Yes

	Concomitant medications interference Addendum 4: One human plasma blank with antibody-conjugated MMAE at low QC (1.00 nM) and high QC (39.0 nM) levels was fortified with the following compounds and analyzed: • 8.00 mg/mL BTCT4465A (mosunetuzumab) o Low QC, % difference from theoretical: 4.28% o High QC, % difference from theoretical: -0.658% • 100 mM mesna and 25.0 mg/mL idasanutlin o Low QC, % difference from theoretical: 4.24 % (initial) and -5.20% (confirmation for the correct preparation) o High QC, % difference from theoretical: 0.944% (initial) and -1.57% (confirmation for the correct preparation)	Yes
Hemolysis effect	One pooled normal plasma lot prepared in 5% hemolyzed plasma was analyzed at low QC (1.00 nM) and high QC (39.0 nM) levels; no effect on quantitation of antibody-conjugated MMAE was shown. • % difference from theoretical: o Low QC: -7.31% o High QC: -5.90%	Yes
Lipemic effect	NA	NA
Dilution linearity & hook effect	Dilution linearity was validated by analyzing six replicate QCs containing 5.00 nM antibody-conjugated MMAE with subsequent two-fold dilutions. • % difference from theoretical: 1.96% Dilution linearity was validated by analyzing six replicate QCs containing 1000 nM antibody-conjugated MMAE with subsequent 1000-fold dilutions. • % difference from theoretical: -2.61%	Yes
Bench-top/process stability	Anti-CD79b-MMAE in neat plasma at low QC (1.0 nM), high QC (39.0 nM), and ultra-high-concentration (8000 nM) levels is stable thawed and stored for 24 hours at room temperature prior to analysis. • % difference from theoretical: o Low QC: 0.244% o High QC: -2.15% o Ultra-high QC: -5.04% Anti-CD79b-MMAE in neat plasma at low QC (1.0 nM) and high QC (39.0 nM) levels has a post-preparative extract stability at 2°C-8°C of 259 hours. • % difference from theoretical: o Low QC: -5.67% o High QC: -1.70%	Yes

Freeze-Thaw stability	Anti-CD79b-MMAE in neat plasma at low QC (1.0 nM), high QC (39.0 nM), and ultra-high-concentration (8000 nM) levels is stable through 5 freeze/thaw cycles at -20°C and -70°C. • % difference from theoretical at -20°C: ○ Low QC: -4.50% ○ High QC: -3.85% ○ Ultra-high QC: -3.31% • % difference from theoretical at -70°C: ○ Low QC: 0.316% ○ High QC: -3.00% ○ Ultra-high QC: -4.14%	Yes
Long-term storage	Addendum 2: Anti-CD79b-MMAE in neat plasma at Low QC (0.718 ng/mL) and High QC (28.0 ng/mL) is stable at -25°C for up to 405 days and at -80°C for up to 1038 days. • % difference from theoretical at -25°C: ○ Low QC: 9.74% ○ High QC: -0.894% • % difference from theoretical at -80°C: ○ Low QC: -12.0% ○ High QC: -11.9% Additionally, an above-the-curve QC level (5740 ng/mL) was assessed and is stable at -25°C for up to 454 days and at -80°C for up to 425 days. • % difference from theoretical at -25°C: ○ Ultra-high QC: -3.56% • % difference from theoretical at -80°C: ○ Ultra-high QC: -9.05% Addendum 4: Anti-CD79b-MMAE in neat plasma at Low QC (1.0 nM) and High QC (39.0 nM) levels is stable at -80°C for up to 2780 days. • % difference from theoretical at -80°C: ○ Low QC: 10.6% ○ High QC: 6.29% Furthermore, an above-the-curve QC level (2790 nM) was assessed and is stable at -80°C for up to 1260 days. • % difference from theoretical at -80°C: ○ Ultra-high QC: -3.00%	Yes Yes Yes
Carry over	Carryover was evaluated by injecting duplicate extracted matrix blanks immediately after the ULOQ calibration standards in each validation run. Carryover as a percentage of the LLOQ was less than or equal to 20% in every run.	Yes
Method performance in study GO39942 *GO39942* Quantitation of Antibody-Conjugated MMAE from DCDS4501A, Anti-CD79b-vc-MMAE in Human Plasma via HPLC with MS/MS Detection		
Assay passing rate	49/56 runs (87.5%) acceptable	Yes
Standard curve performance	• Cumulative Bias Range: -1.67 to 1.57% • Cumulative Precision: ≤ 6.18% CV	Yes
QC performance	• Cumulative Bias Range: -0.123 to 2.52% • Cumulative Precision: ≤ 8.41% CV	Yes

Method reproducibility	Incurred sample reanalysis was performed in 10.2% of study samples and 95.2% of samples met the pre-specified criteria	Yes
Study sample analysis/ stability	All samples were analyzed within the 2780 days demonstrated long-term storage stability in human serum at -80 °C.	

Source: Table 1 in Applicant's 11 August 2022 response to 04 August 2022 information request

Table 38: Summary Method Performance of a Bioanalytical Method to Measure Unconjugated MMAE from Polatuzumab Vedotin in Human Plasma

Bioanalytical method validation report name, amendments, and hyperlinks	The Validation History of the Method for the Determination of MMAE in Lithium-Heparin Human Plasma (Report P277) Consists of the following reports: (b) (4) Quantitative Determination of MMAE in Human Plasma by LC/MS/MS 08-0805 ((b) (4) Labs Report No. (b) (4)) 08-0805 Addendum 1 ((b) (4) Labs Report No. (b) (4)) 08-0805 Addendum 2 ((b) (4) Labs Report No. (b) (4)) 08-0805 Addendum 3 ((b) (4) Labs Report No. (b) (4)) (b) (4) Quantitation of Unconjugated MMAE in Human Plasma via HPLC with MS/MS Detection LCMSD 698, Project RCIX2 LCMSD 698 Addendum 1, Project RCIX3 LCMSD 698 Addendum 2, Project RCIX4 LCMSD 698 Addendum 3, Project RCIX4 LCMSD 698 Addendum 4, Project RCIX5
Method description	The method for the determination of monomethyl auristatin E (MMAE) using liquid chromatography tandem mass spectrometry (LC MS/MS) in human plasma samples was developed at Genentech (South San Francisco, CA) and validated at (b) (4) by 12 February 2009. The method was then transferred to and fully validated at (b) (4) by 10 October 2014. Lithium-heparin human plasma samples containing MMAE were analyzed in 50.0-mL aliquots using a protein-precipitation extraction procedure followed by LC-MS/MS. MMAE was analyzed using MMAE-d_8 as an internal standard. The API 5000ä LC-MS/MS instrument (SelectScience[a]; Corston, UK) was operated in the Selected Reaction Monitoring mode with conditions optimized for the detection of MMAE and the MMAE-d_8 positive ions formed by electrospray ionization. The lower limit of quantitation is 0.500 nM at (b) (4) and 0.0500 nM at (b) (4) (b) (4):
Materials used for calibration curve & concentration	MMAE: Source, Genentech; Lot 2002E; Expiry, 15 December 2008 (dry powder, purity of 92.0%) MMAE: Source, (b) (4); Lot (b) (4) Expiry, 30 April 2010 (dry powder, purity of 92.80%) MMAE: Source, (b) (4); Lot (b) (4) Expiry, 31 March 2012 (dry powder, purity of 95.77%) MMAE: Source, (b) (4); Lot (b) (4) Expiry, 31 March 2013 (dry powder, purity of 95.77%) MMAE d8: Source, (b) (4); Lot (b) (4); Expiry, 26 May 2009 (dry powder, purity of 100%)

	MMAE d8: Source, (b) (4); Lot (b) (4); Expiry, 26 May 2011 (dry powder, purity of 95.3%) MMAE d8: Source, (b) (4); Lot (b) (4); Expiry, 26 May 2014 (dry powder, purity of 95.3% (b) (4) MMAE: Source, Genentech; Lot SG10-018; Expiry, 1 November 2014, extended to 31 October 2016 (dry powder, purity of 94.7%) MMAE: Source, (b) (4); Lot (b) (4) Expiry, 16 September 2017 (dry powder, purity of 98.0%) MMAE: Source, (b) (4).; Lot (b) (4) Expiry, 8 September 2019 (dry powder, purity of 99.5%) MMAE d8: Source, Genentech; Lot XS517 113A; Expiry, 5 June 2019 (dry powder, purity of 95.3%) MMAE d8: Source, Genentech; Lot 1010 2H 01; Expiry, 29 May 2020 (dry powder, purity of 95.3%)		
Validated assay range	(b) (4): MMAE nominal range of 0.0500-25.0 nM (equivalent to 0.0359-17.9 ng/mL) using MMAE-d_8 as an IS (b) (4) 0.0500-25.0 nM		
Material used for QCs & concentration	(b) (4) Same as above for calibration curve and concentration (b) (4) Same as above for calibration curve and concentration		
Minimum required dilutions (MRDs)	NA		
Source & lot of reagents (LBA)	NA for LC-MS/MS		
Regression model & weighting	Linear, $1/x^2$ ((b) (4)); Linear 1/x ((b) (4)		
Validation parameters	**Method validation summary**		**Acceptability**
Standard calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	8	Yes
	(b) (4) Cumulative accuracy from LLOQ to ULOQ (% bias)	-2.5% to 4.7%	Yes
	(b) (4) Cumulative accuracy from LLOQ to ULOQ (% difference from theoretical)	-1.41% to 1.06%	Yes
	(b) (4) Cumulative precision (% CV) from LLOQ to ULOQ	3.0% to 5.2%	Yes
	(b) (4) Cumulative precision (% CV) from LLOQ to ULOQ	1.91% to 9.56%	Yes

QCs performance during accuracy & precision	(b) (4) Cumulative accuracy (% bias) in four QCs	-4.6% to 4.0%	Yes
	(b) (4) % Difference from theoretical in five QCs	-6.10% to 2.42%	Yes
	(b) (4) Interbatch % CV	0.0% to 5.4%	Yes
	(b) (4) Interbatch % CV	4.15% to 8.32%	Yes
	Total error: not calculated for LC-MS/MS	NA	NA
Selectivity & matrix effect	Unfortified specificity (b) (4) Not tested. (b) (4) Six individual normal human plasma (containing lithium heparin) lots were analyzed for unconjugated MMAE and its IS. Unfortified and fortified samples were analyzed using an IS. Significant chromatographic peaks were not detected. Fortified specificity (b) (4) Not tested. (b) (4) Six individual normal human plasma (containing lithium heparin) lots, fortified with unconjugated MMAE (0.0500 nM), were analyzed. • % CV: 3.40%-14.3% • % Difference from theoretical range: -15.5% to 5.53% Matrix factor (b) (4) Six individual normal human plasma lots were fortified with MMAE and IS. • % CV of IS-corrected analyte matrix factor: 1.6% (b) (4) Eight individual matrix lots were fortified with MMAE and IS at low and high QC levels. The matrix lots included four normal human plasma lots, two hemolyzed lots (5% hemolysis), and two lipemic lots (> 300 mg/dL triglyceride). Matrix factor results were acceptable. • % CV of IS-corrected analyte matrix factor (low QC): 6.15% • % CV of S-corrected analyte matrix factor (high QC): 4.05%		Yes Yes Yes

Interference & specificity	Concomitant medications interference
	(b) (4) Not tested.
	
	(b) (4)
	One human plasma blank with unconjugated MMAE, at low and high QC levels, was fortified with the following compounds and analyzed:
	• 50.0 mg/mL of acetaminophen, ibuprofen, and salicylic acid; 20.0 mg/mL caffeine; 50 ng/mL chlorpheniramine; 500 pg/mL ethinyl estradiol; 100 ng/mL norethindrone; 25 ng/mL norgestrel; 10.0 mg/mL acetylsalicylic acid; and 100 mg/mL naproxen
	  • Low QC, % difference from theoretical: -5.70%
	  • High QC, % difference from theoretical: 1.01%
	
	One human plasma blank with unconjugated MMAE, at low and high QC levels, was fortified with the following compounds and analyzed:
	• 56.0 mg/mL cyclophosphamide, 0.600 mg/mL doxorubicin, 1.60 mg/mL prednisone, and 35.0 mg/mL mesna
	  • Low QC, % difference from theoretical: 2.29%
	  • High QC, % difference from theoretical: 2.26%
	• 10.0 mg/mL bendamustine
	  • Low QC, % difference from theoretical: 1.21%
	  • High QC, % difference from theoretical: -4.93%
	• 28.0 mg/mL cyclophosphamide, 0.300 mg/mL doxorubicin, 0.800 mg/mL prednisone, 1.50 mg/mL lenalidomide, and 16.4 mg/mL MPDL3280A
	  • Low QC, % difference from theoretical: 8.79%
	  • High QC, % difference from theoretical: 3.41%
	• 1550 mg/mL obinutuzumab and 588 mg/mL rituximab
	  • Low QC, % difference from theoretical: 11.3%, outside acceptance limits
	  • High QC, % difference from theoretical: 3.57%
	• 1550 mg/mL obinutuzumab
	  • Low QC, % difference from theoretical: -0.947%
	• 588 mg/mL rituximab
	  • Low QC, % difference from theoretical: 2.76%
	• 25.0 mg/mL idasanutlin, 100 mM mesna, and 1000 mg/mL MPDL3280A
	  • Low QC, % difference from theoretical: -9.66%
	  • High QC, % difference from theoretical: 5.09%
		Yes
		
		Yes
		
		Yes
		
		Yes
		
		Yes
		
		Yes
		
		Yes

	One human plasma blank with unconjugated MMAE, at low and high QC levels, was fortified with the below compounds and analyzed:
	• 100 mg/mL venetoclax
	  • Low QC, % difference from theoretical: -5.89%
	  • High QC, % difference from theoretical: 1.13%
	• 30.0 mg/mL gemcitabine
	  • Low QC, % difference from theoretical: 15.0%
	  • High QC, % difference from theoretical: 4.38%
	• 1.0 mg/mL oxaliplatin
	  • Low QC, % difference from theoretical: 4.29%
	  • High QC, % difference from theoretical: 4.24%
	• 8.00 mg/mL BTCT4465A
	  • Low QC, % difference from theoretical: -7.74%
	  • High QC, % difference from theoretical: -2.64%
		Yes
		
		Yes
		
		Yes
		
		Yes

Hemolysis effect	(b) (4) Low QC was analyzed in one pooled normal plasma lot; prepared in 2% hemolyzed plasma:
	• No effect on MMAE quantitation was observed
	• % Difference from theoretical: 0.2%
	
	(b) (4) Low and high QCs prepared in 5% hemolyzed whole blood were evaluated
	• No effect on MMAE quantitation was observed
	• % Difference from theoretical
	  • Low QC: -11.1%
	  • High QC: -8.17%
		Yes
		
		Yes

Lipemic effect	(b) (4) Not tested
	
	(b) (4) Low and high QCs prepared in lipemic plasma (triglyceride concentration, > 300 mg/dL)
	• % Difference from theoretical
	  • Low QC: 4.19%
	  • High QC: 1.06%
		
		Yes

Dilution linearity & hook effect	(b) (4) Dilution linearity was evaluated by analyzing six replicate QCs containing 71.8 ng/mL MMAE and subsequent ten-fold dilutions • % Difference from theoretical: 3.8% (b) (4) Dilution linearity was evaluated by analyzing six replicate QCs containing 1.20 nM MMAE and subsequent two-fold dilutions • % Difference from theoretical: -1.96% The hook effect was evaluated by analyzing six replicate QCs containing 100 nM MMAE and subsequent 10-fold dilutions • No hook effect was observed • % Difference from theoretical: 0.420%	Yes Yes Yes

Bench-top/process stability	(b) (4)
	Post-extracted MMAE, at low, medium, and high QC levels, has a room temperature reinjection stability of 93 hours
	• % Bias:
	  • Low QC: 12.4%
	  • Medium QC: 1.0%
	  • High QC: -3.9%
	MMAE in neat plasma, at low and high QC levels, has a room temperature bench-top stability of 6 hours
	• % Of theoretical:
	  • Low QC: -0.6%
	  • High QC: -0.67%
	MMAE in neat plasma, at low and high QC levels, has a post-preparative extract stability of 72 hours at room temperature
	• % Difference from theoretical:
	  • Low QC: 7.7%
	  • Low-medium QC: 12.1%
	  • Medium QC: 5.9%
	  • High QC: 1.7
	(b) (4)
	Post-extracted MMAE, at five QC levels, has a room temperature reinjection stability of 6.5 hours
	• % difference from theoretical
	  • Low QC: -9.35%
	  • QC 2: -2.89%
	  • Medium QC: -5.06%
	  • QC 4: -3.27%
	  • High QC: -5.01%
	
	MMAE in neat plasma, at low and high QC levels, is stable when thawed at room temperature for 27 hours prior to extraction
	• % Difference from theoretical:
	  • Low QC: 2.04%
	  • High QC: -5.27%
	MMAE in neat plasma, at low and high QC levels, has a post-preparative extract stability time of 103 hours at room temperature
	• % Difference from theoretical:
	  • Low QC: 1.86%
	  • High QC: -3.82%
	MMAE in neat plasma, at low and high QC levels, is stable when thawed on ice for 6 hours prior to extraction
	• % Difference from theoretical:
	  • Low QC: 1.01%
	  • High QC: 1.58%
		Yes
		Yes
		Yes
		Yes
		Yes

	MMAE stability, in thawed matrix, in the presence of DCDS4501S was evaluated by allowing an ADC-only QC sample, a set of low- and high-level QCs fortified with both DCDS4501S and MMAE, and a set of monitoring QCs (fortified with MMAE only) to thaw and remain on ice for 24 hours prior to extraction and analysis
	• % Difference from theoretical:
	  • Low QC (fortified with 200 mg/mL DCDS4501S and 0.00 nM MMAE): 5.44%
	  • Low QC (fortified with 200 mg/mL DCDS4501S and 0.200 nM MMAE): 8.21%
	  • High QC(fortified with 200 mg/mL DCDS4501S and 19.0 nM MMAE: 3.03%
	Additional MMAE stability, in thawed matrix, in the presence of DCDS4501S was evaluated by allowing an ADC-only QC sample and a set of low- and high-level QC samples fortified with both DCDS4501S and MMAE to thaw and remain at room temperature for 8 hours prior to extraction and analysis
	• % Difference from theoretical:
	  • Low QC (fortified with 200 mg/mL DCDS4501S and 0.00 nM MMAE): 32.8%
	  • Low QC (fortified with 200 mg/mL DCDS4501S and 0.200 nM MMAE): 20.2%
	  • High QC (fortified with 200 mg/mL DCDS4501S and 19.0 nM MMAE): 1.50%
	Based on above freeze/thaw stability results, the method's thawing conditions will be updated from thawing at room temperature to thawing on ice.
		Yes
		
		Yes

Freeze-Thaw stability	(b) (4)
	MMAE in neat plasma, at low and high QC levels, is stable through four freeze/thaw cycles at -20°C.
	• % Bias:
	  • Low QC: -0.6%
	  • High QC: -6.7%
	
	(b) (4)
	MMAE in neat plasma, at low and high QC levels is stable through five freeze/thaw cycles when frozen to either -20°C or -70°C
	• % Difference from theoretical (-20°C)
	  • Low QC: -2.68%
	  • High: -0.841%
	• % Difference from theoretical (-70°C)
	  • Low QC: -2.4%
	  • High QC: -1.54%
	MMAE in neat plasma, at low and high QC levels, was evaluated through six freeze/thaw cycles to -80°C
	• % Difference from theoretical (-80°C)
	  • Low QC: 13.1%
	  • High QC: 3.00%
		Yes
		
		Yes
		
		Yes

	Freeze/thaw stability in the presence of DCDS4501S was evaluated by analyzing an ADC-only QC, a set of low- and high-level QCs fortified with both DCDS4501S and MMAE, and a set of monitoring QCs (fortified with MMAE only). All were subjected to five freeze/thaw cycles. Samples were thawed on ice for a minimum of 2 hours and frozen at -80°C (FTC) for each freeze cycle
	• % Difference form theoretical (thawed on ice)
	  • Low QC (fortified with 200 mg/mL DCDS4501S and 0.00 nM MMAE): 5.29%
	  • Low QC (fortified with 200 mg/mL DCDS4501S and 0.200 nM MMAE): 9.03%
	  • High QC (fortified with 200 mg/mL DCDS4501S and 19.0 nM MMAE): 6.21%
	• % Difference from theoretical (thawed at room temperature)
	  • Low QC (fortified with 200 mg/mL DCDS4501S and 0.00 nM MMAE): 41.1%
	  • Low QC (fortified with 200 mg/mL DCDS4501S and 0.200 nM MMAE): 22.4%
	  • High QC (fortified with 200 mg/mL DCDS4501S and 19.0 nM MMAE): 0.815%
	
	Based on the freeze/thaw stability results of MMAE alone and in the presence of DCDS4501S, the method's thawing conditions will be updated from thawing at room temperature to thawing on ice.
		Yes
		
		Yes

Long-term storage	(b) (4)
	MMAE in neat plasma, at low and high QC levels, is stable at -20°C up to 117 days and at -70°C for up to 679 days
	• % Difference from theoretical (-20°C)
	  • Low QC: -0.6%
	  • High QC: -4.6%
	• % Bias (-70°C)
	  • Low QC: 8.6%
	  • High QC: 7.9%
	(b) (4)
	MMAE in neat plasma, at low and high QC levels, is stable at -80°C for up to 1132 days
	• % Difference from theoretical
	  • Low QC: 12.2%
	  • High QC: 6.76%
	MMAE in neat plasma, at over-the-curve-level QC sample, is stable at -80°C for up to 1340 days
	• % Difference from theoretical
	  • Over-the-curve-level QC, after 10´ dilution: 5.99%
		Yes
		
		Yes
		
		Yes
		
		Yes

	MMAE stability, in frozen matrix, in the presence of DCDS4501S was evaluated by analyzing a set of ADC-only QCs and a set of low- and high-level QCs fortified with both DCDS4501S and MMAE that had been stored for 8 days at -80°C (STABC) versus freshly prepared calibration standards
	• % Difference from theoretical (thawed at room temperature)
	  • Low QC (fortified with 200 mg/mL DCDS4501S and 0.00 nM MMAE): 3.46%
	  • Low QC (fortified with 200 mg/mL DCDS4501S and 0.200 nM MMAE): 2.84%
	  • High QC (fortified with 200 mg/mL DCDS4501S and 19.0 nM MMAE): 0.142%
	Additional MMAE stability in frozen matrix was evaluated by analyzing low- and high-level QC samples (thawed at room temperature) fortified with both DCDS4501A and MMAE that had been stored for 42, 43, 180, and 181 days at -80°C versus freshly prepared calibration standards
	• % Difference from theoretical (42 days)
	  • Low QC: 3.68%
	  • High QC: 0.634%
	• % Difference from theoretical (43 days)
	  • Low QC: 9.16%
	  • High QC: 2.77%
	• % Difference from theoretical (180 days)
	  • Low QC: -2.72%
	  • High QC: -1.95%
	• % Difference from theoretical (181 days)
	  • Low QC: 3.66%
	  • High QC: 1.20%
		Yes
		
		Yes
		
		Yes
		
		Yes

Carry over	(b) (4) Carryover was evaluated in each accuracy and precision run by injecting a control blank after at least one of the highest calibration standards. Carryover is considered acceptable if no peaks greater than 20% of the peak area from the lowest acceptable LLOQ standard are detected in the control blank samples at the retention time of the analyte. The carryover was acceptable because neither analyte nor IS peaks were observed in the carryover blanks in any of the validation runs. The results were not reported in the assay validation report, but the raw data are available. (b) (4) Carryover was evaluated by injecting duplicate extracted matrix blanks immediately after the ULOQ calibration standards. Carryover was observed in the early runs; however, it was reduced to less than 20% of the mean LLOQ response in later runs, after it was discovered that a faulty injection syringe was the root cause of the high carryover. There were contributions from chromatographic peaks, at the expected retention time of the analyte in the blank samples, greater than 20% of the mean analyte response for the LLOQ calibration. To minimize the impact of potential carryover, study samples should be analyzed in pharmacokinetic order, can be batched based on timepoint, or if C_{max} timepoints (high-concentration samples) are injected prior to predose or	Yes Yes

	elimination timepoints (low-concentration samples), two matrix blanks should be injected after the high-concentration samples	
Method performance in study GO39942 GO39942 Determination of unconjugated MMAE in Human Plasma by HPLC with MS/MS Detection for Protocol Number GO39942		
Assay passing rate	17/18 runs (94.4%) acceptable	Yes
Standard curve performance	• Cumulative Bias Range: -1.2 to 1.7% • Cumulative Precision: 4.0 to 8.0% CV	Yes
QC performance	• Cumulative Bias Range: -0.1 to 2.6% • Cumulative Precision: 5.1 to 9.9% CV	Yes
Method reproducibility	Incurred sample reanalysis was performed in 11.0% of study samples and 67.8% of samples met the pre-specified criteria	Yes
Study sample analysis/ stability	The maximum number of days between date of sample collection to the last analysis date was 1144 days. All samples were analyzed within the 1340 days of demonstrated long-term storage stability in human plasma containing lithium heparin at -60 to -80°C	

Source: Table 2 in Applicant's 11 August 2022 response to 04 August 2022 information request

Table 39: Summary Method Performance of a Bioanalytical Method to Measure Polatuzumab Vedotin Total Antibody in Human Serum

Bioanalytical method validation report name, amendments, and hyperlinks	The Validation History of the Method for the Determination of Polatuzumab Vedotin Total Antibody in Human Serum (Report P201) Consists of the following reports: BA.MET.CD79.011.AVR_0 Assay Validation Report CD79.011.AVR_1 Assay Validation Report ICD 569 Project RCOI2 Validation Report ICD 569 Project RCOI4 Validation Report Addendum 1 ICD 569 Project RC0I6 Validation Report Addendum 2 ICD 569 Project RCOI7 Validation Report Addendum 3 ICD 569 Project RCOI9 and RCOI10 Validation Report Addendum 4 CD79.011.CVR_0
Method description	The method for the quantitation of the total concentration of polatuzumab vedotin in human serum samples by ELISA was developed and validated at Genentech, Inc. (San Francisco, CA) by 25 April 2013 and partially validated at (b) (4) by 2 April 2015, and later cross validated at (b) (4) by 21 October 2019. The method for the determination of polatuzumab vedotin total antibody (fully conjugated, partially deconjugated, and fully deconjugated anti-CD79b antibodies) in human serum was an indirect sandwich ELISA. Microtiter plates were coated with an anti-complementarity determining region specific monoclonal antibody against anti-CD79b antibody to capture polatuzumab vedotin total antibody. Diluted standards, controls, and samples were added to the plate and incubated. Horseradish peroxidase (HRP) conjugated to an anti-framework monoclonal antibody (10C4.1) was added and incubated for detection. Tetramethyl benzidine peroxidase was added for color development, and the reaction was stopped with 1 M phosphoric acid. The plates were read at 450 nm for detection absorbance and 630/620 nm for reference absorbance. The absorbance is proportional to the amount of polatuzumab vedotin total antibody present in the sample. The lower limit of quantitation is 50 ng/mL

Materials used for calibration curve & concentration	20.0, 10.0, 5.00, 2.50, 1.25, 0.625, 0.313, and 0.156 ng/mL • Polatuzumab Vedotin Reference Material, Genentech, Lot 79bvcMMAE809-2 at 10.3 mg/mL; Stock I at 100 mg/mL Polatuzumab Vedotin Reference Material, Genentech, Lot 608785 at 19.7 mg/mL; Stock I at 100 mg/mL		
Validated assay range	Lower Limit of Quantitation (LLOQ) to Upper Limit of Quantitation (ULOQ) range is 0.500 to 15.0 ng/mL prior to dilution correction		
Material used for QCs & concentration	50.0 (LLOQ), 100 (Low QC), 400 (Middle [Mid] QC), 1000 (High QC), and 1500 ng/mL (ULOQ) • Polatuzumab Vedotin Reference Material, Genentech, Lot 79bvcMMAE809-2 at 10.3 mg/mL Polatuzumab Vedotin Reference Material, Genentech, Lot 608785 at 19.7 mg/mL		
Minimum required dilutions (MRDs)	1/100		
Source & lot of reagents (LBA)	Naïve Normal Human Serum (NHS) Matrix Pool: (b) (4) Lot (b) (4) (Progeny 100100) and (b) (4) (Progeny ID 105267) Coat Antibody Source: Anti-complementarity determining region (CDR) mouse monoclonal antibody (MAb) to Anti-CD79b antibody; Genentech; Cell Line: 3A10.2, MAb ID 7953 and 7955; Lots: 70309-08 at 1 mg/mL in phosphate-buffered saline (PBS) and luanp-07Jul14-4 at 0.470 mg/mL in PBS; Stock I lot at 200 mg/mL in PBS Horseradish peroxidase (HRP) Conjugate: HRP conjugated to Anti-framework mouse MAb ID 10C4.1; Lots: 72879-01 and marstera-09Apr14-1 at 0.5 mg/mL in PBS/0.5% bovine serum albumin (BSA)/0.05% polysorbate 20/0.05% ProClin 300, pH 7.4 ± 0.1		
Regression model & weighting	4-parameter logistic fit, curve-weighting factor of 1		
Validation parameters	**Method validation summary**		**Acceptability**
Standard calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	8	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-1.60% to 2.54%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	0.406% to 5.36%	Yes
QCs performance during accuracy & precision	**Cumulative accuracy (%bias) in 5 QCs** QCs 1-5 for polatuzumab vedotin total antibody	Genentech: -1% to 9% (b) (4) -6.62% to 4.17%	Yes
	Inter-batch %CV QCs 1-5 for polatuzumab vedotin total antibody	Genentech: 3% to 8% (b) (4) 3.41% to 9.69%	Yes
	Total Error (TE) QCs 1-5 for polatuzumab vedotin total antibody	Genentech: 5% to 19% (b) (4) 6.02% to 16.3%	Yes
Selectivity & matrix effect	5 individual human serum lots from patients with each of the following disease states: Non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukemia (CLL) Range of observed bias not calculated, recovery shown instead • 5/5 NHL lots fortified with polatuzumab vedotin at		

	80 ng/mL; % recovery range: 97% to 116% • 5/5 NHL lots fortified at 1000 ng/mL (High QC); recovery range: 97% to 100% • 5/5 NHL lots unfortified; 5/5 < LLOQ • 5/5 CLL lots fortified with polatuzumab vedotin at 80 ng/mL; % recovery range: 99% to 104% • 5/5 CLL lots fortified at 1000 ng/mL; % recovery range: 96% to 101% • 5/5 CLL lots unfortified; 5/5 < LLOQ 10 individual human serum lots from patients with NHL • 10/10 NHL lots fortified with polatuzumab vedotin at 100 ng/mL (Low QC); bias range: -10.9% to 0.565% • 10/10 NHL lots fortified with polatuzumab vedotin at 1000 ng/mL (High QC); bias range: -10.2% to 15.0% • 10/10 NHL lots unfortified; 10/10 < LLOQ	Yes Yes
Interference & specificity	Rituximab: (range of observed bias not calculated, recovery shown instead) • 1 pooled normal human serum (NHS) lot with rituximab at 50, 100, and 500 mg/mL and polatuzumab vedotin at 0 ng/mL; no cross-reactivity observed. • 1 pooled NHS lot with rituximab at 50, 100, and 500 mg/mL and polatuzumab vedotin at 100 ng/mL (Low QC); recovery range is 97% to 103%; no interference • 1 pooled NHS lot with rituximab at 50 and 100 mg/mL and polatuzumab vedotin at 1000 ng/mL (High QC); recovery range is 97% to 99%; no interference • 1 pooled NHS lot with rituximab at 500 mg/mL and polatuzumab vedotin at 100,000 ng/mL; recovery was 103%; no interference Obinutuzumab: (range of observed bias not calculated, recovery shown instead) • 1 pooled NHS lot with obinutuzumab at 100 and 800 mg/mL and polatuzumab vedotin at 0 ng/mL; no cross-reactivity observed • 1 pooled NHS lot with obinutuzumab at 100 and 800 mg/mL and polatuzumab vedotin at 100 ng/mL (Low QC); recovery range: 103% to 108%; no interference • 1 pooled NHS lot with obinutuzumab at 100 and 800 mg/mL and polatuzumab vedotin at 1000 ng/mL (High QC); recovery range: 79.8% to 105%, interference at only 100 mg/mL; obinutuzumab at 100 mg/mL repeated, recovery range: 93.1% to 105%; no interference Atezolizumab (MPDL3280A): • 1 pooled NHS lot with atezolizumab at 1.00 and 1000 mg/mL and polatuzumab vedotin at 0 ng/mL; no cross-reactivity observed • 1 pooled NHS lot with atezolizumab at 1.00 and 1000 mg/mL and polatuzumab vedotin at 100 ng/mL (Low QC); % bias range: -0.396% to 4.76%; no interference	Yes Yes Yes

	• 1 pooled NHS lot with atezolizumab at 1.00 and 1000 mg/mL and polatuzumab vedotin at 1000 ng/mL (High QC); % bias range: -3.11% to 3.95%; no interference Mosunetuzumab: • 1 pooled NHS lot with mosunetuzumab at 25.0, 1000, and 5000 ng/mL and polatuzumab vedotin at 0 ng/mL; no cross-reactivity observed • 1 pooled NHS lot with mosunetuzumab at 25.0, 1000, and 5000 ng/mL and polatuzumab vedotin at 100 ng/mL (Low QC); range of observed bias -12.6% to 3.29%; no interference • 1 pooled NHS lot with mosunetuzumab at 25.0, 1000, and 5000 ng/mL and polatuzumab vedotin at 1000 ng/mL (High QC); range of observed bias: -5.50% to 3.10%; no interference Tocilizumab: • 1 pooled NHS lot with 50.0 and 200 mg/mL tocilizumab and polatuzumab vedotin at 0 ng/mL; no cross-reactivity observed • 1 pooled NHS lot with 50.0 and 200 mg/mL tocilizumab and polatuzumab vedotin at 100 ng/mL (Low QC); range of observed bias: -5.66% to 2.12%; no interference • 1 pooled NHS lot with 50.0 and 200 mg/mL tocilizumab and polatuzumab vedotin at 1000 ng/mL (High QC); range of observed bias: 2.04% to 4.80%; no interference	Yes Yes
Hemolysis effect	1 pooled normal matrix lot tested at 2% and 10% hemolyzed serum. Range of observed bias not calculated, recovery shown instead. Low QC (100 ng/mL): 94% to 97%; no cross-reactivity or interference High QC (1000 ng/mL): 104% to 106% no cross-reactivity or interference	Yes
Lipemic effect	1 pooled normal matrix lot tested at a 150 and 500 mg/dL lipemic serum concentration. Range of observed bias not calculated, recovery shown instead. Low QC (100 ng/mL): 99% to 101%; no cross-reactivity or interference High QC (1000 ng/mL): 100% to 102%; no cross-reactivity or interference	Yes
Dilution linearity & hook effect	Highest concentration was 200 mg/mL of polatuzumab vedotin and unconjugated anti-CD79b antibody (MCDS4409A) with 8 dilution factors tested. Bias range for polatuzumab vedotin: -8% to 8% Bias range for unconjugated anti-CD79b antibody: 0% to 4% Hook effect not observed and accuracy/linearity was acceptable.	Yes
Bench-top/process stability	Only combined temperature and freeze/thaw stability testing was conducted. Analyte in neat serum with combined storage of 12 hours at room temperature, 96 hours at 2°C-8 C and through 5 freeze/thaw cycles at -60°C or below were stable Low, Mid, High QC % Recovery Range: 80%-87%	Yes

	Analyte in neat serum with combined storage of 27 hours at room temperature and through 7 freeze/thaw cycles at -80C were stable Low QC and High QC Bias Range: -5.70% to 0.171%.	
Freeze-Thaw stability	Analyte in neat serum stability stored through 5 and 7 freeze/thaw cycles. Testing was combined with room temperature testing. See Bench top/process stability.	Yes
Long-term storage	Analyte in neat serum at Low QC (100 ng/mL), Mid QC (400 ng/mL), High QC (1000 ng/mL), and at an ultra-high level (100 mg/mL) Stable at £ -60°C for 48 months; bias range: -13% to 17% Analyte in neat serum at stability was further evaluated by analyzing Low QC (100 ng/mL) and High QC (1000 ng/mL) at -25°C Stable at -25°C for 40 days, range of observed bias: -14.0% to -6.25%	Yes
Parallelism	See summary in Dilution linearity & hook effect	Yes
Carry over	Not applicable (NA)	Yes
Method performance in study GO39942 GO39942 Analysis of Samples Using an ELISA Method for the Quantitation of DCDS4501A in Human Serum		
Assay passing rate	81/95 runs (85.3%) acceptable	Yes
Standard curve performance	• Cumulative %Difference from Theoretical Range: -10.7 to 1.30% • Cumulative Precision: 0.599 to 24.3% CV	Yes
QC performance	• Cumulative %Difference from Theoretical Range: -2.16 to 1.27% • Cumulative Precision: 10.1 to 10.3% CV	Yes
Method reproducibility	Incurred sample reanalysis was performed in 4.93% of study samples and 85.0% of samples met the pre-specified criteria	Yes
Study sample analysis/ stability	All samples were analyzed within the 1470 days demonstrated long-term storage stability in human serum at -80 °C.	

Source: Table 3 in Applicant's 11 August 2022 response to 04 August 2022 information request

18.3.2. Population PK Analysis

18.3.2.1. Executive Summary

The FDA's Assessment:
The PPK model is acceptable for the purpose of predicting acMMAE and MMAE plasma exposure (C_{avg} and C_{trough}) in POLARIX subjects with previously untreated DLBCL.

No clinically significant differences in acMMAE or MMAE plasma exposure were identified according to body weight, sex, age, White or Asian racial category, mild hepatic impairment, or mild to moderate renal impairment (CrCl 30 to 89 mL/min). Also refer to Section 6.2.2.2 for summary of information on therapeutic individualization.

18.3.2.2. PPK Assessment Summary

The Applicant's Position:
The polatuzumab vedotin (pola) population PK (PopPK) analysis based on POLARIX study at one dose level of 1.8 mg/kg Q3W up to 6 cycles (N=429 for patients with PK data) is summarized below:
A two-analyte (acMMAE-MMAE) integrated PopPK analysis (Report 1090510) based on PK data from 460 NHL patients from Studies DCS4968g, GO27834, GO29044, and GO29365 (excluding Arm G and Arm H) was previously established to characterize the PK properties of acMMAE and unconjugated MMAE.

This previous legacy PopPK model was used to characterize pola PK for Arm A (pola+R-CHP) of POLARIX using an external validation approach.

The previously developed population PK model provides a good description of acMMAE and unconjugated MMAE concentrations following intravenous administration of pola in patients with DLBCL in POLARIX. The model is appropriate to be used for simulations and to evaluate the E-R relationships of pola in POLARIX study.

Following 1.8 mg/kg Q3W dosing, body weight, age, sex, race (Asian versus non-Asian), region (Asia country versus non-Asia country), renal function impairment (mild or moderate impairment), mild hepatic impairment, disease characteristics (bulky disease, Ann Arbor stage; IPI score, DLBCL subgroup, Double Expressor by IHC, LDH) were not associated with clinically relevant difference of acMMAE and unconjugated MMAE exposures. Patients with moderate hepatic impairment had similar acMMAE exposures to patients with normal hepatic function but moderately higher unconjugated MMAE exposures (46% higher for AUC and 35% for Cmax).

Less than 2% of patients had ADA positive status. The presence of ADAs did not seem to impact the key PK parameters and exposures for acMMAE and did not increase exposure to unconjugated MMAE.

General Information		
Objectives of PPK Analysis		• Characterize Polatuzumab vedotin's PK profile • Identify the source of PK variability to support individualized dosing • Predict individual exposure for E-R assessment
Study Included		GO39942 (POLARIX)
Dose(s) Included		1.8 mg/kg Q3W pola for 6 cycles concomitant with R-CHP regimen
Population Included		Previously untreated CD20-positive DLBCL
Population Characteristics (**Table 40, Table 41**)	General	Age median (range): 65 [19-80] yr, 51.7% subj ≥65 yr, 12.8% subj ≥75 yr) Weight median (range): 74.4 [38.4-228]kg Male: 233 (54.3%) Race: White: 228 (53.1%) Asian: 84 (19.6%) Unknown or Other: 117 (27.3%)
	Organ Impairment	Hepatic (Hepatic function was defined based on National Cancer Institute Organ Dysfunction Working Group Classification of Hepatic Dysfunction): normal hepatic function: 338 (78.8%) mild hepatic impairment: 79 (18.4%) moderate hepatic impairment: 9 (2.1%) severe hepatic impairment: 1 (0.2%) Renal (CrCL): normal renal function: 171 (39.9%) mild renal impairment: 200 (46.6%) moderate renal impairment: 54 (12.6%) severe renal impairment: 1 (0.2%)
	Pediatrics (if any)	NA
No. of Patients, PK Samples, and BLQ		The data from 429 patients who contributed 1122 acMMAE and 1175 unconjugated MMAE concentration values were included in the population

		PK analysis. Observations more than 6 weeks after the last dose were excluded from the population PK analysis: • 2 (<1%) acMMAE post-dose BQL observations with time after dose ≤6 weeks • 33 (<3%) post-dose unconjugated MMAE BQL observations with time after dose ≤ 6 weeks
Sampling Schedule	Rich Sampling	NA
	In ITT Population	At C1D1 pre-dose, only a serum PK sample for total antibody was taken, while at C1D1 30 minutes post-dose as well as C4D1 pre-dose and 30 minutes post-dose, PK samples were taken for measuring all the three pola analytes: total antibody (serum), acMMAE (plasma) and unconjugated MMAE (plasma). In addition, PK samples were taken at treatment completion or early treatment termination visit for the three analytes and at 3-month post-treatment follow-up visit for the total antibody only.
Covariates Evaluated	Static	No formal covariates analysis was performed for the external validation. Simulations from the final model were conducted to assess the impact of covariates on model projected acMMAE and unconjugated MMAE exposure for groups of patients of clinical interest. The exposure parameters used for this analysis are the simulated Cycle 6 AUC and Cmax of acMMAE and unconjugated MMAE based on Cycle 1 dose of each individual (i.e, 1.8 mg/kg), the Empirical Bayes Estimates (EBE) PK parameters of each individual without covariate adjustment to reference values, and a hypothetical Q3W dosing of 6 cycles. The following covariate categories were compared: age (≥65 vs. <65 years old), sex (males vs. females), race (Asian vs. non- Asian), region (Asian Country vs. non-Asian Country), hepatic impairment (mild, or moderate versus normal), renal impairment (mild, moderate, or severe versus normal), ECOG performance status (1 verus 0 and 2 versus 1), body weight (≥100 kg. vs. <100 kg), bulky tumor (bulky vs. not bulky), Ann Arbor stage at study entry (3-4-5 vs. 1-2), number of IPI score (3 vs. 1-2, and 4-5 vs. 1-2), Double expression by IHC (DEL vs. not DEL), cells of origins (GCB vs. ABC), NHL type (HGBL, NOS, DHL/THL or Other types vs. DLBCL NOS, ABS, GCB), LDH level at baseline (>ULN vs. ≤ULN), ADA status (ADA positive versus negative).
	Time-varying	NA

Final Model	Summary	Acceptability [FDA's comments]
Software and Version	• NONMEM software, Version 7.5.0 (ICON Development Solutions) • R, version 4.0.2 for Windows	The PPK model is generally acceptable for the purpose of predicting acMMAE and MMAE exposure in plasma in POLARIX subjects with previously untreated DLBCL.
Model Structure	A complex four-compartment model that consisted of the acMMAE model and the unconjugated MMAE model. The unconjugated MMAE model had parallel linear and Michaelis-Menten elimination and time-dependent relative conversion fraction from acMMAE to unconjugated MMAE	
Model Parameter Estimates	External validation was used. **Table 42, Table 43**, and **Table 44** summarize the model parameters estimates for the legacy model	Model parameter values were fixed to the final estimates in the legacy

Final Model	Summary	Acceptability [FDA's comments]
	(integrated model 201, Report 1090510). **Table 45** summarizes the shrinkage (integrated model 301)	model (i.e., integrated model 201) and parameters were not re-estimated using POLARIX data.
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	**Table 42, Table 43**, and **Table 44** provide RSE and IIV for the final model. **Table 45** summarizes the shrinkage. • Low shrinkage values (27.7% and 22.6% respectively) of the random effects on acMMAE time- independent clearance (η2) and central volume (η3) indicate that computation of the individual Cycle 6 acMMAE AUC and Cmax values is not shrinking toward the population mean and can be used for the exposure-response analysis. • Although shrinkage of the random effects on unconjugated MMAE model parameters is high, unconjugated MMAE exposure is mostly defined by the FRAC parameter, unconjugated MMAE central volume (for unconjugated MMAE Cmax value), and by the ratio of CLMMAE/FRAC (for unconjugated MMAE AUC value). Shrinkage of the FRAC parameter is low (19.3%), and unconjugated MMAE central volume does not have the random effect. The expected value of CLMMAE/FRAC variance is the sum of CLMMAE and FRAC variances estimated by the model (equal to 0.212) while the observed variance of the ratio is the variance of the difference η8-η7 (equal to 0.161). Due to the high correlation of the random effects on CLMMAE and FRAC, the resulting shrinkage of the ratio of CLMMAE/FRAC is low (13.0%). Thus, unconjugated MMAE AUC and Cmax values are not shrinking toward the population mean and can be used for the exposure-response analysis.	Shrinkage on variance parameters was larger with the POLARIX PPK data (i.e., model 301) compared to the PPK dataset used to develop the previous model 201 (**Table 45**). The IIV on peripheral clearance (Q), MMAE peripheral volume of distribution (V2,MMAE), and acMMAE peripheral volume of distribution (V2) had the largest shrinkage with the POLARIX PPK data (97.8%, 83.8%, and 74.6%, respectively).
BLQ for Parameter Accuracy	BLQ samples were excluded from the analysis, which should not have impact on analysis due to low percentage of BLQ samples (less than 1% acMMAE and less than 3% for unconjugated MMAE)	Handling of BLQ samples was generally acceptable.
GOF, VPC	**Figure 12** and **Figure 13** (GOF), **Figure 14** and **Figure 15** (VPC)	GOF and VPC plots indicate that the acMMAE PPK model adequately describes PK of plasma acMMAE up of concentrations of 700 ng/mL and that the MMAE PPK model adequately describes plasma MMAE over the observed concentration range. Due to the model's tendency to under-predict acMMAE concentrations above

Final Model	Summary	Acceptability [FDA's comments]
		roughly 700 ng/mL, acMMAE exposure metrics of Cavg and Ctrough are likely more accurate than Cmax.
Significant Covariates and Clinical Relevance	**Figure 16, Figure 17**	No clinically significant differences in acMMAE or MMAE plasma exposure were identified according to body weight (38 to 148 kg), sex, age (19 to 80 years), Asian or White racial category, mild hepatic impairment, or mild to moderate renal impairment (CrCl 30 to 89 mL/min). The effects of severe renal impairment (CLcr 15 to 29 mL/min), end-stage renal disease, and moderate or severe hepatic impairment (total bilirubin greater than 1.5 × ULN and any AST) on the PK of acMMAE and MMAE are not fully characterized. The incidence of ADA was low and the effects of ADA on PK, PD, safety, and effectiveness are unknown.
Analysis Based on Simulation (optional)	Simulations from the final model were conducted to assess the impact of covariates on model projected acMMAE and unconjugated MMAE exposure. Simulation of Cycle 6 exposures (AUC, Cmax) based on individual empirical Bayes estimates of PK parameters were performed. • Heavy patients (body weight ≥ 100 kg) had mildly higher acMMAE exposures (14% for AUC, 18% for Cmax) and higher unconjugated MMAE exposures (54% for AUC and 48% for Cmax). Age, sex, race (Asian versus non-Asian), region (Asian country versus non-Asian country), renal function impairment (mild or moderate impairment), ECOG performance status, disease characteristics (bulky disease, Ann Arbor stage; IPI score, DLBCL subgroup, Double Expressor by IHC, LDH) were not associated with clinically relevant difference of acMMAE and unconjugated MMAE exposures. • Patients with mild hepatic impairment had similar acMMAE exposures to patients with normal hepatic function but moderately higher unconjugated MMAE exposures (46% higher for AUC and 35% for Cmax). • ADA were detected in only 1.4% (6/429) PK evaluable patients. Simulation of Cycle 6 exposures (AUC, Cmax) based on individual empirical Bayes estimates of PK parameters were performed. There are no clinically relevant impacts of ADA status on acMMAE or unconjugated MMAE exposures, although it was observed that unconjugated MMAE exposures were lower (by 30-31%) in ADA positive patients.	

Labeling Language	Description	Acceptability [FDA's comments]
12.3 PK	The clinical pharmacology of pola has been well characterized in the initial BLA. Pola PK observed in POLARIX and Study GO29044 were comparable to previous monotherapy and combination studies. The legacy PopPK model successfully characterized pola PK in POLARIX. Therefore, there are no	The proposed labeling is acceptable upon the Applicant and FDA reaching agreements to the FDA-recommended revisions to the labeling. The plasma exposure of acMMAE and unconjugated MMAE increased proportionally over a polatuzumab vedotin-piiq dose range from 0.1 to 2.4 mg/kg (0.06 to 1.33 times the approved recommended dosage). Cycle 3 acMMAE AUC were predicted to increase by

Labeling Language	Description	Acceptability [FDA's comments]
	proposed updates in Section 12.3 PK except for the following (redlined): 1. Updated the age range based on new data from POLARIX and added clarification for MMAE source in patients with mild hepatic impairment under the Special Populations • (b) (4) 2. Updated the pola DDI risk with R- CHP under the Drug Interaction Studies • Rituximab, Cyclophosphamide, Doxorubicin, or Prednisone (R- CHP): No clinically significant differences in the pharmacokinetics of acMMAE or unconjugated MMAE when polatuzumab vedotin is used concomitantly with R-CHP.	approximately 30% over Cycle 1 AUC, and achieved more than 90% of the Cycle 6 AUC. Unconjugated MMAE plasma exposures were <3% of acMMAE exposures, and the AUC and C_{max} were predicted to decrease after repeated every-3-week dosing. Distribution The acMMAE central volume of distribution is 3.15 L. For humans, MMAE plasma protein binding is 71% to 77% and the blood-to-plasma ratio is 0.79 to 0.98, in vitro. Elimination At the end of Cycle 6, the median (min, max) acMMAE terminal half-life was 12.2 days (4.5 to 36.7 days) and the clearance was 0.9 L/day in patients with Bcell malignancies. The median (min, max) unconjugated MMAE terminal half-life was 3.74 days (1.58 to 10.1 days) days after the first polatuzumab vedotin-piiq dose. Metabolism Polatuzumab vedotin-piiq catabolism has not been studied in humans; however, it is expected to undergo catabolism to small peptides, amino acids, unconjugated MMAE, and unconjugated MMAE-related catabolites. MMAE is a substrate for CYP3A4. Specific Populations No clinically significant differences in the pharmacokinetics of acMMAE or unconjugated MMAE were observed based on age (19 to 89 years), sex (males vs. females), race (White 69%, Asian 11%), or mild to moderate renal impairment (CLcr 30 to 89 mL/min). The effect of severe renal impairment (CLcr 15 to 29 mL/min) or end-stage renal disease with or without dialysis on the pharmacokinetics of acMMAE or unconjugated MMAE is unknown. *Patients with Hepatic Impairment* Compared to patients with normal hepatic function, geometric mean MMAE exposure was 11% higher in patients with previously untreated DLBCL and mild hepatic impairment (total bilirubin 1 to 1.5 × ULN or AST > ULN) and 40% higher in patients with relapsed or refractory DLBCL and mild hepatic impairment. The effect of mild hepatic impairment on MMAE exposure is not expected to have a clinically significant impact. Mild hepatic impairment was not associated with a significant difference in acMMAE exposure.

Labeling Language	Description	Acceptability [FDA's comments]
		The effect of moderate to severe hepatic impairment (total bilirubin >1.5 × ULN and any AST) or liver transplantation on the PK of acMMAE or unconjugated MMAE is unknown.

Source: Applicant's 11 August 2022 response to 04 August 2022 information request

Table 40: Summary of Continuous Covariates

Covariate	Description	Mean (SD)	Median [Range]
BAGE	Age (years)	62.9 (11.4)	65 [19-80]
BWT	Weight (kg)	75.9 (20)	74.4 [38.4-228]
BBSA	Body Surface Area (m2)	1.86 (0.266)	1.85 [1.28-3.4]
BBMI	Body Mass Index(kg/m2)	26.7 (6)	26.2 [16.4-68.1]
BLBWT	Lean Body Weight (kg)	53.5 (10.7)	51.9 [31.5-87.5]
BHT	Height (cm)	168 (10.2)	168 [144-200]
BALBUM	Albumin (g/L)	36.8 (6.14)	37 [17.1-54.2]
BTPROT	Total Protein (g/L)	66.6 (8.09)	67.3 [39.4-85]
BALP	Alkaline Phosphatase (u/L)	122 (139)	87 [1.52-1960]
BALT	Alanine Amino-transferase (u/L)	26.7 (21.2)	21 [0.3-149]
BAST	Aspartate Amino-transferase (u/L)	28.6 (23.9)	23 [0.35-288]
BBILI	Bilirubin (umol/L)	9.69 (7.09)	8 [1.71-79]
HGB	Hemoglobin (g/L)	121 (19)	123 [65-170]
BLDH	Lactate Dehydrogenase (u/L)	425 (422)	297 [4.2-4820]
BSCR	Serum Creatinine (umol/L)	75.1 (22.5)	71 [35-200]
BCRCL	Creatinine Clearance (ml/min)	94.8 (38)	88.1 [29.3-441]
BBCC	Absolute B Cell Count (106/L)	263 (1100)	90.5 [0-19100]
Log BBCC	Log of BBCC (106/L)	4.41 (1.42)	4.51 [0-9.86]
BTMBD	Tumor SPD (mm2)	7420 (12900)	4690 [96-227000]

Source: PPK Assessment Table 1.1 in Applicant's 11 August 2022 response to 04 August 2022 information request

Table 41: Summary of Categorical Covariates

Covariate	Level	Number Percent)
Race (RACE)	White	228 (53.1%)
	Asian	84 (19.6%)
	Unknown or Other	117 (27.3%)
Gender (SEX)	Female	196 (45.7%)
	Male	233 (54.3%)
Region	West. Europe	159 (37.1%)
	East. Europe	46 (10.7%)
	South and Central America	6 (1.4%)
	North America	117 (27.3%)
	Asia	80 (18.6%)
	Pacific	21 (4.9%)
ECOG Performance Status (BECOG)	0	169 (39.4%)
	1	196 (45.7%)
	2	64 (14.9%)
Bulky Disease (BBULKY)	Absent	242 (56.4%)

Covariate	Level	Number Percent)
	Present	187 (43.6%)
Computed Hepatic Impairment (HEPA)	Missing	2 (0.5%)
	Normal	338 (78.8%)
	Mild	79 (18.4%)
	Moderate	9 (2.1%)
	Severe	1 (0.2%)
Renal Impairment (RENAL)	Missing	3 (0.7%)
	Normal	171 (39.9%)
	Mild	200 (46.6%)
	Moderate	54 (12.6%)
	Severe	1 (0.2%)
ADA Status (ATAP)	Missing	7 (1.6%)
	Present	6 (1.4%)
	Absent	416 (97%)
DLBCL Subgroup (ABCGCB)	ABC	99 (23.1%)
	GCB	180 (42%)
	Unclassified	44 (10.3%)
	Unknown	106 (24.7%)
Number of Risk Factors for IPI (BIPIN)	1	1 (0.2%)
	2	159 (37.1%)
	3	170 (39.6%)
	4	75 (17.5%)
	5	24 (5.6%)
NHL Subtype (NHL)	DLBCL NOS, ABC, GCB	363 (84.6%)
	HGBL, NOS, DHL/THL	42 (9.8%)
	Other Large B-cell	24 (5.6%)
LDH level (LDH)	>ULN	283 (66%)
	≤ ULN	143 (33.3%)
	missing	3 (0.7%)
Double Expressor by IHC (DEL)	DEL	135 (31.5%)
	No DEL	220 (51.3%)
	Unknown	74 (17.2%)
Ann Arbor Stage at Study Entry	1	2 (0.5%)
	2	43 (10%)
	3	120 (28%)
	4	264 (61.5%)

Source: PPK Assessment Table 1.2 in Applicant's 11 August 2022 response to 04 August 2022 information request

Table 42: Estimates of Structural Fixed-Effect Parameters, Integrated Model 201

Parameter		Description	Value	RSE%	95% CI
acMMAE parameters					
K_{des} (1/hr)	θ1	rate constant of CLt decrease	0.0046	7.95	0.00389 - 0.00532
CL_T (L/hr)	θ2	initial time-dependent CL	0.00623	19.6	0.00383 - 0.00862
CL_{INF} (L/hr)	θ3	non-specific linear clearance after repeated dosing	0.0344	3.6	0.032 - 0.0368
V_1 (L)	θ4	central volume	3.15	1.58	3.05 - 3.25
V_2 (L)	θ5	peripheral volume	3.98	2.92	3.75 - 4.2
Q (L/hr)	θ6	inter-compartment rate	0.0145	2.53	0.0138 - 0.0153

Parameter		Description	Value	RSE%	95% CI
V_{max} (ng/mL/hr)	θ7	maximum MM elimination	0.0203	14.3	0.0146 - 0.026
K_M (ng/mL)	θ8	MM constant	0.604	36.2	0.175 - 1.03
$CL_{INF,MAX}$	θ9	maximum effect of time on CLNS	0.223	8.6	0.185 - 0.261
T_{50} (month)	θ10	time of the half-effect of CLINF,MAX	3.53	6.77	3.07 - 4
γ	θ11	Sigmoidicity of CLNS(t) function	2.27	12.5	1.71 - 2.82
Unconjugated MMAE parameters					
V_{MMAE} (L)	θ12	unconjugated MMAE apparent central volume	82.2	8.15	69.1 - 95.4
CL_{MMAE} (L/hr)	θ13	unconjugated MMAE apparent clearance	1.89	8.14	1.59 - 2.2
Q_{MMAE} (L/hr)	θ14	unconjugated MMAE apparent inter-compartment clearance	36.3	12.3	27.5 - 45.1
$V_{2,MMAE}$ (L)	θ15	unconjugated MMAE apparent peripheral volume	200	6.13	176 - 224
$V_{MAX,MMAE}$ (ng/mL/hr)	θ16	maximum MM elimination	0.0307	9.17	0.0252 - 0.0362
K_{SS} (ng/mL)	θ17	MM constant	0.581	10.5	0.461 - 0.701
$FRAC_{CLT}$	θ18	factor for relative conversion fraction of CLt pathway	3.70	3.11	3.48 - 3.93
$FRAC_{MM}$	θ19	factor for relative conversion fraction of MM pathway	2.72	9.45	2.21 - 3.22
ALPH (1/month)	θ20	rate constant of FRACt decrease	0.167	38.5	0.0411 - 0.293
$FRAC_T$	θ21	initial time-dependent part of FRAC	0.139	21.0	0.0816 - 0.196

SE: Standard Error; PE: Parameter Estimate; RSE%: Relative Standard Error = 100·SE/PE; CI: confidence interval.
Source: PPK Assessment Table 2.1 in Applicant's 11 August 2022 response to 04 August 2022 information request

Table 43: Estimates of Covariate Fixed-Effect Parameters, Integrated Model 201

Parameter		Description	Value	RSE%	95% CI
Effect on acMMAE Model Parameters					
$CL_{INF,\ WT}$	θ_{22}	Weight effect on CL_{INF}	0.73	8.18	0.613 - 0.848
$V_{1,WT}$; $V_{2,WT}$; Q_{WT}	θ_{23}	Weight effect on V_1, V_2 and Q	0.50	6.24	0.439 - 0.561
$V_{1,\ males}$	θ_{24}	Male vs. female effect on V_1	1.20	1.83	1.16 - 1.24
$V_{1,\ ASIAN}$	θ_{25}	Asian race effect on V_1	0.929	4.18	0.852 - 1
$V_{1,\ NAIVE}$	θ_{26}	Treatment-naive effect on V_1	1.2	1.96	1.16 - 1.25
$CL_{INF,\ SEX}$	θ_{27}	Gender effect on CL_{INF}	1.1	2.66	1.04 - 1.15
$CL_{INF,\ ALBUM}$	θ_{28}	Albumin effect on CL_{INF}	-0.247	36.3	-0.423 - -0.0712
$CL_{INF,\ RTX,Ob}$	θ_{29}	Combination therapy effect on CL_{INF}	0.844	2.95	0.795 - 0.892
$CL_{INF,\ B\text{-}cells}$	θ_{30}	B-cell count effect on CL_{INF}	0.0212	17.9	0.0138 - 0.0286
$CL_{INF,TMBD}$	θ_{31}	Tumor SPD effect on CL_{INF}	0.0521	27.4	0.0241 - 0.0801
$k_{des,NAIVE}$	θ_{32}	Prior treatment effect on k_{des}	3.38	12.7	2.54 - 4.22
$K_{DES,RTX,Ob}$	θ_{33}	Combination therapy effect on k_{des}	0.932	11.2	0.727 - 1.14
$CL_{T,NAIVE}$	θ_{34}	Treatment-naive effect on CL_T	3.53	34.7	1.13 - 5.93
$CL_{T,TMBD}$	θ_{35}	Tumor SPD of 50% effect on CL_T	1150	46.0	114 - 2190
$CL_{T,Threshold}$	θ_{36}	Threshold of B-cells on CL_T	121	46.0	11.9 - 229
$CL_{T,B\text{-}cells}$	θ_{37}	B-cell count effect on CL_T	0.578	24.6	0.3 - 0.856
Effect on acMMAE-MMAE relative conversion fraction					
$FRAC_{WT}$	θ_{38}	Weight effect on FRAC	-0.467	23.1	-0.679 - -0.256
$FRAC_{SEX}$	θ_{39}	Gender effect on FRAC	0.911	4.72	0.827 - 0.995
$FRAC_{NAIVE}$	θ_{40}	Treatment-naive effect on FRAC	0.756	5.95	0.668 - 0.844

Parameter		Description	Value	RSE%	95% CI
$FRAC_{RTX,Ob}$	θ_{41}	Combination therapy effect on FRAC	0.709	5.54	0.632 - 0.786
$FRAC_{HEPA}$	θ_{42}	Hepatic Impairment on FRAC	1.19	5.58	1.06 - 1.32
$FRAC_{ECOG}$	θ_{43}	ECOG (=0) effect on FRAC	0.905	4.34	0.828 - 0.982
$FRAC_{ALB}$	θ_{44}	Albumin effect on FRAC	-0.613	23.2	-0.892- -0.334

SE: Standard Error; PE: Parameter Estimate; RSE%: Relative Standard Error = 100·SE/PE; 95% CI: 95% confidence interval.
Source: PPK Assessment Table 2.2 in Applicant's 11 August 2022 response to 04 August 2022 information request

Table 44: Estimates of Variance Parameters, Integrated Model 201

Parameter		Description	Value	RSE%	95% CI	CV	Shrinkage
$\omega 2_{CLT}$	Ω_{11}	Random effect on CL_T	1.89	9.96	1.52 - 2.26	1.38	17.4%
$\omega 2_{CLINF}$	Ω_{22}	Random effect on CL_{INF}	0.0376	6.83	0.0325 - 0.0426	0.194	8.1%
$\omega 2_{V1}$	Ω_{33}	Random effect on V_1	0.0151	9.98	0.0122 - 0.0181	0.123	11.8%
$\omega 2_{V2}$	Ω_{44}	Random effect on V_2	0.107	9.94	0.0859 - 0.127	0.327	21.6%
$\omega 2_{Q}$	Ω_{55}	Random effect on Q	0.0538	13.3	0.0398 - 0.0678	0.232	30.6%
$\omega 2_{VMAX}$	Ω_{66}	Random effect on V_{MAX}	0.462	19.8	0.283 - 0.641	0.679	33.4%
$\omega 2_{FRAC}$	Ω_{77}	Random effect on conversion fraction	0.0972	9.63	0.0788 - 0.115	0.312	11.1%
$\omega 2_{CLMMAE}$	Ω_{88}	Random effect on CL_{MMAE}	0.115	11.9	0.088 - 0.141	0.339	21.5%
$\omega 2_{V2,MMAE}$	Ω_{99}	Random effect on $V_{2,MMAE}$	0.0422	24.5	0.0219 - 0.0625	0.205	48.5%
$\omega 2_{\sigma acMMAE}$	$\Omega_{10,10}$	Random effect on σ_{acMMAE}	0.0521	9.08	0.0428 - 0.0614	0.228	-2.7%
R $\omega_{\sigma acMMAE}$ $\omega_{\sigma MMAE}$	$\Omega_{11,10}$	$\sigma_{acMMAE} - \sigma_{MMAE}$ Correlation	0.038	9.32	0.0311 - 0.045	0.806	-
$\omega 2_{\sigma MMAE}$	$\Omega_{11,11}$	Random effect on σ_{MMAE}	0.0427	12.2	0.0325 - 0.0529	0.207	0.1%
$\sigma 2_{acMMAE}$	Σ_{11}	Residual error for acMMAE	0.0254	4.1	0.0233 - 0.0274	0.159	9.2%
$\sigma 2_{MMAE}$	Σ_{22}	Residual error for unconjugated MMAE	0.0726	3.86	0.0671 - 0.0781	0.27	6.4%

ω^2 and σ^2: variances of inter-individual and residual variability, respectively, R: correlation coefficient, SE: standard error; PE: parameter estimate; RSE (%): relative standard error = 100·SE/PE; 95% CI: 95% confidence interval, CV: coefficient of variation.
Source: PPK Assessment Table 2.3 in Applicant's 11 August 2022 response to 04 August 2022 information request

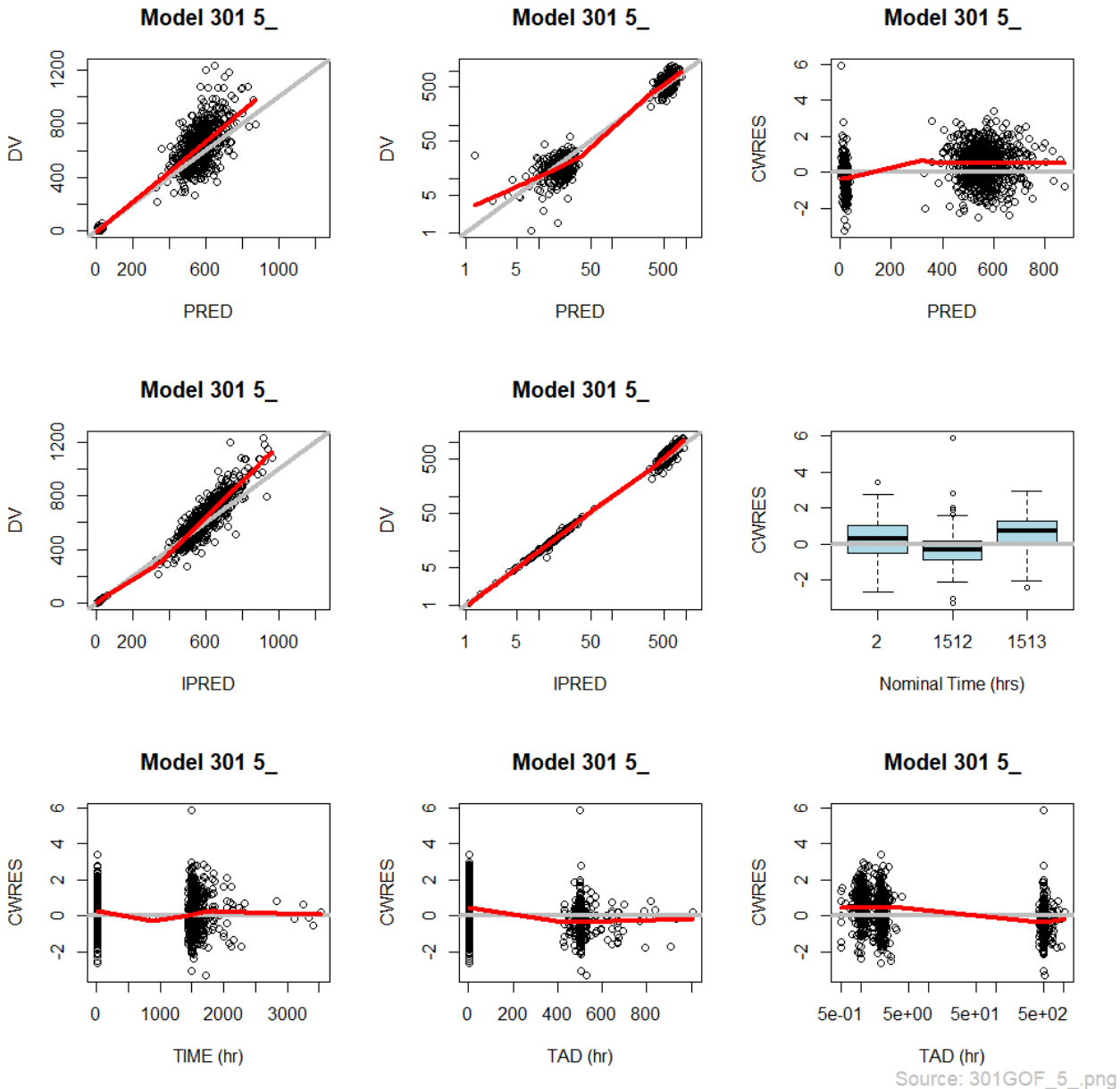
Table 45: Shrinkage of Variance Parameters, Integrated Model 301

Parameter		Description	Value	Shrinkage of Model 201	Shrinkage of Model 301
$\omega 2_{CLT}$	Ω_{11}	Random effect on CL_T	1.89	17.4%	43.5%
$\omega 2_{CLINF}$	Ω_{22}	Random effect on CL_{INF}	0.0376	8.1%	27.7%
$\omega 2_{V1}$	Ω_{33}	Random effect on V_1	0.0151	11.8%	22.6%
$\omega 2_{V2}$	Ω_{44}	Random effect on V_2	0.107	21.6%	74.6%
$\omega 2_{Q}$	Ω_{55}	Random effect on Q	0.0538	30.6%	79.8%
$\omega 2_{VMAX}$	Ω_{66}	Random effect on V_{MAX}	0.462	33.4%	66.6%
$\omega 2_{FRAC}$	Ω_{77}	Random effect on conversion fraction	0.0972	11.1%	19.3%
$\omega 2_{CLMMAE}$	Ω_{88}	Random effect on CL_{MMAE}	0.115	21.5%	51.4%
$\omega 2_{V2,MMAE}$	Ω_{99}	Random effect on $V_{2,MMAE}$	0.0422	48.5%	83.8%
$\omega 2_{\sigma acMMAE}$	$\Omega_{10,10}$	Random effect on σ_{acMMAE}	0.0521	-2.7%	63.2%
R $\omega_{\sigma acMMAE}$ $\omega_{\sigma MMAE}$	$\Omega_{11,10}$	$\sigma_{acMMAE} - \sigma_{MMAE}$ Correlation	0.038	-	-

Parameter		Description	Value	Shrinkage of Model 201	Shrinkage of Model 301
$\omega 2_{\sigma MMAE}$	$\Omega_{11,11}$	Random effect on σ_{MMAE}	0.0427	0.1%	65.3%
$\sigma 2_{acMMAE}$	Σ_{11}	Residual error for acMMAE	0.0254	9.2%	26.8%
$\sigma 2_{MMAE}$	Σ_{22}	Residual error for unconjugated MMAE	0.0726	6.4%	43.6%

ω^2 and σ^2: variances of inter-individual and residual variability, respectively, R: correlation coefficient, SE: standard error; PE: parameter estimate; RSE (%): relative standard error = 100·SE/PE; 95% CI: 95% confidence interval, CV: coefficient of variation.
Source: PPK Assessment Table 2.4 in Applicant's 11 August 2022 response to 04 August 2022 information request

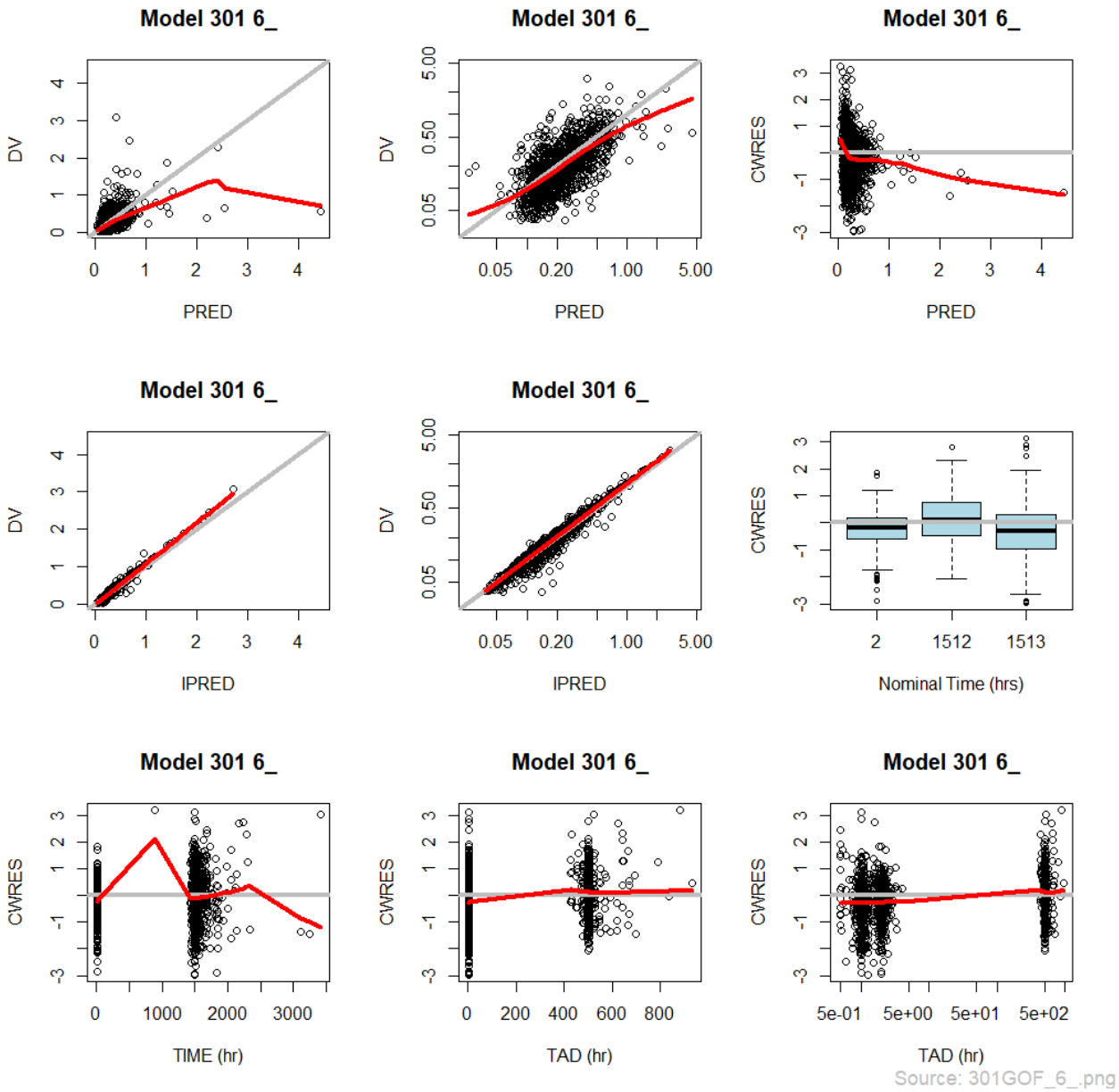
Figure 12: Goodness-of-Fit for Integrated Model 301: acMMAE



DV: Observed concentrations, PRED: population predictions of the model, IPRED: individual predictions of the model, CWRES: conditional weighted residuals, TIME: time after the first dose, TAD: time after most recent dose.

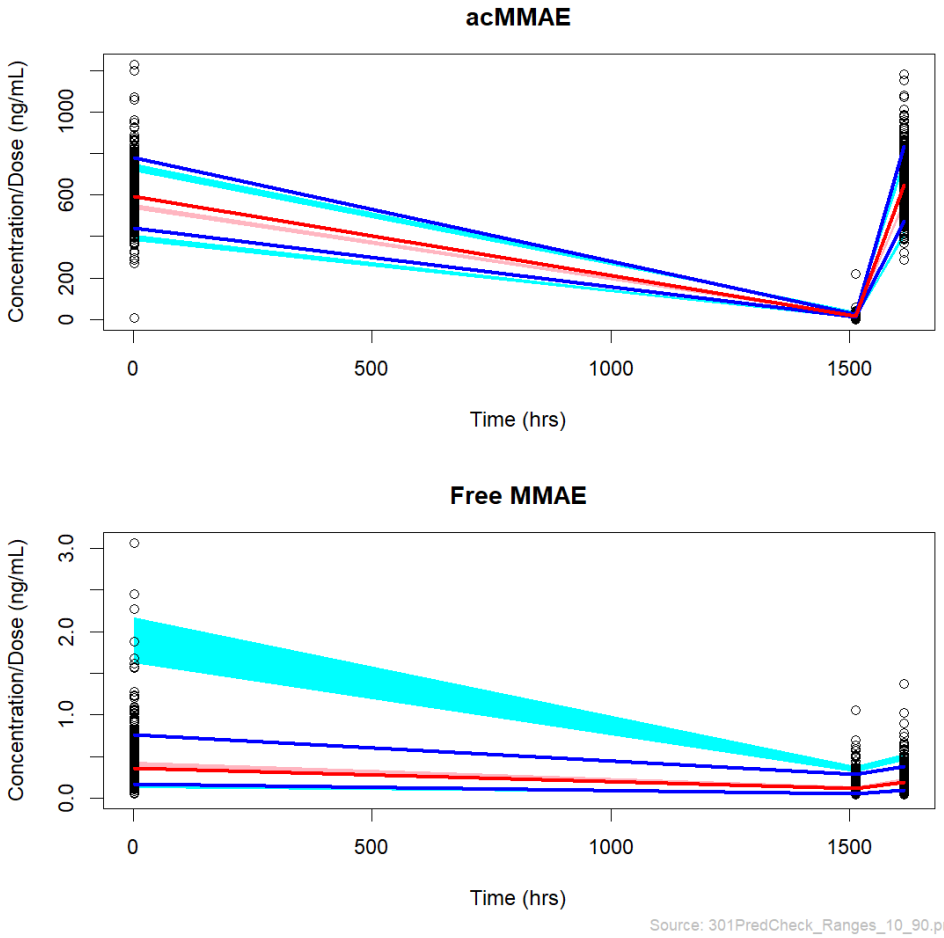
The gray solid y=x or y=0 lines are included for reference. The bold red lines are the lowess (local regression smoother) trend lines.
Source: PPK Assessment Figure 1.1 in Applicant's 11 August 2022 response to 04 August 2022 information request

Figure 13: Goodness- of-Fit for Integrated Model 301: Unconjugated MMAE



DV: Observed concentrations, PRED: population predictions of the model, IPRED: individual predictions of the model, CWRES: conditional weighted residuals, TIME: time after the first dose, TAD: time after most recent dose. The gray solid y=x or y=0 lines are included for reference. The bold red lines are the lowess (local regression smoother) trend lines.
Source: PPK Assessment Figure 1.2 in Applicant's 11 August 2022 response to 04 August 2022 information request

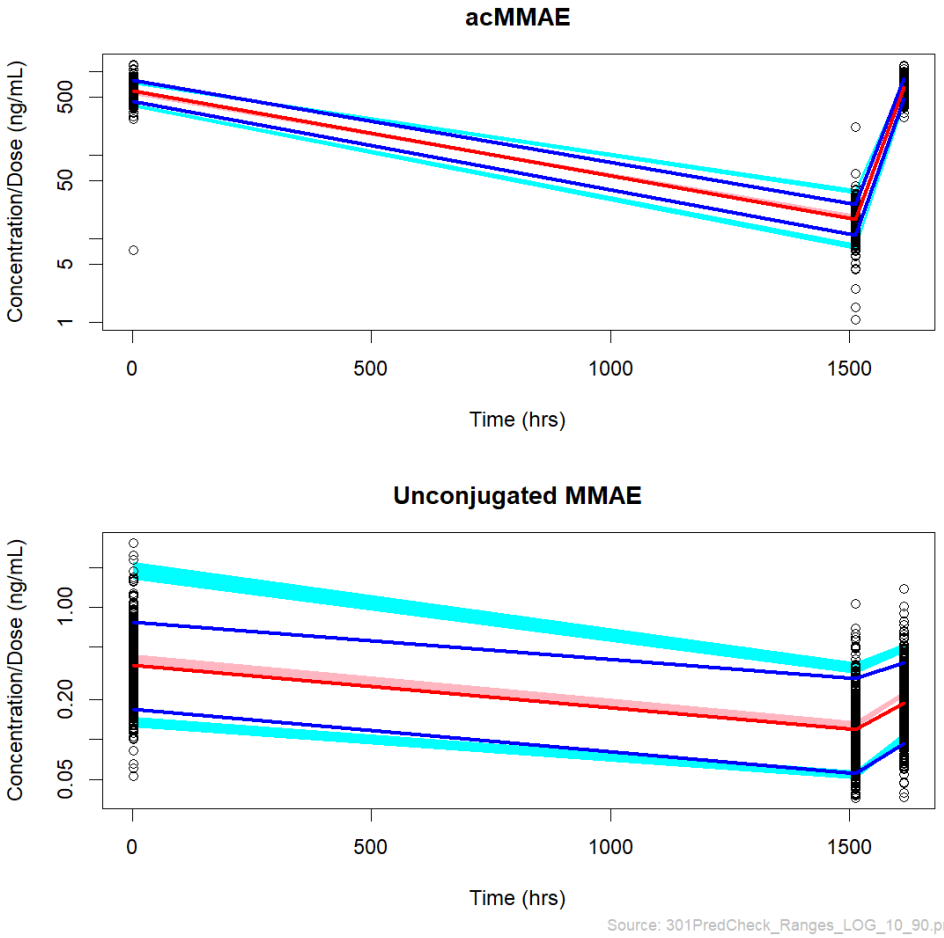
Figure 14: Visual Predictive Check for Integrated Model 301: Original Scale



Source: 301PredCheck_Ranges_10_90.png

Points are observed concentrations. The lines are median (red), and the 10th and 90th percentiles (blue) of the observed concentrations. The shaded regions show the 80% confidence intervals on the respective predicted percentiles obtained by simulations. The simulated values were computed from 500 trials with dosing, sampling, and the covariate values of the analysis dataset. Nominal time point of 1513 hours was shifted for better visibility.
Source: PPK Assessment Figure 2.1 in Applicant's 11 August 2022 response to 04 August 2022 information request

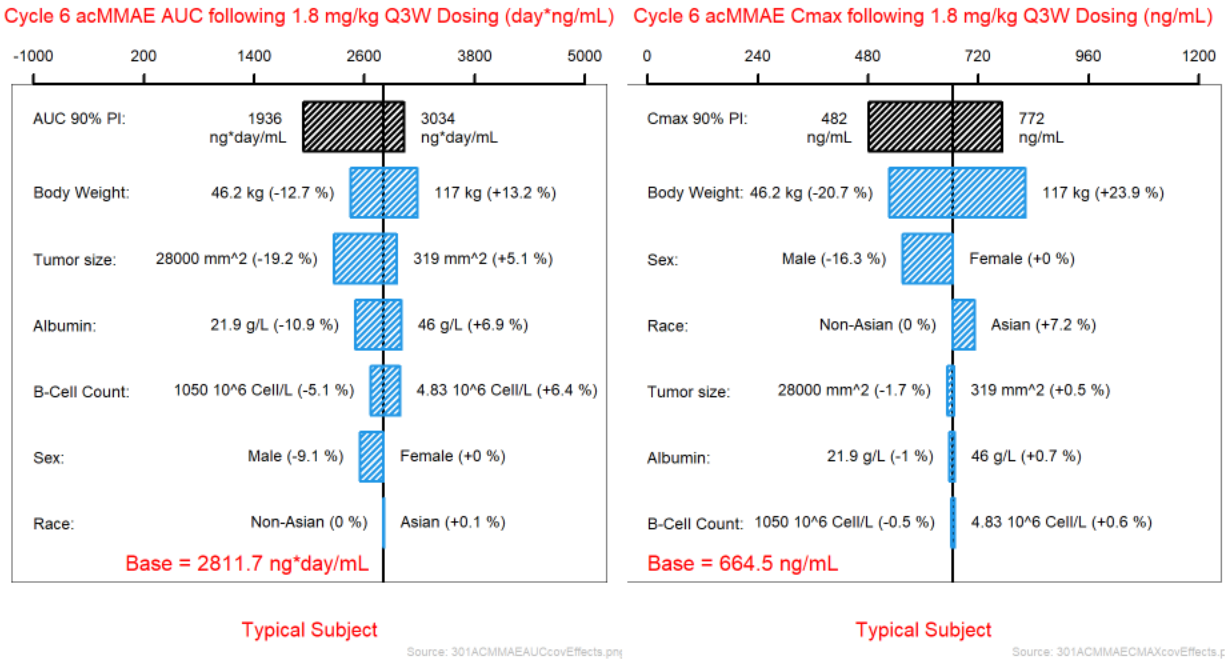
Figure 15: Visual Predictive Check for Integrated Model 301: Semi-log Scale



Source: 301PredCheck_Ranges_LOG_10_90.png

Points are observed concentrations. The lines show median (red), and the 10th and 90th percentiles (blue) of observed concentrations. The shaded regions show the 80% confidence intervals on the respective predicted percentiles obtained by simulations. The simulated values were computed from 500 trials with dosing, sampling, and the covariate values of the analysis dataset. Nominal time point of 1513 hours was shifted for better visibility. Source: PPK Assessment Figure 2.2 in Applicant's 11 August 2022 response to 04 August 2022 information request

Figure 16: Impact of Covariates on acMMAE AUC and Cmax in Cycle 6

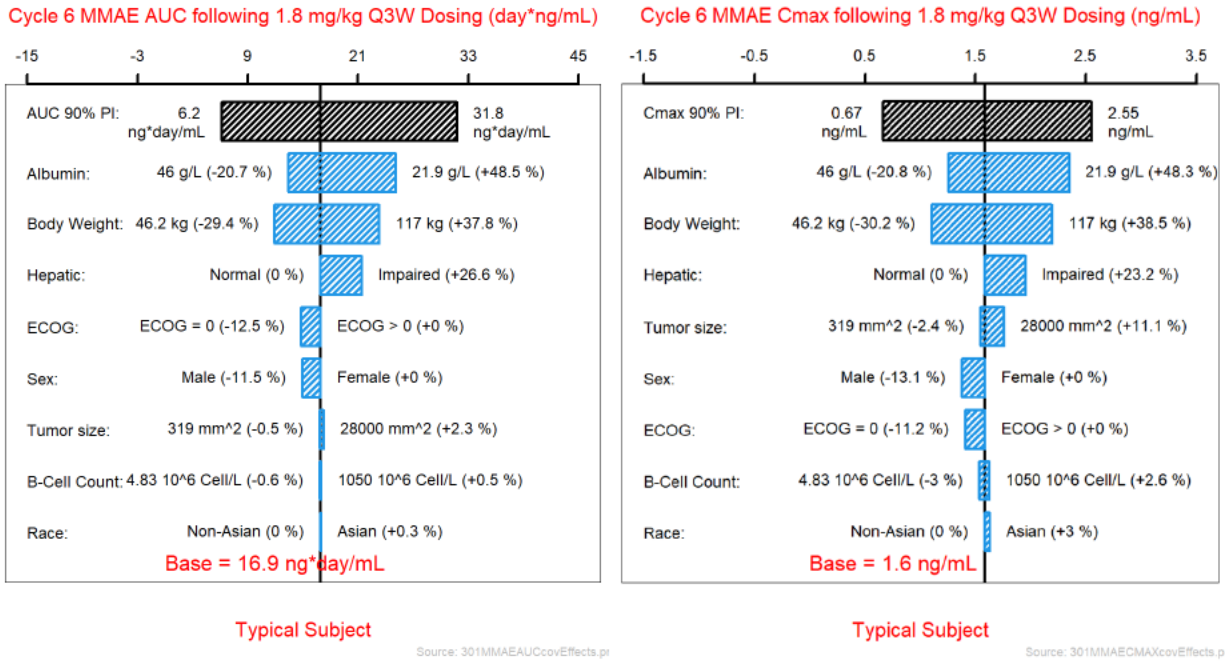


acMMAE = antibody-conjugated monomethyl auristatin E; AUC=area under the concentration-time curve; Cmax=maximum concentration; Q3W=every 3 weeks.

Note: Base, as represented by the black vertical line and red values, refers to the predicted Cycle 6 exposure (AUC and Cmax) of acMMAE in a typical patient. The black shaded bar with value at each end shows the minimum and maximum exposure range across the entire population based on individual predictions (IPRED). Each blue shaded bar represents the influence of a single covariate on the Cycle 6 exposure after repeated polatuzumab vedotin dose of 1.8 mg/kg q3w for 6 cycles. The label at left end of the bar represents the covariate being evaluated. For each covariate, if continuous, two subjects were generated with extreme covariate values (2.5th and 97.5th percentile); if categorical, one subject from each category was created, with other covariates fixed at reference value (continuous) or at reference category (categorical). The length of each bar describes the potential impact of that particular covariate on acMMAE exposure at Cycle 6, with the percentage value in the parentheses at each end representing the percent change of exposure from the base. The most influential covariate is at the top of the plot for each exposure parameter. Typical patient is a white male 1 L DLBCL patient receiving pola+R-CHP treatment with baseline body weight as 75 kg, baseline albumin as 35 g/L, baseline tumor size as 5000 mm^2, normal hepatic function and baseline ECOG as 1 and baseline B cell counts as 90X10^6 cell/L.

Source: PPK Assessment Figure 3.1 in Applicant's 11 August 2022 response to 04 August 2022 information request

Figure 17: Impact of Covariates on Unconjugated MMAE AUC and Cmax in Cycle 6



AUC= area under the concentration-time curve; Cmax=maximum concentration; ECOG = Eastern Cooperative Oncology Group; MMAE =monomethyl auristatin E;Q3W=every 3 weeks.
Note: Base, as represented by the black vertical line and red values, refers to the predicted Cycle 6 exposure of unconjugated MMAE in a typical patient. The black shaded bar with value at each end shows the minimum and maximum exposure range across the entire population based on IPRED. Each blue shaded bar represents the influence of a single covariate on the Cycle 6 exposure after repeated polatuzumab vedotin dose of 1.8 mg/kg Q3W for 6 cycles. The label at left end of the bar represents the covariate being evaluated. For each covariate, if continuous, two subjects were generated with extreme covariate values (2.5th and 97.5th percentile); if categorical, one subject from each category was created, with other covariates fixed at reference value (continuous) or at reference category (categorical). The length of each bar describes the potential impact of that particular covariate on unconjugated MMAE exposure at Cycle 6, with the percentage value in the parentheses at each end representing the percent change of exposure from the base. The most influential covariate is at the top of the plot for each exposure parameter. Typical patient is a white male 1 L DLBCL patient receiving pola+R-CHP treatment with baseline body weight as 75 kg, baseline albumin as 35 g/L, baseline tumor size as 5000 mm^2, normal hepatic function and baseline ECOG as 1 and baseline B cell counts as 90 x 10^6 cell/L.
Source: PPK Assessment Figure 3.2 in Applicant's 11 August 2022 response to 04 August 2022 information request

The FDA's Assessment:

The Applicant's previously developed PPK model, which is referred to as integrated model 201, is described in **Table** 42, **Table** 43, and **Table** 44. The previous model 201 was submitted and reviewed under the original BLA 761121 for the proposed indication of R/R DLBCL (Reference ID: 4437531). The previous model 201 was developed using data from 460 subjects with NHL, which included 191 (42%) subjects with R/R DLBCL, 75 (16%) subjects with previously untreated DLBCL, 176 (38%) subjects with FL, 9 (2%) subjects with MCL, and 9 (2%) subjects with other NHL.

The structure and final estimates of the previous model 201 was used to describe PK in 429 POLARIX subjects with treatment-naïve DLBCL who received 1.8 mg/kg polatuzumab vedotin IV Q3W for 3 cycles in combination with R-CHP. Parameter values were not re-estimated using POLARIX data.

Shrinkage on variance parameters was larger with the POLARIX PPK data (i.e., model 301) compared to the original PPK dataset used to develop the previous model 201, as shown in **Table** 45. The inter-individual variability (IIV) on peripheral clearance (Q), MMAE peripheral volume of distribution (V2,MMAE), and acMMAE peripheral volume of distribution (V2) had the largest shrinkage with the POLARIX PPK data (97.8%, 83.8%, and 74.6%, respectively). The IIV on the maximum Michaelis Menten elimination (Vmax) also had relatively high shrinkage (66.6%).

The goodness-of-fit plots indicate that the structure and parameter values from the previous model 201 adequately described the PK of plasma MMAE over the range of observed MMAE concentrations (**Figure** 13). The PK for acMMAE concentrations up to roughly 700 ng/mL were adequately described, but the model under-estimated acMMAE concentrations above 700 ng/mL (**Figure** 12). The VPC for acMMAE also shows that the model tends to under-predict acMMAE concentrations (**Figure** 14).

The model's tendency to under-predict higher acMMAE concentrations in POLARIX may be due to worse fit with POLARIX data and lack of parameter re-estimation. As a result of the model's tendency to under-predict higher acMMAE concentrations, individual predicted maximum concentration (C_{max}) and exposure following high doses are likely less accurate than exposure metrics such as average concentration over the dosage interval (C_{avg}) following lower doses and trough concentration (C_{trough}).

Although individual predicted acMMAE exposures may be under-estimated by the model, the PPK model is adequate for the purpose of predicting acMMAE and MMAE exposure in plasma for use in E-R analyses.

Covariate Effects on Exposure
No clinically significant differences in acMMAE or MMAE plasma exposure were identified according to body weight (38.4 kg to 148.2 kg), sex, age (19 to 80 years), White (53.1%) or Asian (19.6%) racial category, mild hepatic impairment, or mild to moderate renal impairment (CrCl 30 to 89 mL/min). Following the proposed dosage of 1.8 mg/kg Q3W, lower body weight was associated with lower exposure of acMMAE and MMAE in plasma; however, current data suggest that differences in plasma exposure due to body weight do not have a significant impact on clinical safety or efficacy.

The effects of severe renal impairment (CLcr 15 to 29 mL/min), end-stage renal disease, and moderate or severe hepatic impairment (total bilirubin greater than 1.5 × ULN and any AST) on the PK and exposure of acMMAE and MMAE are not fully characterized. The incidence of treatment emergent anti-drug antibodies (ADA) was low and the effects of ADA on PK and exposure are unknown.

In POLARIX, PK data were available in 228 White subjects (53.1%), 102 subjects with unknown or unrecorded race (23.8%), 84 Asian subjects (19.6%), 8 Black or African American subjects (1.9%), 6 subjects who identified as "other" race (1.4%), and 1 American Indian or Alaska Native subject (0.2%). Therefore, data are inadequate to assess the impact of racial categories other than White or Asian on polatuzumab vedotin PK.

Model-predicted covariate effects on plasma acMMAE exposure are presented in **Figure** 16, while covariate effects on plasma MMAE exposure are presented in **Figure** 17**.**

Body Weight
Higher body weight was associated with higher acMMAE clearance and volume of distribution. The range of recorded baseline body weight was 38.4 kg to 227.9 kg (**Table** 40), which included an outlier patient with significantly higher recorded baseline body weight compared to other subjects. The baseline body weight range was 38.4 kg to 148.2 kg without this outlier subject. Following the proposed weight-based dosage of 1.8 mg/kg IV Q3W dosage, subjects with low body weight (46 kg) are predicted to have 13% lower Cycle 6 acMMAE AUC and 21% lower Cycle 6 acMMAE C_{max} compared to subjects with typical body weight (75 kg). Subjects with high body weight (117 kg) are predicted to have 13% higher Cycle 6 acMMAE AUC and 24% higher Cycle 6 acMMAE C_{max} compared to subjects weighing 75 kg. The difference in acMMAE exposure according to body weight is not large and therefore not expected to have a clinically relevant impact on outcomes.

In addition to the effects of body weight on acMMAE parameters, higher body weight was associated with a lower fraction of acMMAE converted to MMAE in plasma. The effects of weight on acMMAE clearance still led to higher plasma MMAE exposure in subjects with higher body weight. Following the proposed weight-based dosage of 1.8 mg/kg IV Q3W dosage, subjects with low body weight (46 kg) are predicted to have 29% lower Cycle 6 MMAE AUC and 30% lower Cycle 6 MMAE C_{max} compared to subjects with typical body weight (75 kg). Subjects with high body weight (117 kg) are predicted to have 38% higher Cycle 6 MMAE AUC and 39% higher Cycle 6 MMAE C_{max} compared to subjects weighing 75 kg.

There were no clear trends between lower body weight quartile and CR rate, OS, or PFS, and the association between lower exposure and lower body weight is not expected to impact clinical efficacy outcomes. The proposed weight-based polatuzumab vedotin dosage of 1.8 mg/kg is acceptable for subjects with previously untreated DLBCL across all body weights.

18.3.3. Exposure-Response Analysis

18.3.3.1. E-R Efficacy Executive Summary

The FDA's Assessment:
Higher acMMAE exposure was associated with better progression-free survival (PFS) in POLARIX, but no E-R associations were identified with overall survival (OS) or complete response (CR) rate at end of treatment.

The E-R efficacy analysis did not identify any clinical pharmacology problems and generally supports the proposed dosage of 1.8 mg/kg polatuzumab vedotin IV Q3W for 6 cycles in combination with R-CHP in subjects with previously untreated DLBCL.

18.3.3.2. E-R Efficacy Assessment Summary

The Applicant's Position:
The exposure-efficacy analysis based on POLARIX study at one dose level of 1.8 mg/kg Q3W up to 6

cycles (N=429 for patients with PK data) is summarized below:

- The Cox analysis suggested a significant correlation (p = 0.01 by Cox regression) between acMMAE AUC and PFS, with higher exposure leading to a longer PFS. The forward inclusion identified baseline bulky disease and B cell count as significant covariates at α = 0.01 level. The E-R relationship remained significant in the presence of those covariates in the model. Only bulky disease remained in the final model at α = 0.001 level during the backward elimination.
- The Cox analysis suggested a significant correlation (p = 0.01 by Cox regression) between acMMAE AUC and EFS_{eff}, with higher exposure leading to a longer EFS_{eff}. The forward inclusion identified baseline bulky disease as a significant covariate at α = 0.01 level. The E-R relationship remained significant in the presence of this covariate in the model. Bulky disease remained in the final model at α = 0.001 level during the backward elimination.
- The Cox analysis suggested no significant correlation between acMMAE AUC and interim OS.
- Probability of CR at the EOT did not correlate with acMMAE exposure (AUC).

General Information		
Goal of ER analysis		The objectives of the E-R analysis were to assess the relationship of acMMAE exposures with efficacy and safety in POLARIX and to assess the relationship of unconjugated MMAE exposures with safety in POLARIX, to support the proposed dosing regimen for the label.
Study Included		GO39942 (POLARIX)
Endpoint		Primary: Progression-free survival as determined by the investigator (PFS); Secondary: • Event-free survival for efficacy reasons as determined by the investigator (EFSeff); • Complete response at end of treatment by FDG- PET as determined by blinded independent central review (CREOT); • Overall survival (OS).
No. of Patients (total, and with individual PK)		429 (all 429 patients have observed individual PK data and were included in the population PK analysis)
Population Characteristics (Table 46)	General	Age median (range): 65 [19-80] yr Weight median (range): 74.4 [38.4-228]kg Male: 233 (54.3%) Race: White: 228 (53.1%) Asian: 84 (19.6%) Unknown or Other: 117 (27.3%)
	Pediatrics (if any)	NA
Dose(s) Included		1.8 mg/kg Q3W pola for 6 cycles concomitant with R- CHP regimen
Exposure Metrics Explored (range)		simulated Cycle 6 AUC of acMMAE based on Cycle 1 dose of each individual (i.e, 1.8 mg/kg), the Empirical Bayes Estimates (EBE) PK parameters of each individual without covariate adjustment to reference values, and a hypothetical Q3W dosing of 6 cycles: • Range [1690, 4510] (ng/mL*day)
Covariates Evaluated		• Demographics: body weight, sex, age, race, region; • Baseline Laboratory Measurements: lactate dehydrogenase (LDH), serum albumin, B-cell (CD19) count, neutrophil-to-lymphocyte ratio (NLR), neutrophil count, hemoglobin level (HGB), platelet count; • Baseline disease characteristics and history: ECOG performance

	status, bulky disease, tumor SPD, Ann Arbor stage, NHL subtype, DLBCL cell origin, International prognostic index (IPI) score, double-expressor by IHC status, extra nodal involvement, active peripheral neuropathy status, baseline peripheral neuropathy active status; • Anti-drug antibody (ADA) status for pola • The following covariates were included only in the exposure-efficacy analyses as they were not expected to affect safety: B-cell (CD19) count, NLR, tumor SPD, Ann Arbor stage (stage 1-2 vs. stage 3 vs. stage 4-5), DLBCL cell origin (ABC vs. GCB vs. unclassified or unknown), double- expressor by IHC status (DEL vs. no DEL), IPI score (IPI 1-2 vs. 3 vs. 4-5), and bulky disease (yes versus no).

Final Model Parameters	Summary	Acceptability [FDA's comments]
Model Structure	1. Logistic regression models of CREOT probability versus exposure. 2. KM plots and Cox proportional hazard models of PFS, EFSeff, and interim OS versus exposure	Although the E-R efficacy analysis was limited by the lack of data from doses other than 1.8 mg/kg, higher acMMAE Cycle 6 AUC was appeared to be associated with better PFS in subjects with previously untreated LBCL. No clear E-R associations were identified with CR rate or OS.
Model Parameter Estimates	**Table 48, Table 49, Table 50, Table 51** (for primary and major secondary endpoints)	
Model Evaluation	NA	
Covariates and Clinical Relevance	• In the Cox analysis of PFS and EFSeff, bulky disease was identified as a significant covariate on the top of positive relationship between Cycle 6 acMMAE AUC and PFS and EFSeff • Covariate analysis did not identify any significant covariates affecting the probability of other efficacy endpoint	Bulky disease at baseline was associated with worse PFS and lower probability of CR. After accounting for the impact of bulky disease, the impact of acMMAE Cycle 6 AUC on PFS remained significant.
Simulation for Specific Population	NA	N/A
Visualization of E-R relationships	**Figure 18** through **Figure 26** (**Table 47** is baseline demographics stratified by acMMAE cycle 6 AUC median and Tertiles)	Kaplan-Meier plots comparing acMMAE Cycle 6 AUC quartile versus PFS and OS are displayed in **Figure 25** and **Figure 26**, respectively.
Overall Clinical Relevance for ER	E-R analyses further support the recommended 1.8 mg/kg Q3W of pola for 6 cycles in combination with R-CHP. The E-R analysis based on POLARIX study suggested that a higher pola exposure may be associated with a higher incidence of some safety endpoints (e.g., Grade ≥ 2 peripheral neuropathy, Grade ≥ 3 anemia and Grade ≥ 3	The E-R efficacy analysis generally supports the proposed dosage of 1.8 mg/kg in subjects with previously untreated DLBCL.

	thrombocytopenia) and a lower pola exposure may be associated with lower efficacy on PFS and EFSeff. Pola dose modifications due to AE were not correlated with acMMAE or unconjugated MMAE exposures. Dose intensity for pola, rituximab, doxorubicin, and cyclophosphamide was correlated with pola exposure, but not considered clinically relevant given the overall high dose intensity observed for these components in POLARIX. Therefore, a positive benefit-risk profile with highly favorable efficacy was achieved with a manageable safety profile at the recommended 1.8 mg/kg Q3W of pola in combination with R-CHP.	E-R safety analysis is discussed in Section 18.3.3.4.
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	No new information is currently proposed	Lower acMMAE exposure (i.e., AUC) was associated with lower efficacy in patients with relapsed or refractory DLBCL.

Table 46: Summary of Continuous Covariates at Baseline and Exposure Measures

Covariate (units) (Variable Name)	Mean (SD)	Median (range)
Weight (kg) (BWT)	75.8 (20)	74.2 [38.4-228]
Age (years) (BAGE)	62.9 (11.4)	65 [19-80]
Lactate Dehydrogenase (u/L) (BLDH)	424 (421)	297 [4.2-4820]
Albumin (g/L) (BALBUM)	36.8 (6.07)	37 [17.1-54.2]
Hemoglobin (g/L) (BHGB)	121 (19)	123 [65-170]
Platelet count (10^9/L)	286 (121)	259 [25-881]
Neutrophil count (10^9/L)	6.07 (3.39)	5.3 [0.46-25.4]
B-Cell Count (10^9/L)	242 (1030)	90.5 [0-19100]
Log of B-Cell Count (10^9/L)	4.42 (1.33)	4.51 [0-9.86]
Neutrophil-to-lymphocyte ratio (NLR)	6.78 (8.12)	4.26 [0.311-84.7]
Tumor size (mm2)	7420 (12800)	4680 [96-227000]
acMMAE Cycle 6 AUC (ng/mL*day)	2550 (361)	2530 [1690-4510]
acMMAE Cycle 6 Cmax (ng/mL)	636 (96)	632 [419-1010]
Unconjugated MMAE Cycle 6 AUC (ng/mL*day)	15.5 (8.18)	13.7 [4.13-72.4]
Unconjugated MMAE Cycle 6 Cmax (ng/mL)	1.45 (0.63)	1.32 [0.442-5.41]

Missing values were replaced by the medians of non-missing values.
Source: E-R Efficacy Table 1.1 in Applicant's 11 August 2022 response to 04 August 2022 information request

Table 47: Mean (SD) of Continuous Covariates at Baseline and Exposure Measures by Median and Tertile of acMMAE AUC

	Groups by Median		Groups by Tertile		
	Below	Above	First	Second	Third
Number of Patients	214	215	143	141	145
acMMAE Cycle 6 AUC (ng/mL*day)	2270 (189)	2830 (268)	2180 (159)	2530 (81.6)	2940 (265)

	Groups by Median		Groups by Tertile		
	Below	**Above**	**First**	**Second**	**Third**
acMMAE Cycle 6 Cmax (ng/mL)	589 (72.5)	682 (94)	574 (65.1)	629 (76.7)	703 (95.9)
Unconjugated MMAE Cycle 6 AUC (ng/mL*day)	14 (7.33)	17.1 (8.7)	14 (7.59)	15.1 (7.06)	17.4 (9.37)
Unconjugated MMAE Cycle 6 Cmax (ng/mL)	1.36 (0.595)	1.55 (0.649)	1.37 (0.622)	1.43 (0.563)	1.56 (0.685)

Source: E-R Efficacy Assessment Table 2.1 in Applicant's 11 August 2022 response to 04 August 2022 information request

Table 48: Summary of the Results for Exposure-Efficacy Analysis: Base Models

Endpoint	Analysis Type	N Evaluable	N (%) with Event	p-value
PFS	Cox PH model	429	105 (24.5%)	0.011
EFSeff		429	110 (25.6%)	0.010
OS		429	51 (11.9%)	0.117
CREOT	Logistic regression	429	339 (79%)	0.149

CREOT= complete response at the end of treatment; EFSeff= event-free survival for efficacy reasons; OS= overall survival; PFS= progression-free survival. The p-values presented in all the models were nominal and not adjusted for multiple multiplicity Shaded cells show analyses with p-value ≤ 0.05
Source: E-R Efficacy Table 3.1 in Applicant's 11 August 2022 response to 04 August 2022 information request

Table 49: Final PFS Survival Model

Parameters	**β**	**SE**	**RSE (%)**	**HR**	**HR95CI**	**p-value**
Slope of acMMAE AUC, $(ng/mL*day)^{-1}$	-0.00073	0.000297	40.44	0.9993	0.9987-0.9998	0.013
Bulky disease	0.6327	0.1977	31.24	1.883	1.278-2.774	0.001

β = estimate for exposure parameter(s); SE = standard error of β estimate; RSE = relative standard error of β estimate (%); HR = hazard ratio computed as exp(β); HR95CI = 95% confidence intervals on hazard ratio.
Source: E-R Efficacy Table 3.2 in Applicant's 11 August 2022 response to 04 August 2022 information request

Table 50: Full EFSeff Survival Model

Parameters	**β**	**SE**	**RSE (%)**	**HR**	**HR95CI**	**p-value**
Slope of acMMAE AUC, $(ng/mL*day)^{-1}$	-0.00072	0.000288	39.93	0.9993	0.9987-0.9998	0.012
Bulky disease	0.6821	0.1938	28.41	1.978	1.353-2.892	<0.0005

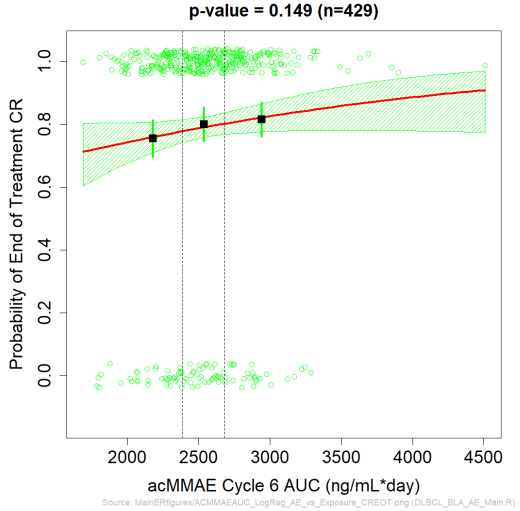
Note: Full model is the final model
β = estimate for exposure parameter(s); SE = standard error of β estimate; RSE = relative standard error of β estimate (%); HR = hazard ratio computed as exp(β); HR95CI = 95% confidence intervals on hazard ratio.
Source: E-R Efficacy Table 3.3 in Applicant's 11 August 2022 response to 04 August 2022 information request

Table 51: Logistic Regression Model for CREOT

Endpoint	**Coefficient**	**SE**	**RSE**	**P95CI**	**P-value**	**Parameter**
CREOT	0.07061	0.8725	1235.6	-1.639; 1.781		Intercept
Bulky disease	0.000496	0.000344	69.34	-0.0001779; 0.001169	0.149	Exposure, $(ng/mL*day)^{-1}$

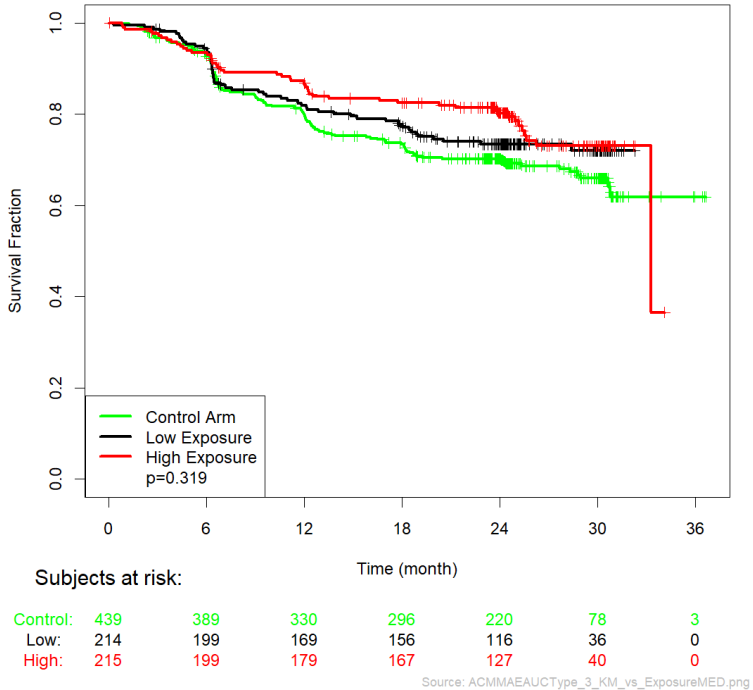
Source: E-R Efficacy Table 3.4 in Applicant's 11 August 2022 response to 04 August 2022 information request

Figure 18: Logistic Regression of acMMAE AUC and Complete Response at the End of Treatment Based on POLARIX Study



ac = antibody conjugated; AUC=area under the concentration−time curve; CR= complete response; MMAE=monomethyl auristatin E.
The red solid line and green shaded area represent the logistic regression model prediction and 90% confidence interval of predictions. Points show exposure of individual patients with events (p=1) and without events (p=0). Black squares and vertical green lines show observed fraction of subjects with events in each exposure group and 90% confidence interval for these fractions. Dashed vertical lines show bounds of exposure groups.
Source: E-R Efficacy Figure 1.1 in Applicant's 11 August 2022 response to 04 August 2022 information request

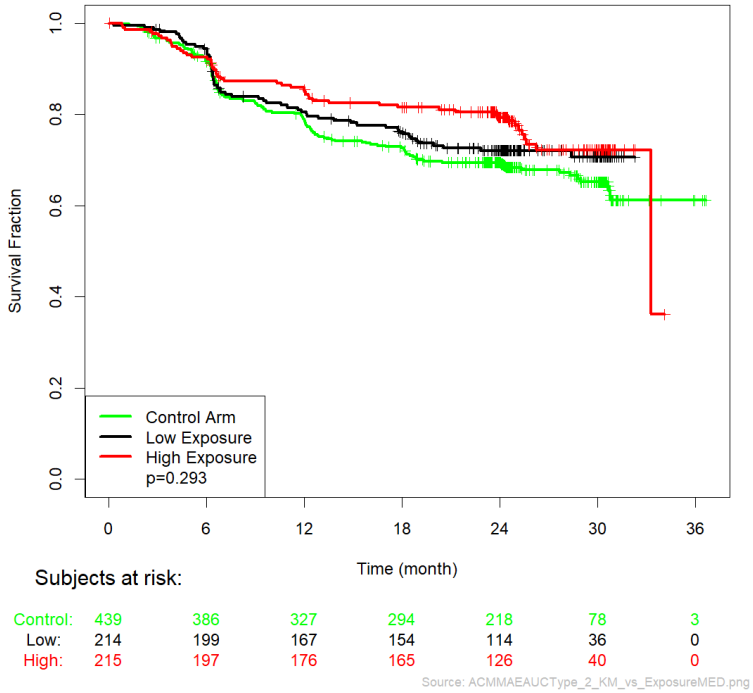
Figure 19: Kaplan-Meier Plot of Time to Progression (PFS), Halves of acMMAE AUC



ac = antibody conjugated; AUC=area under the concentration−time curve; MMAE=monomethyl auristatin E.
Note: Low exposure: ≤median, High exposure > median. P-value: p-value of the log-rank test comparing patients with low and high exposure. Event-free survival: progression free survival.

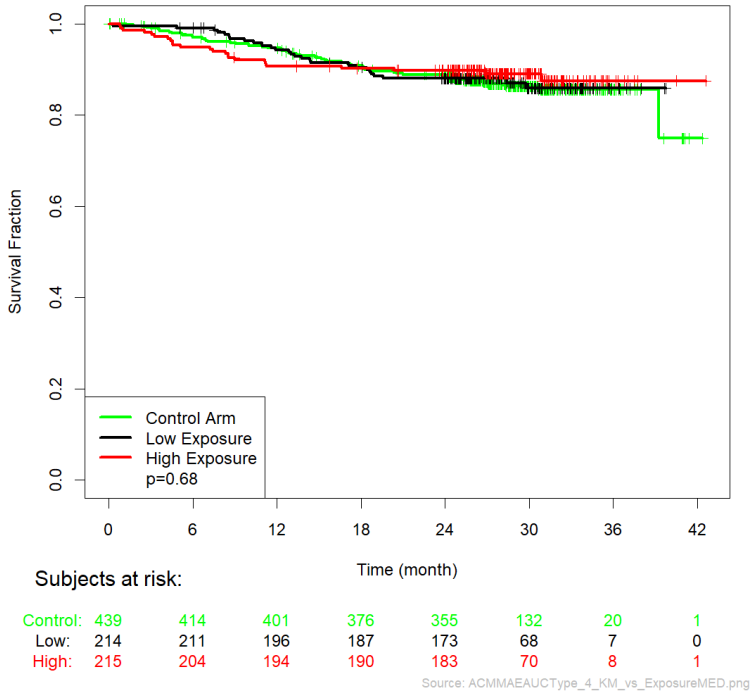
Source: E-R Efficacy Figure 1.2 in Applicant's 11 August 2022 response to 04 August 2022 information request

Figure 20: Kaplan-Meier Plot of Time to Event for Efficacy Reasons (EFSeff): Halves of acMMAE AUC



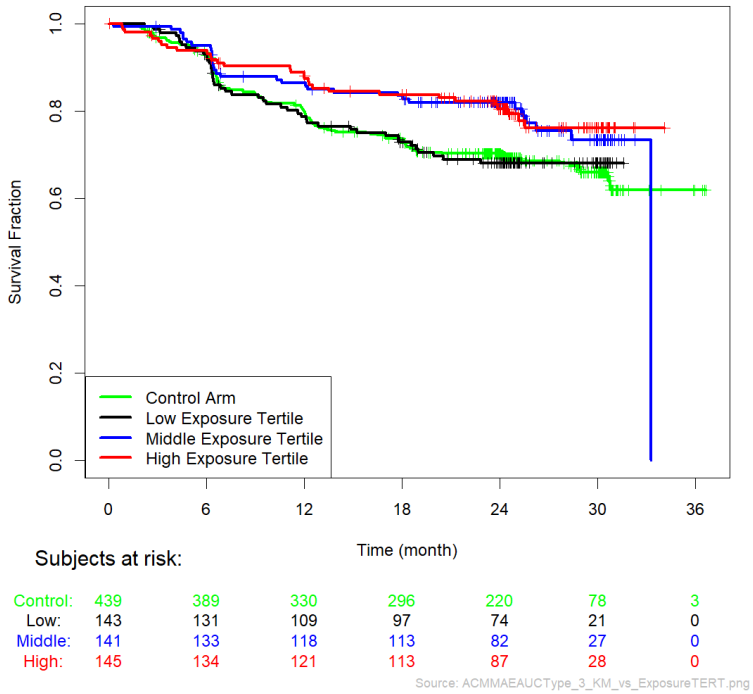
ac = antibody conjugated; AUC=area under the concentration−time curve; MMAE=monomethyl auristatin E; Note: Low exposure: ≤ median, High exposure > median. P-value: p-value of the log-rank test comparing patients with low and high exposure. Event-free survival: event-free survival for efficacy reasons.
Source: E-R Efficacy Figure 1.3 in Applicant's 11 August 2022 response to 04 August 2022 information request

Figure 21: Kaplan-Meier Plot of Time to Death (OS), Halves of acMMAE AUC



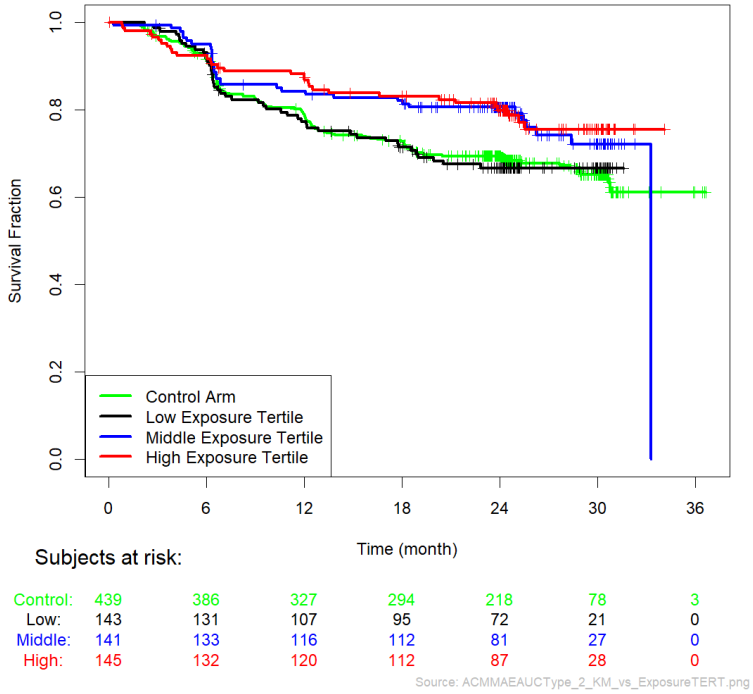
Source: E-R Efficacy Figure 1.4 in Applicant's 11 August 2022 response to 04 August 2022 information request

Figure 22: Kaplan-Meier Plot of Time to Progression (PFS), Tertiles of acMMAE AUC



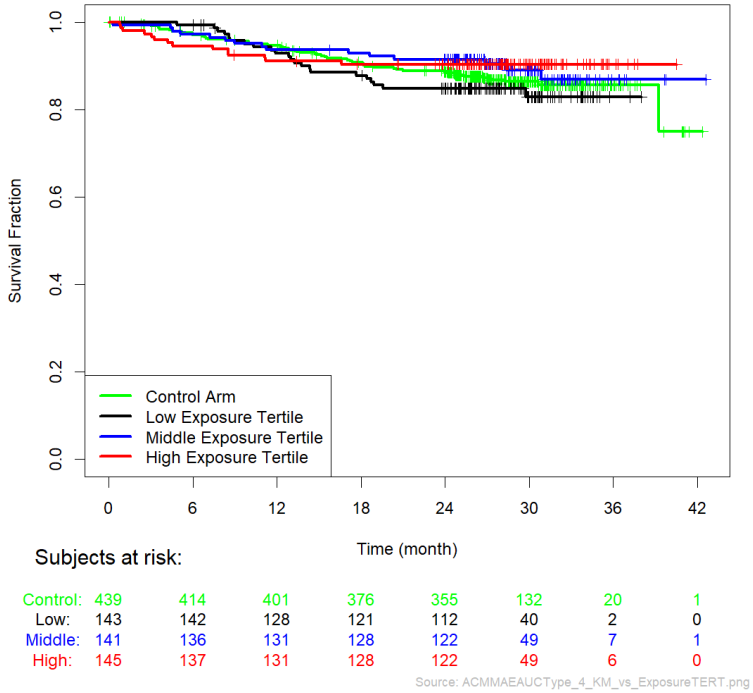
Source: E-R Efficacy Figure 1.5 in Applicant's 11 August 2022 response to 04 August 2022 information request

Figure 23: Kaplan-Meier Plot of Time to Event for Efficacy Reasons (EFSeff): Tertiles of acMMAE AUC



Source: E-R Efficacy Figure 1.6 in Applicant's 11 August 2022 response to 04 August 2022 information request

Figure 24: Kaplan-Meier Plot of Time to Death (OS), Tertiles of acMMAE AUC



Source: E-R Efficacy Figure 1.7 in Applicant's 11 August 2022 response to 04 August 2022 information request

The FDA's Assessment:

Although the E-R efficacy analysis was limited by the lack of data from doses other than 1.8 mg/kg, higher acMMAE Cycle 6 AUC was appeared to be associated with better PFS in subjects with previously untreated LBCL.

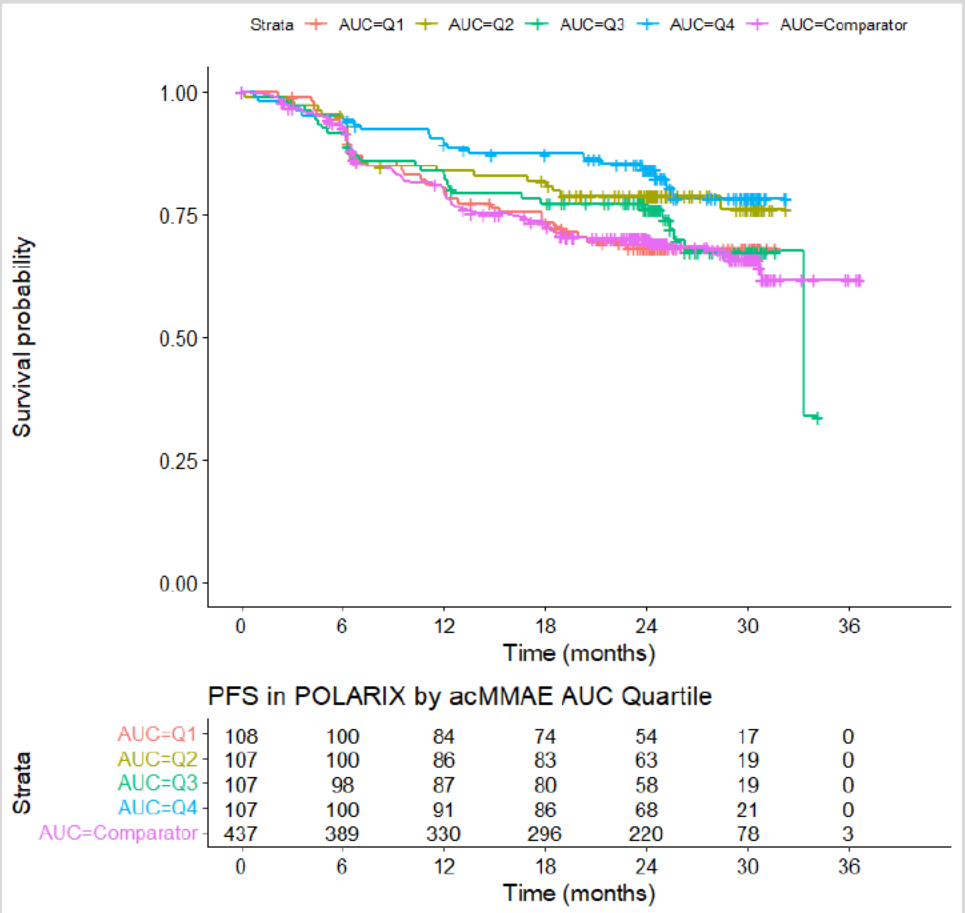
Higher Cycle 6 acMMAE AUC was generally associated with better PFS in POLARIX, which is demonstrated in **Figure** 25. After accounting for the statistically significant association between worse PFS and presence of bulky disease at baseline, the association between better PFS and higher acMMAE AUC remained statistically significant (**Table** 49).

No clear association was identified between acMMAE AUC and rate of CR at end of treatment based on univariate logistic regression (**Figure** 18) and multivariate logistic regression. Although CR rate had no clear association with acMMAE exposure, bulky disease at baseline was associated with lower rates of CR at the end of treatment (**Table** 51).

No clear association was identified between acMMAE Cycle 6 AUC and overall survival (OS), which may due to the relatively low number of OS events at the E-R efficacy data cut-off (clinical cut off 28 June 2021 and PK cut off of 16 March 2021). **Table** 48 describes the E-R analysis of OS based on Cox proportional hazard modeling and **Figure** 26 displays observed OS by acMMAE AUC quartile.

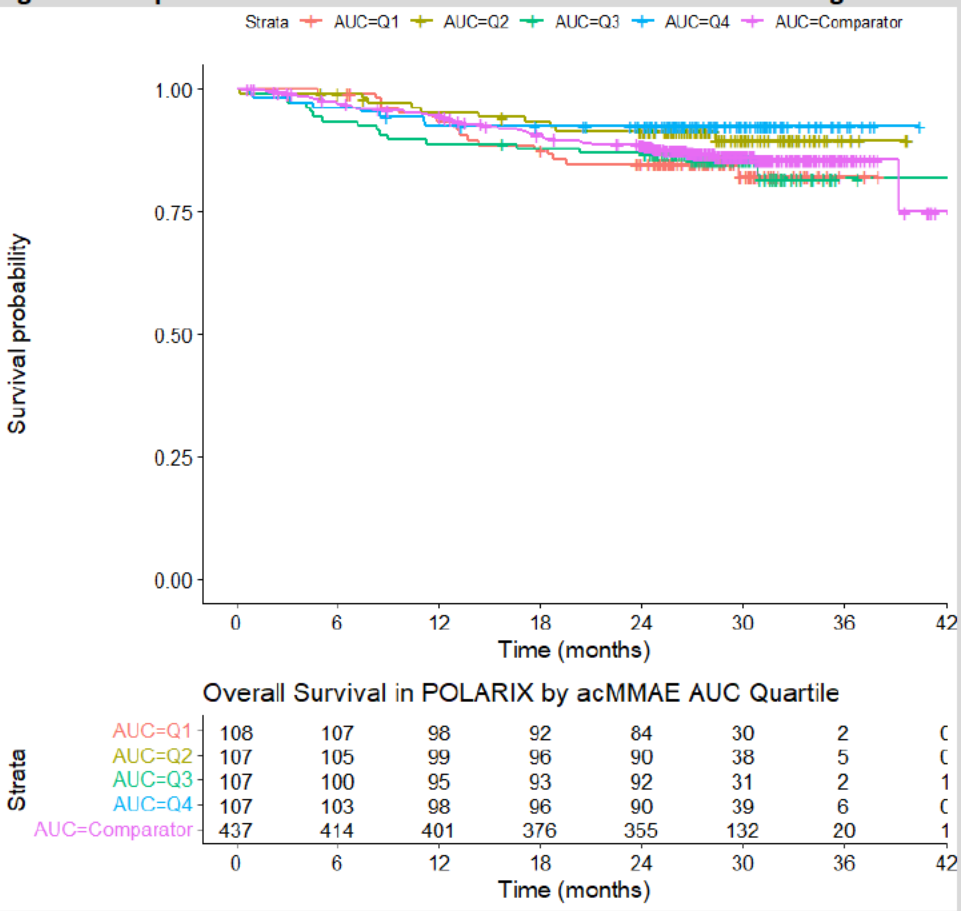
E-R efficacy analysis of plasma MMAE exposure was not conducted because MMAE is the toxic payload released by polatuzumab vedotin intracellularly to inhibit cell division and induce apoptosis, and therefore plasma MMAE is not expected to contribute to efficacy.

Figure 25: Kaplan-Meier Plot of Progression-Free Survival in POLARIX According to acMMAE AUC Quartile



AUC was calculated as the Cycle 6 AUC following 1.8 mg/kg polatuzumab vedotin IV Q3W in the POLA+R-CHP arm of POLARIX. Dashed lines = 95% confidence interval for each stratum. Comparator arm = R-CHOP.
acMMAE = antibody-conjugated monomethyl auristatin E; AUC = area under the concentration-versus-time curve; PFS = progression-free survival; Q=quartile; Q1 = 1st quartile (i.e., lowest exposure quartile).
Source: Reviewer's analysis

Figure 26: Kaplan-Meier Plot of Overall Survival in POLARIX According to acMMAE AUC Quartile



AUC was calculated as the Cycle 6 AUC following 1.8 mg/kg polatuzumab vedotin IV Q3W in the POLA+R-CHP arm of POLARIX. Dashed lines = 95% confidence interval for each stratum. Comparator arm = R-CHOP.
acMMAE = antibody-conjugated monomethyl auristatin E; AUC = area under the concentration-versus-time curve; Q=quartile; Q1 = 1st quartile (i.e., lowest exposure quartile).
Source: Reviewer's analysis

18.3.3.3. E-R Safety Executive Summary

The FDA's Assessment:

E-R safety analysis did not identify any safety concerns with the proposed 1.8 mg/kg dosage.

Higher Cycle 6 AUC and Cycle 6 C_{max} were associated with increased rates of multiple TEAEs of interest, including Grade ≥2 peripheral neuropathy, Grade ≥3 anemia, and Grade ≥3 thrombocytopenia. MMAE exposure in plasma generally had stronger E-R safety associations and a greater number of identified E-R safety compared to acMMAE exposure in plasma, which is consistent with the mechanism of action of polatuzumab vedotin.

18.3.3.4. E-R Safety Assessment Summary

The Applicant's Position:

The exposure-safety analysis based on POLARIX study at one dose level of 1.8 mg/kg Q3W up to 6

cycles (N=429 for patients with PK data) is summarized below:

- Higher acMMAE exposures (AUC and Cmax) were significantly correlated with higher incidence of Grade ≥ 2 peripheral neuropathy, Grade ≥ 3 anemia (only AUC), and Grade ≥ 3 thrombocytopenia ($p < 0.05$). The covariate analyses were performed only for the acMMAE AUC models. The forward inclusion identified increased hemoglobin (HGB) and increased LDH as the significant covariates associated with increased probability of Grade ≥ 3 anemia at $\alpha = 0.01$ level. The E-R relationship remained significant ($p < 0.05$) in the presence of these covariates. Only HGB was retained in the model at $\alpha = 0.001$ level during the backward elimination.
- Higher unconjugated MMAE exposures (AUC, Cmax) were significantly correlated with higher incidence of Grade ≥ 3 neutropenia, Grade ≥ 3 infections and infestations, Grade ≥ 3 anemia, Grade ≥ 3 thrombocytopenia, and Grade ≥ 3 febrile neutropenia ($p< 0.05$). The covariate analyses were performed only for the unconjugated MMAE AUC models. The forward inclusion identified increased HGB as a significant covariate associated with increased probability of Grade ≥ 3 anemia, and Asian race as a significant covariate associated with increased probability of Grade ≥ 3 neutropenia at $\alpha = 0.01$ level. The E-R relationship remained significant in the presence of these covariates in the model; both covariates were retained in the final model at $\alpha = 0.001$ level during the backward elimination.
- acMMAE and unconjugated MMAE exposures (AUC, Cmax) were not significantly correlated with probability of dose modification due to AEs and time to first dose modification due to AE.
- There were statistically significant correlations between increased acMMAE/ unconjugated MMAE exposures (AUC, Cmax) and decreased dose intensity of pola, rituximab, doxorubicin, and cyclophosphamide ($p < 0.05$). However, given an overall high dose intensity (mean, median, and geometric mean >96%) across each tertile of the acMMAE and unconjugated MMAE exposure, these statistically significant associations between exposure and dose intensity were not considered clinically relevant.
- For all other safety endpoints assessed, there were no statistically significant correlations with the exposure of acMMAE or unconjugated MMAE.

General Information	
Goal of ER analysis	The objectives of the E-R analysis were to assess the relationship of acMMAE exposures with efficacy and safety in POLARIX and to assess the relationship of unconjugated MMAE exposures with safety in POLARIX, to support the proposed dosing regimen for the label.
Study Included	GO39942 (POLARIX)
Population Included	Previously untreated DLBCL patients
Endpoint	1. Probability of a treatment-emergent adverse events (AE) as follows: Grade ≥3 Neutropenia; Grade ≥3 Febrile Neutropenia; Grade ≥2 Peripheral Neuropathy; Grade ≥3 Infections and Infestations; Grade ≥3 Anemia; Grade ≥3 Thrombocytopenia; Grade ≥3 AST increase (by lab); Grade ≥3 ALT increase (by lab); Grade ≥3 Bilirubin increase (by lab); Grade ≥3 Hepatic toxicity; Grade ≥ 3 Hyperglycemia; Grade ≥3 Cardiac Arrhythmia; 2. Probability of a pola dose modification (reduction, delay, or discontinuation) due to AE; 3. Time to the first pola dose modification (reduction, delay, or

		discontinuation) due to AE; 4. Dose intensity • Pola dose intensity; • Rituximab dose intensity; • Doxorubicin dose intensity; • Cyclophosphamide dose intensity; • Prednisone dose intensity.
No. of Patients (total, and with individual PK)		429 (all 429 patients have observed individual PK data and were included in the population PK analysis)
Population Characteristics	General	Age median (range): 65 [19-80] yr Weight median (range): 74.4 [38.4-228]kg Male: 233 (54.3%) Race: White: 228 (53.1%) Asian: 84 (19.6%) Unknown or Other: 117 (27.3%)
	Organ impairment	Hepatic (Hepatic function was defined based on National Cancer Institute Organ Dysfunction Working Group Classification of Hepatic Dysfunction): normal hepatic function: 338 (78.8%) mild hepatic impairment: 79 (18.4%) moderate hepatic impairment: 9 (2.1%) severe hepatic impairment: 1 (0.2%) Renal (CrCL): normal renal function: 171 (39.9%) mild renal impairment: 200 (46.6%) moderate renal impairment: 54 (12.6%) severe renal impairment: 1 (0.2%)
	Pediatrics (if any)	NA
	Geriatrics (if any)	Age median (range): 65 [19-80] yr, 51.7% subj >=65 yr, 12.8% subj >=75 yr) Male: 233 (54.3%)
Dose(s) Included		1.8 mg/kg Q3W pola for 6 cycles concomitant with R- CHP regimen
Exposure Metrics Explored (range)		simulated Cycle 6 AUC and Cmax of acMMAE and unconjugated MMAE
Covariates Evaluated		• Demographics: body weight, sex, age, race, region; • Baseline Laboratory Measurements: lactate dehydrogenase (LDH), serum albumin, B-cell (CD19) count, neutrophil-to-lymphocyte ratio (NLR), neutrophil count, hemoglobin level (HGB), platelet count; • Baseline disease characteristics and history: ECOG performance status, bulky disease, tumor SPD, Ann Arbor stage, NHL subtype, DLBCL cell origin, International prognostic index (IPI) score, double-expressor by IHC status, extra nodal involvement, active peripheral neuropathy status, baseline peripheral neuropathy active status; • Anti-drug antibody (ADA) status for pola • The following covariates were included only in the exposure-safety analyses: baseline neutrophil count for the analysis of neutropenia; baseline hemoglobin level for anemia; baseline platelet count for thrombocytopenia; peripheral neuropathy history and peripheral neuropathy status at baseline for peripheral neuropathy.

Final Model Parameters	Summary	Acceptability [FDA's comments]
Model Structure	1. Logistic regression models of AE probability versus exposure for each type of AEs with more that 5% frequency rate (Endpoint 1) 2. Logistic regression models of probability of pola dose modification due to AE versus exposure (Endpoint 2) 3. KM plots and Cox proportional hazard models for time to the first dose modification due to AE (Endpoint 3) 4. Summaries of dose intensity of pola, rituximab, doxorubicin, cyclophosphamide, and prednisone by tertiles of pola exposure; linear regression and box plots (Endpoint 4).	Logistic regression indicates several TEAEs of interest are associated with higher MMAE and acMMAE exposure in plasma. Higher MMAE exposure (Cycle 6 AUC and Cycle 6 Cmax following planned dosing) was associated with higher rates of the following safety events: • Grade ≥3 neutropenia (**Figure 27**) • Grade ≥3 febrile neutropenia (**Figure 28**) • Grade ≥3 infections (**Figure 30**) • Grade ≥3 anemia (**Figure 32**) • Grade ≥3 thrombocytopenia (**Figure 34**) • Grade ≥3 lymphocyte count decreased (**Figure 41**) • Grade ≥3 hemoglobin decreased (**Figure 41**) • Grade ≥3 platelet count decreased (**Figure 41**) • Grade ≥3 leukocyte count decreased (**Figure 41**) • TEAE leading to dose modification of any drug in the POLA+R-CHP regimen and dose modification of polatuzumab vedotin (**Figure 39**) Higher acMMAE exposure (Cycle 6 AUC and Cycle 6 Cmax following planned dosing) was associated with higher rates of the following safety events: • Grade ≥2 peripheral neuropathy (**Figure 29**) • Grade ≥3 anemia (**Figure 31**) • Grade ≥3 thrombocytopenia (**Figure 33**) • Grade ≥3 hemoglobin decreased (**Figure 42**) • TEAE leading to dose modification of any drug in the POLA+R-CHP regimen and dose modification of polatuzumab vedotin (**Figure 40**)
Model Parameter Estimates	**Table 52** (for primary and major secondary endpoints)	
Model Evaluation	NA	
Covariates and Clinical Relevance	1. Covariate analysis identified Asian race as a significant factor correlated with increased probability of Grade ≥3 Neutropenia with increasing unconjugated MMAE exposure (**Table 53**). However, Asian race was not identified as the significant covariate for other endpoints potentially related to neutropenia including febrile neutropenia and infections. Overall, the safety profile was generally comparable between White and Asian subgroups with some numerical differences 2. Baseline hemoglobin (HGB) is a significant covariate associated with increased probability of Grade ≥3 anemia with increasing acMMAE AUC and unconjugated MMAE AUC 3. Covariate analysis did not identify any significant covariates affecting the probability of other AE endpoints	
Simulation for Specific Population	NA	

Final Model Parameters	Summary	Acceptability [FDA's comments]
Visualization of E-R relationships	**Figure** 27 through **Figure** 34. (Note: Figures are not shown for logistic regression models of AE probability versus exposure with p-values greater than 0.05 (see **Table** 52))	Rates of dose modifications according to MMAE and acMMAE exposure are displayed in **Figure 39** and **Figure** 40, respectively. Rates of neutropenia, anemia, and thrombocytopenia in **Figure** 27**, Figure** 31**, Figure 32, Figure 33**, and **Figure** 34 were derived from the adverse event dataset and therefore may have lower recorded incidence compared to cytopenia rates derived from the laboratory dataset (**Figure** 41 and **Figure** 42 for MMAE and acMMAE exposure, respectively).
Overall Clinical Relevance for ER	E-R analyses further support the recommended 1.8 mg/kg Q3W of pola for 6 cycles in combination with R-CHP. The E-R analysis based on POLARIX study suggested that a higher pola exposure may be associated with a higher incidence of some safety endpoints (e.g., Grade ≥2 peripheral neuropathy, Grade ≥3 anemia and Grade ≥3 thrombocytopenia) and a lower pola exposure may be associated with lower efficacy on PFS and EFSeff. Pola dose modifications due to AE were not correlated with acMMAE or unconjugated MMAE exposures. Dose intensity for pola, rituximab, doxorubicin, and cyclophosphamide was correlated with pola exposure, but not considered clinically relevant given the overall high dose intensity observed for these components in POLARIX. Therefore, a positive benefit-risk profile with highly favorable efficacy was achieved with a manageable safety profile at the recommended 1.8 mg/kg Q3W of pola in combination with R-CHP.	The E-R safety analysis did not identify any safety concerns with the proposed dosage of 1.8 mg/kg in subjects with previously untreated DLBCL. E-R efficacy analysis is discussed in Section 18.3.3.2.

Labeling Language	Description	Acceptability [FDA's comments]
12.2 Pharmacodynamics	No new information is currently proposed	Over polatuzumab vedotin-piiq dosages of 0.1 to 2.4 mg/kg (0.06 to 1.33 times the approved recommended dosage), higher exposures (i.e., AUC and C_{max}) of acMMAE and unconjugated MMAE were associated with higher incidence of some adverse reactions (including ≥Grade 3 thrombocytopenia and ≥Grade 3

Labeling Language	Description	Acceptability [FDA's comments]
		anemia). Higher exposure of MMAE was also associated with higher incidence of ≥Grade 2 peripheral neuropathy.

Table 52: Summary of the Results for Exposure-Safety Analysis: Base Models

Adverse Event	Analysis Type	N	N (%) with Event	p-value			
				acMMAE		Unconjugated MMAE	
				AUC	Cmax	AUC	Cmax
Grade ≥3 Neutropenia	Logistic regression	429	179 (41.7%)	0.450	0.636	0.001	0.004
Grade ≥3 Febrile Neutropenia		429	58 (13.5%)	0.188	0.504	<0.0005	0.001
Grade ≥2 Peripheral Neuropathy		429	60 (14%)	0.042	0.003	0.525	0.827
Grade ≥3 Infections and Infestations		429	65 (15.2%)	0.099	0.089	<0.0005	<0.0005
Grade ≥3 Anemia		429	52 (12.1%)	0.028	0.060	<0.0005	<0.0005
Grade ≥3 Thrombocytopenia		429	22 (5.1%)	0.011	0.020	<0.0005	<0.0005
Dose Modification due to AE		429	34 (7.9%)	0.199	0.394	0.866	0.757
Time to the First Dose Modification due to AE	Cox proportional hazard (Cox PH) model	429	34 (7.9%)	0.164	0.341	0.797	0.689
Pola Dose intensity	Linear regression	429	-	0.166	0.050	<0.0005	<0.0005
Rituximab Dose intensity		429	-	0.007	0.001	<0.0005	<0.0005
Doxorubicin Dose intensity		429	-	0.035	0.006	0.001	0.001
Cyclophosphamide Dose intensity		429	-	0.029	0.003	<0.0005	<0.0005
Prednisone Dose intensity		429	-	0.563	0.623	0.390	0.341

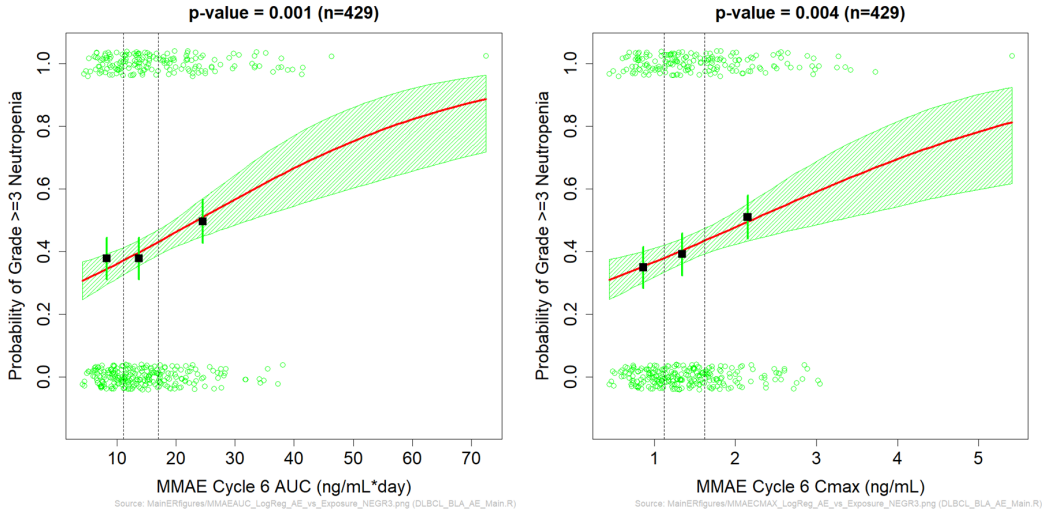
ac=antibody conjugated; AE=adverse event; AUC=area under the concentration-time curve; Cmax=maximum concentration; MMAE=monomethyl auristatin E.
Shaded cell indicates p-value <0.05.
Note: For all significant correlations ($p < 0.05$), a positive correlation between exposure and the indicated safety endpoint was observed, except for dose intensity of pola, rituximab, doxorubicin and cyclophosphamide which was negatively correlated.
The p-values presented in all the models were nominal and not adjusted for multiplicity.
Source: E-R Safety Table 3.1 in Applicant's 11 August 2022 response to 04 August 2022 information request

Table 53: Logistic Regression Final Model for Grade ≥3 Neutropenia

Exposure	Coefficient	SE	RSE	P95CI	p-value	Parameter
unconjugated MMAE AUC, (ng/mL*day)	-1.49	0.2515	16.89	-1.983;-0.9965	<0.0005	Intercept
	0.05598	0.01345	24.02	0.02962;0.08233	<0.0005	Slope of Exposure, (ng/mL*day)-1
	1.378	0.2642	19.17	0.8602;1.896	<0.0005	Asian Effect on intercept

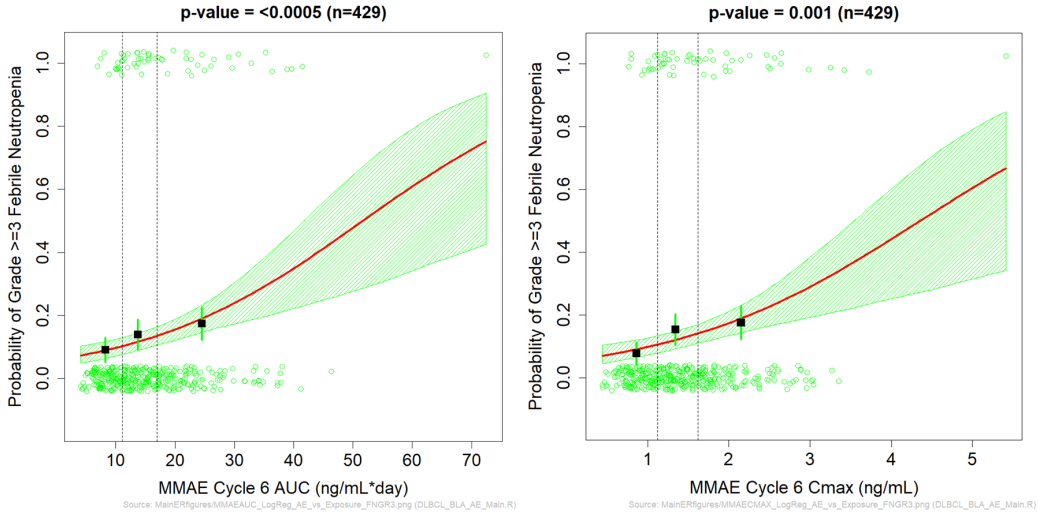
Source: E-R Safety Table 3.3 in Applicant's 11 August 2022 response to 04 August 2022 information request

Figure 27: Logistic Regression for Unconjugated MMAE Exposures and Grade ≥3 Neutropenia Based on POLARIX Study



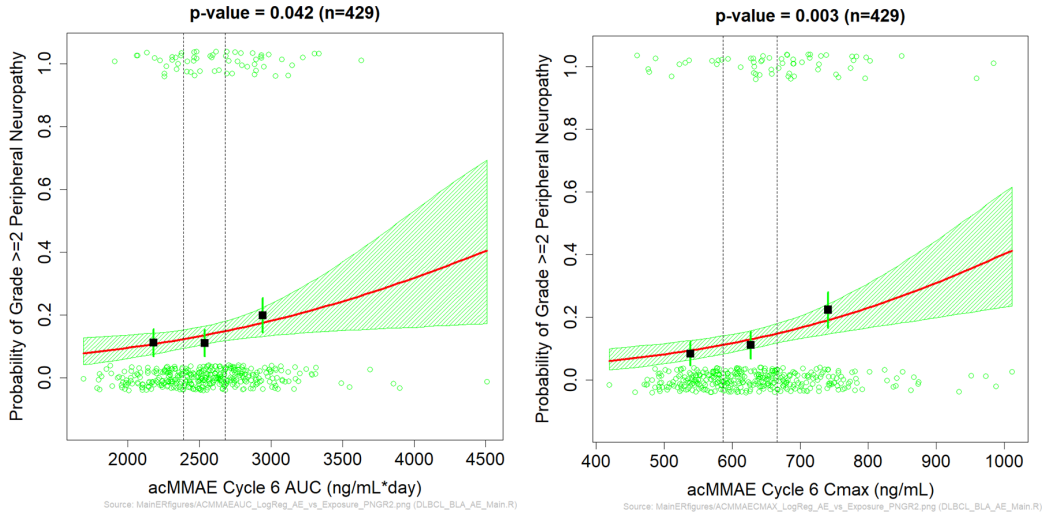
AUC=area under the concentration time curve; Cmax=maximum concentration; MMAE=monomethyl auristatin E. The red solid line and green shaded area represent the logistic regression model prediction and 90% confidence interval of predictions. Points show exposure of individual patients with events (p=1) and without events (p=0). Black squares and vertical green lines show observed fraction of subjects with events in each exposure group and 90% confidence interval for these fractions. Dashed vertical lines show bounds of exposure groups.
Source: E-R Safety Figure 1.1 in Applicant's 11 August 2022 response to 04 August 2022 information request

Figure 28: Logistic Regression for Unconjugated MMAE Exposures and Grade ≥3 Febrile Neutropenia Based on POLARIX Study



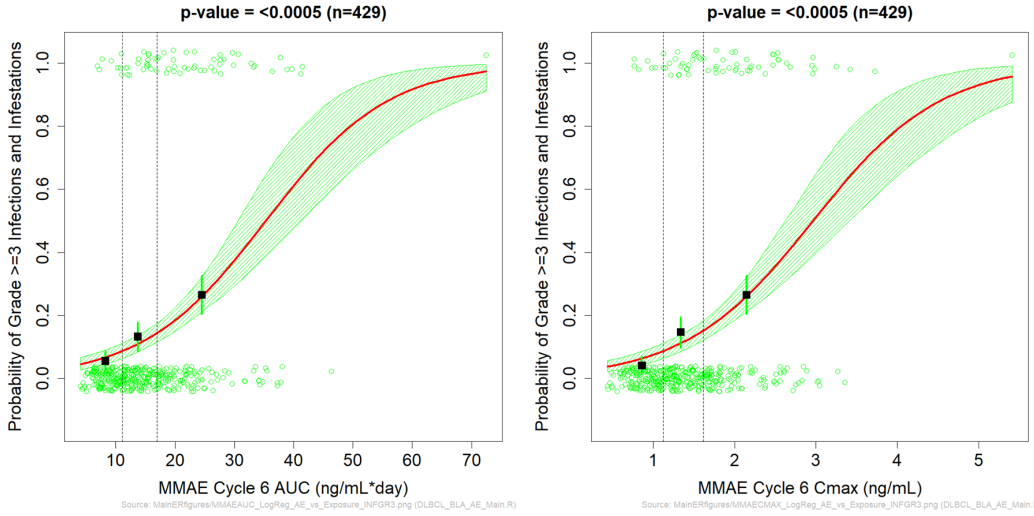
AUC=area under the concentration time curve; Cmax=maximum concentration; MMAE=monomethyl auristatin E. The red solid line and green shaded area represent the logistic regression model prediction and 90% confidence interval of predictions. Points show exposure of individual patients with events (p=1) and without events (p=0). Black squares and vertical green lines show observed fraction of subjects with events in each exposure group and 90% confidence interval for these fractions. Dashed vertical lines show bounds of exposure groups.
Source: E-R Safety Figure 1.2 in Applicant's 11 August 2022 response to 04 August 2022 information request

Figure 29: Logistic Regression for acMMAE Exposures and Grade ≥2 Peripheral Neuropathy Based on POLARIX Study



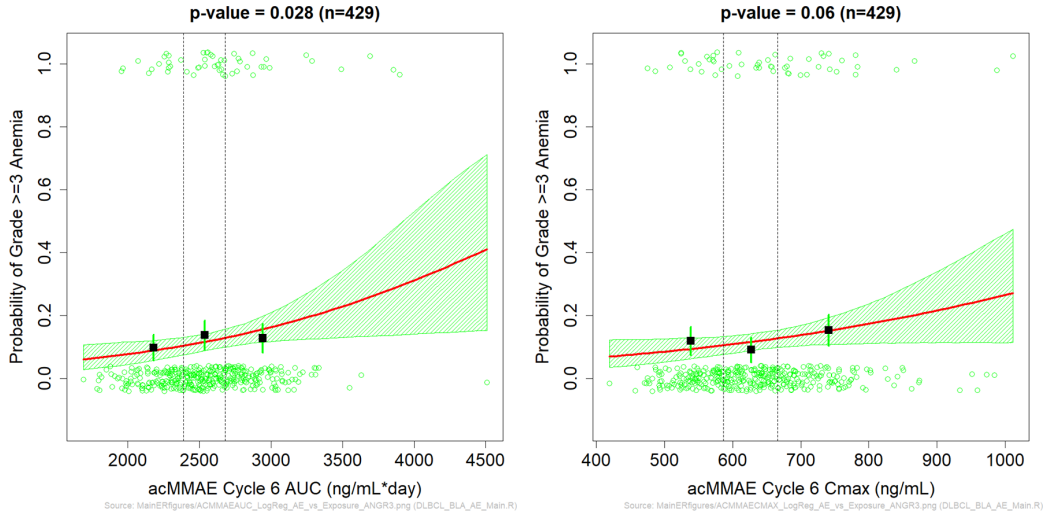
AUC=area under the concentration time curve; Cmax=maximum concentration; MMAE=monomethyl auristatin E. The red solid line and green shaded area represent the logistic regression model prediction and 90% confidence interval of predictions. Points show exposure of individual patients with events (p=1) and without events (p=0). Black squares and vertical green lines show observed fraction of subjects with events in each exposure group and 90% confidence interval for these fractions. Dashed vertical lines show bounds of exposure groups.
Source: E-R Safety Figure 1.3 in Applicant's 11 August 2022 response to 04 August 2022 information request

Figure 30: Logistic Regression for Unconjugated MMAE Exposures and Grade ≥3 Infections and Infestations Based on POLARIX Study



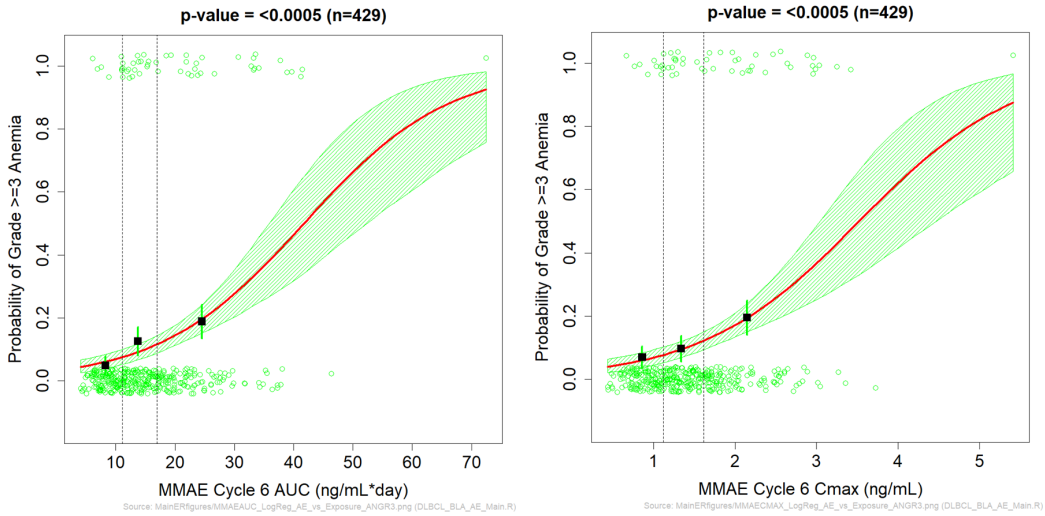
AUC=area under the concentration time curve; Cmax=maximum concentration; MMAE=monomethyl auristatin E.
The red solid line and green shaded area represent the logistic regression model prediction and 90% confidence interval of predictions. Points show exposure of individual patients with events (p=1) and without events (p=0). Black squares and vertical green lines show observed fraction of subjects with events in each exposure group and 90% confidence interval for these fractions. Dashed vertical lines show bounds of exposure groups.
Source: E-R Safety Figure 1.4 in Applicant's 11 August 2022 response to 04 August 2022 information request

Figure 31: Logistic Regression for acMMAE Exposures and Grade ≥ 3Anemia Based on POLARIX Study



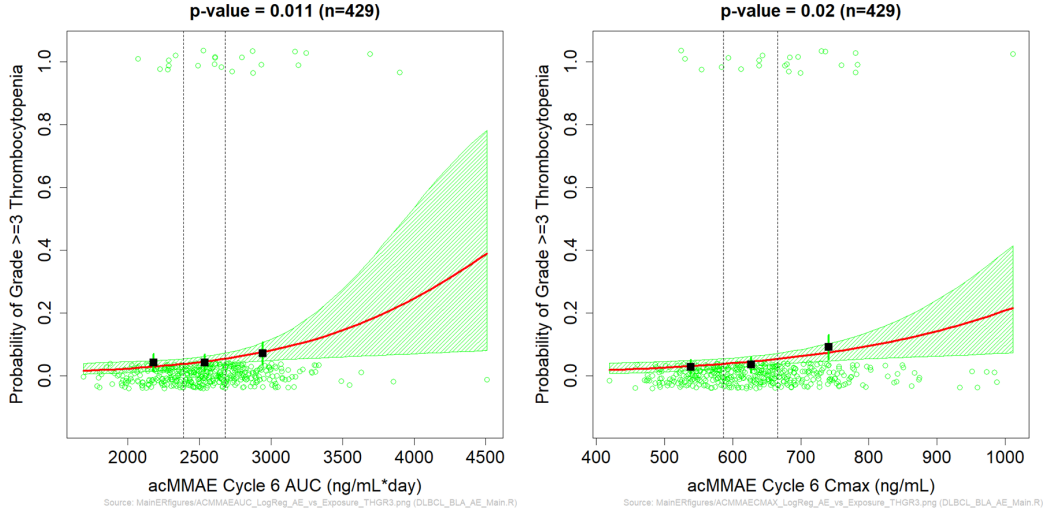
AUC=area under the concentration time curve; Cmax=maximum concentration; MMAE=monomethyl auristatin E.
The red solid line and green shaded area represent the logistic regression model prediction and 90% confidence interval of predictions. Points show exposure of individual patients with events (p=1) and without events (p=0). Black squares and vertical green lines show observed fraction of subjects with events in each exposure group and 90% confidence interval for these fractions. Dashed vertical lines show bounds of exposure groups.
Source: E-R Safety Figure 1.5 in Applicant's 11 August 2022 response to 04 August 2022 information request

Figure 32: Logistic Regression for Unconjugated MMAE Exposures and Grade ≥3 Anemia Based on POLARIX Study



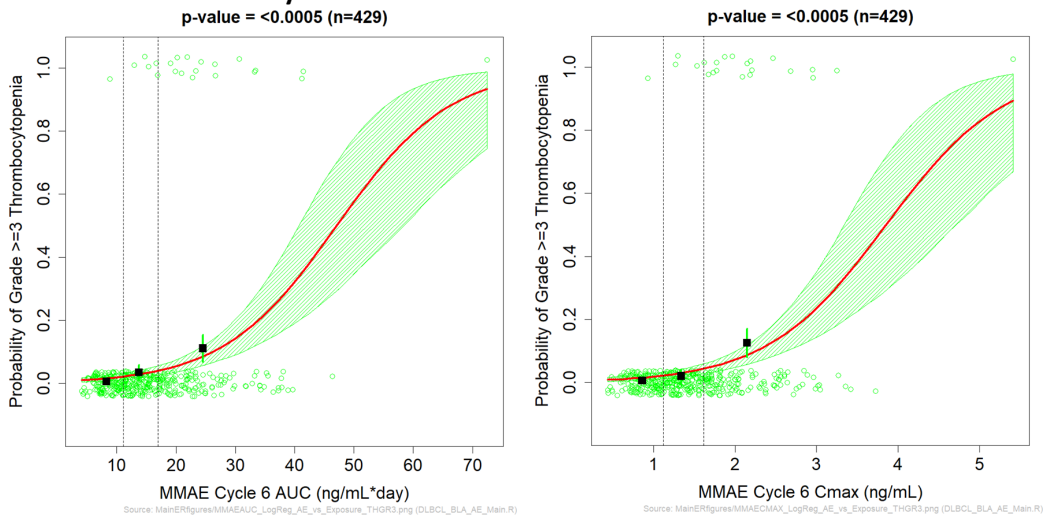
AUC=area under the concentration time curve; Cmax=maximum concentration; MMAE=monomethyl auristatin E. The red solid line and green shaded area represent the logistic regression model prediction and 90% confidence interval of predictions. Points show exposure of individual patients with events (p=1) and without events (p=0). Black squares and vertical green lines show observed fraction of subjects with events in each exposure group and 90% confidence interval for these fractions. Dashed vertical lines show bounds of exposure groups.
Source: E-R Safety Figure 1.6 in Applicant's 11 August 2022 response to 04 August 2022 information request

Figure 33: Logistic Regression for acMMAE Exposures and Grade ≥3 Thrombocytopenia Based on POLARIX Study



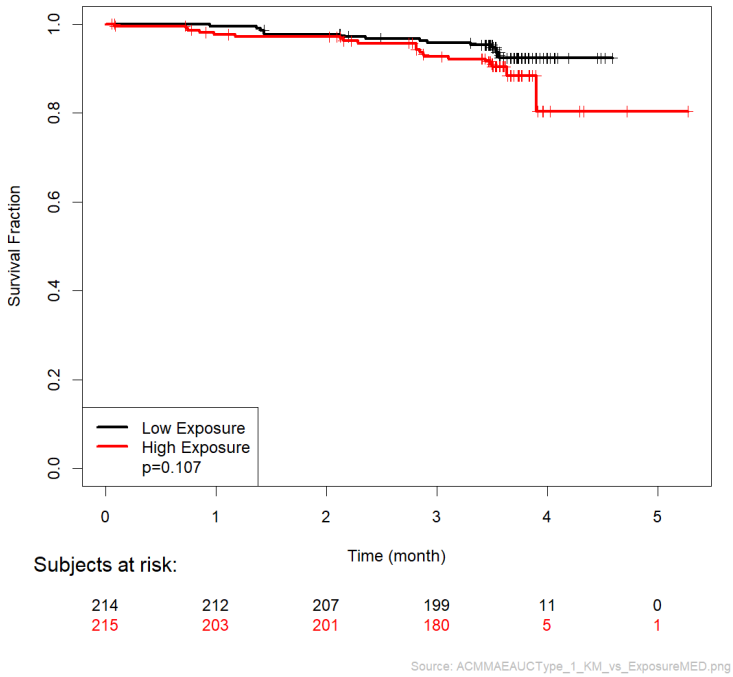
AUC=area under the concentration time curve; Cmax=maximum concentration; MMAE=monomethyl auristatin E. The red solid line and green shaded area represent the logistic regression model prediction and 90% confidence interval of predictions. Points show exposure of individual patients with events (p=1) and without events (p=0). Black squares and vertical green lines show observed fraction of subjects with events in each exposure group and 90% confidence interval for these fractions. Dashed vertical lines show bounds of exposure groups.
Source: E-R Safety Figure 1.7 in Applicant's 11 August 2022 response to 04 August 2022 information request

Figure 34: Logistic Regression for Unconjugated MMAE Exposures and Grade ≥3 Thrombocytopenia Based on POLARIX Study



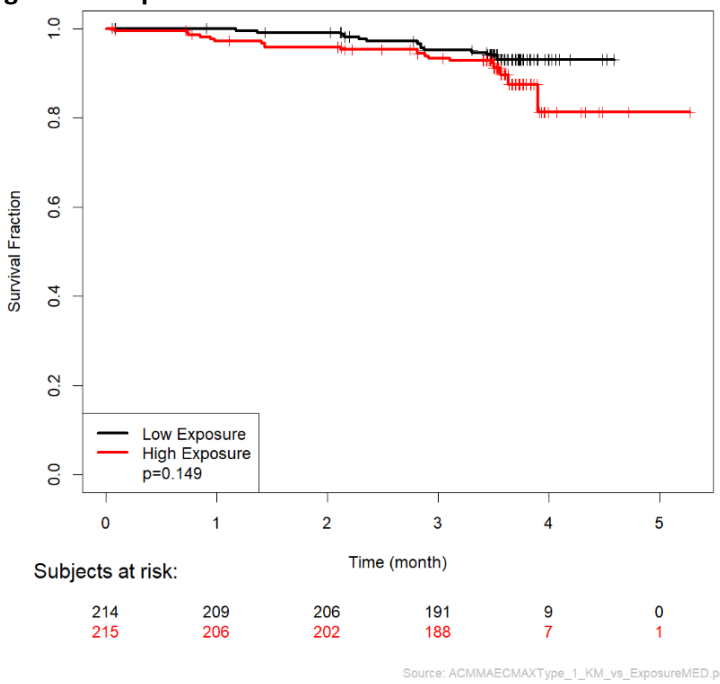
AUC=area under the concentration time curve; Cmax=maximum concentration; MMAE=monomethyl auristatin E. The red solid line and green shaded area represent the logistic regression model prediction and 90% confidence interval of predictions. Points show exposure of individual patients with events (p=1) and without events (p=0). Black squares and vertical green lines show observed fraction of subjects with events in each exposure group and 90% confidence interval for these fractions. Dashed vertical lines show bounds of exposure groups.
Source: E-R Safety Figure 1.8 in Applicant's 11 August 2022 response to 04 August 2022 information request

Figure 35: Kaplan-Meier Plot for Time to the First Dose Modification Due to AE by acMMAE AUC



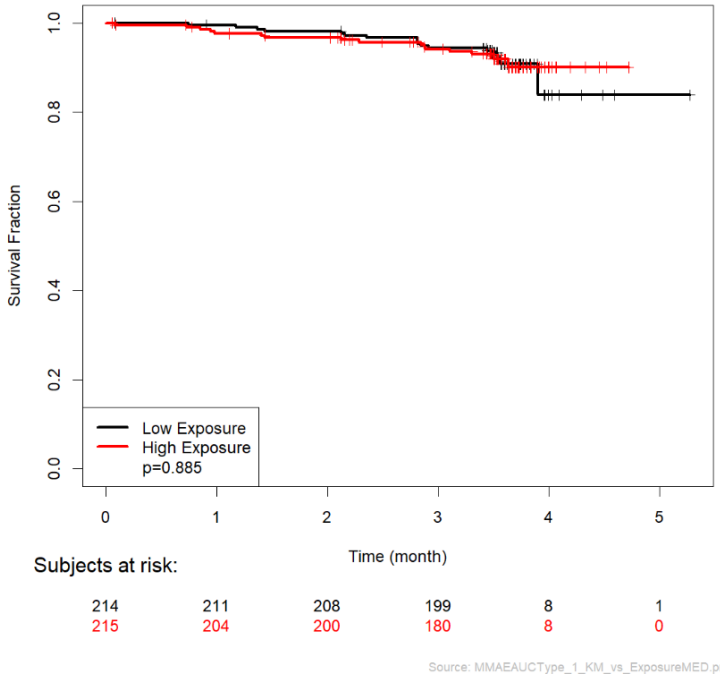
Low exposure: <= median, High exposure > median. P-value: p-value of the log-rank test comparing patients with low and high exposure.
Source: E-R Safety Figure 1.9 in Applicant's 11 August 2022 response to 04 August 2022 information request

Figure 36: Kaplan-Meier Plot for Time to the First Dose Modification Due to AE by acMMAE Cmax



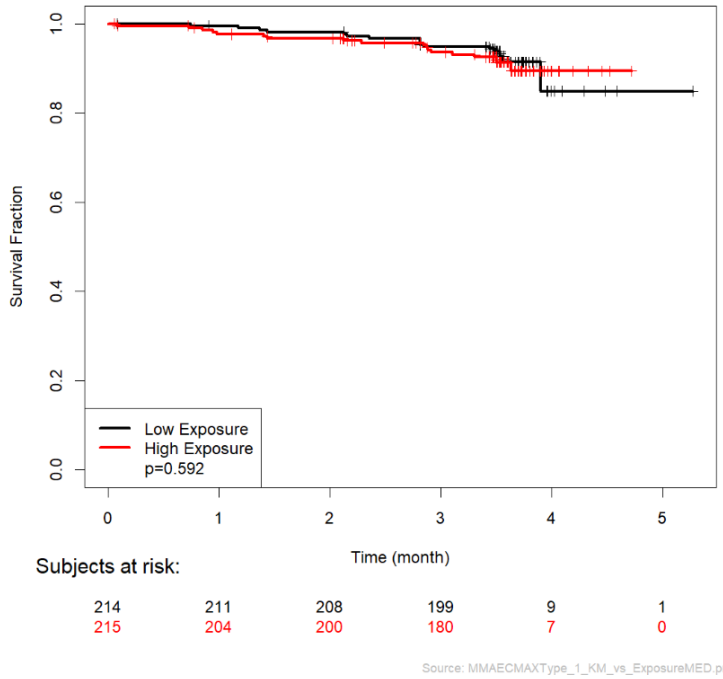
Low exposure: <= median, High exposure > median. P-value: p-value of the log-rank test comparing patients with low and high exposure.
Source: E-R Safety Figure 1.10 in Applicant's 11 August 2022 response to 04 August 2022 information request

Figure 37: Kaplan-Meier Plot for Time to the First Dose Modification Due to AE by Unconjugated MMAE AUC



Low exposure: <= median, High exposure > median. P-value: p-value of the log-rank test comparing patients with low and high exposure.
Source: E-R Safety Figure 1.11 in Applicant's 11 August 2022 response to 04 August 2022 information request

Figure 38: Kaplan-Meier Plot for Time to the First Dose Modification Due to AE by Unconjugated MMAE Cmax



Low exposure: <= median, High exposure > median. P-value: p-value of the log-rank test comparing patients with low and high exposure.
Source: E-R Safety Figure 1.12 in Applicant's 11 August 2022 response to 04 August 2022 information request

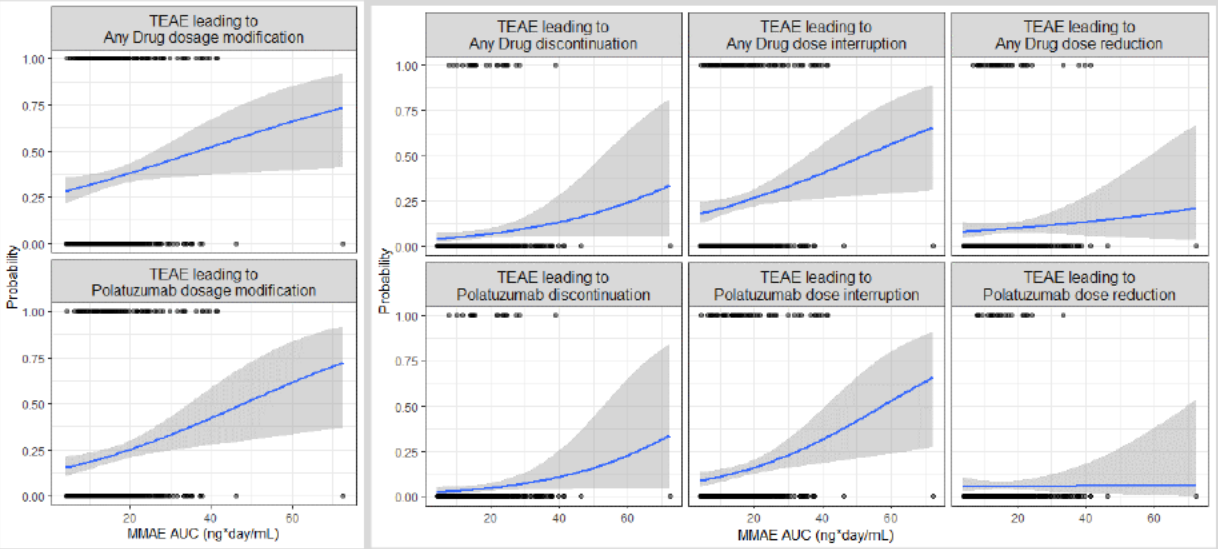
The FDA's Assessment:
Overall, the E-R safety analysis did not identify any safety concerns with the proposed 1.8 mg/kg dosage in subjects with previously untreated DLBCL. Higher exposure was associated with increased rates of multiple TEAEs of interest, including Grade ≥2 peripheral neuropathy, Grade ≥3 anemia, and Grade ≥3 thrombocytopenia.

Compared to acMMAE, higher MMAE exposure in plasma was associated with stronger E-R safety associations as well as a greater number of identified E-R safety associations. This is consistent with the mechanism of action of polatuzumab vedotin, as MMAE (i.e., vedotin) is the toxic anti-mitotic payload conjugated to the monoclonal antibody.

For both MMAE and acMMAE exposure, logistic regression of safety events results did not differ significantly according to Cycle 6 AUC versus Cycle 6 C_{max}. No E-R safety associations with acMMAE or MMAE were identified for Grade ≥3 hyperglycemia, Grade ≥3 cardiac arrhythmia, or Grade ≥3 hepatic toxicity. However, relatively small numbers of these events occurred in POLARIX and the lack of apparent E-R safety associations may be due to the low number of events.

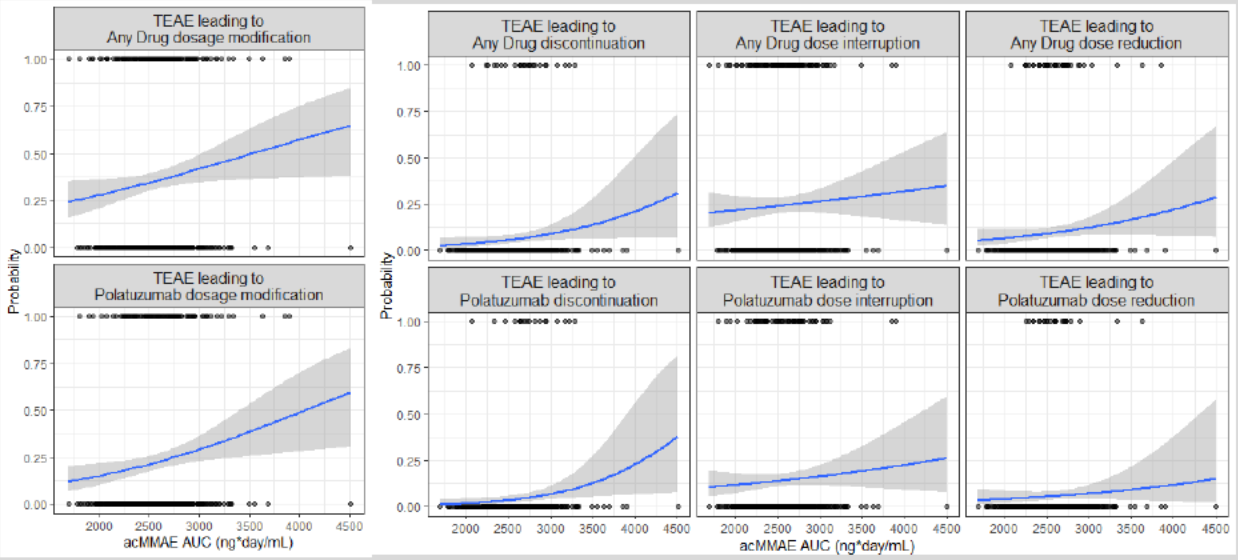
Applicant analysis showed that relative dose intensity (RDI) was similar in both arms (refer to **Table 5** in Section 6.3.1). However, the RDI data censored subjects at the end of the last complete cycle received and thus did not reflect early discontinuation or dose delay. Dose modification rates are more informative regarding clinical safety profile. FDA analysis did not identify significant differences in the rates of dose modification or discontinuation to any drug, to rituximab, and to polatuzumab/pola-placebo between POLARIX arms (refer to **Table 6** in Section 6.3.1). However, increased polatuzumab exposure was associated with higher rates of TEAEs due to dose modifications in the pola+R-CHP arm, as shown in **Figure 39** and **Figure 40** for MMAE and acMMAE exposures, respectively.

Figure 39: Rate of TEAE Leading to Dose Modification Versus Cycle 6 MMAE AUC (Logistic Regression)



Any drug refers to polatuzumab vedotin/placebo, vincristine/placebo, rituximab, doxorubicin, cyclophosphamide, or prednisone. Data shown for pola+R-CHP arm (n=429) of POLARIX following planned dosage of 1.8 mg/kg Q3W; TEAE data derived from adae.xpt dataset.
AUC = area under the concentration-versus-time curve; MMAE = monomethyl auristatin E; pola+R-CHP = polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone; Q3W = every 3 weeks; TEAE = treatment emergent adverse event.
Source: Reviewer's analysis

Figure 40: Rate of TEAE Leading to Dose Modification Versus Cycle 6 acMMAE AUC (Logistic Regression)



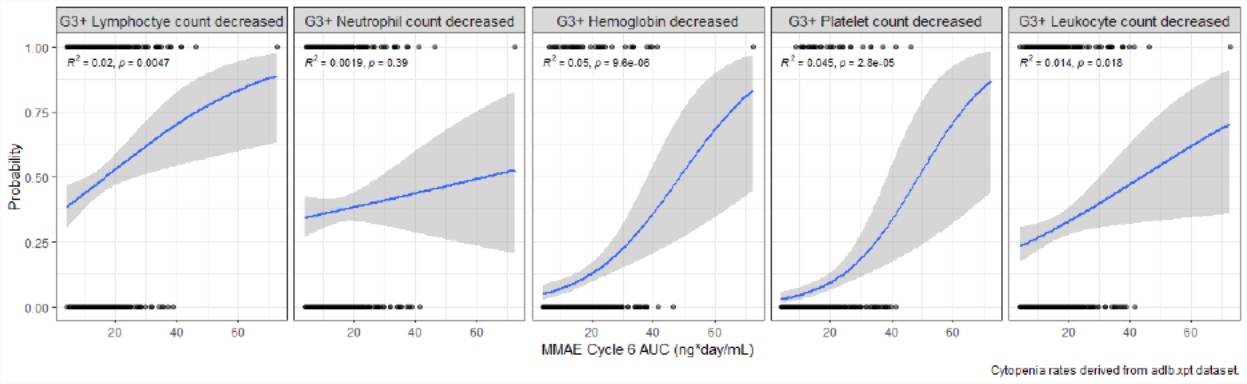
Any drug refers to polatuzumab vedotin/placebo, vincristine/placebo, rituximab, doxorubicin, cyclophosphamide, or prednisone. Data shown for pola+R-CHP arm (n=429) of POLARIX following planned dosage of 1.8 mg/kg Q3W; TEAE data derived from adae.xpt dataset.
acMMAE = antibody-conjugated monomethyl auristatin E; AUC = area under the concentration-versus-time curve; pola+R-CHP = polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone; Q3W = every 3 weeks; TEAE = treatment emergent adverse event.
Source: Reviewer's analysis

E-R Safety Associations with MMAE Exposure in Plasma

Higher MMAE exposure (Cycle 6 AUC and Cycle 6 C_{max} following planned dosing) was associated with higher rates of the following safety events:

- Grade ≥3 neutropenia according to the adverse event dataset (**Figure** 27)
- Grade ≥3 febrile neutropenia (**Figure** 28)
- Grade ≥3 infections (**Figure** 30)
- Grade ≥3 anemia according to the adverse event dataset (**Figure** 32)
- Grade ≥3 thrombocytopenia according to the adverse event dataset (**Figure** 34)
- Grade ≥3 lymphocyte count decreased according to laboratory value dataset (**Figure** 41)
- Grade ≥3 hemoglobin decreased according to laboratory value dataset (**Figure** 41)
- Grade ≥3 platelet count decreased according to laboratory value dataset (**Figure** 41)
- Grade ≥3 leukocyte count decreased according to laboratory value dataset (**Figure** 41)
- TEAE leading to dose modification of any drug in the POLA+R-CHP regimen (**Figure 39**)
- TEAE leading to dose modification of polatuzumab vedotin (**Figure 39**).

Figure 41: Rate of Grade ≥3 and Above Cytopenias Derived from the Laboratory Dataset versus MMAE Cycle 6 AUC (Logistic Regression)



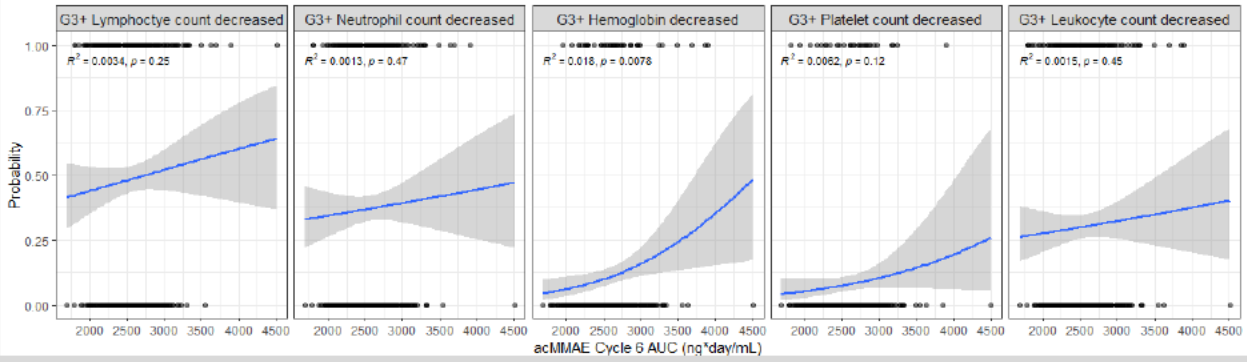
Data shown for pola+R-CHP arm (n=429) of POLARIX following planned dosage of 1.8 mg/kg Q3W; cytopenia data derived from adlb.xpt dataset.
AUC = area under the concentration-versus-time curve; G3+ = Grade ≥3; MMAE = monomethyl auristatin E; pola+R-CHP = polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone; Q3W = every 3 weeks; TEAE = treatment emergent adverse event.
Source: Reviewer's analysis

E-R Safety Associations with acMMAE Exposure in Plasma

Higher acMMAE exposure (Cycle 6 AUC and Cycle 6 C_{max} following planned dosing) was associated with higher rates of the following safety events:

- Grade ≥2 peripheral neuropathy (**Figure 29**)
- Grade ≥3 anemia according to the adverse event dataset (**Figure 31**)
- Grade ≥3 thrombocytopenia according to the adverse event dataset (**Figure 33**)
- Grade ≥3 hemoglobin decreased according to laboratory value dataset (**Figure 42**)
- TEAE leading to dose modification of any drug in the POLA+R-CHP regimen (**Figure 40**)
- TEAE leading to dose modification of polatuzumab vedotin (**Figure 40**)

Figure 42: Rate of Grade ≥3 and Above Cytopenias Derived from the Laboratory Dataset versus acMMAE Cycle 6 AUC (Logistic Regression)



Data shown for pola+R-CHP arm (n=429) of POLARIX following planned dosage of 1.8 mg/kg Q3W; cytopenia data derived from adlb.xpt dataset.
acMMAE = antibody-conjugated monomethyl auristatin E; AUC = area under the concentration-versus-time curve; G3+ = Grade ≥3; pola+R-CHP = polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone; Q3W = every 3 weeks; TEAE = treatment emergent adverse event.

Source: Reviewer's analysis

18.3.3.5. Overall Benefit-Risk Evaluation Based on E-R Analyses

The Applicant's Position:

E-R analysis based on POLARIX study suggested that a higher exposure may be associated with higher incidence of some safety endpoints (e.g., Gr ≥2 PN, Gr ≥3 anemia and Gr ≥3 thrombocytopenia) and a lower exposure may be associated with lower efficacy on PFS and EFSeff. Overall, the E-R analyses and the favorable benefit risk profile of the POLARIX study support the proposed dosing regimen of 1.8 mg/kg pola Q3W up to 6 cycles in combination with R-CHP for treating patients with 1L DLBCL.

It is acknowledged that the E-R analysis is limited by the data from a single dose level of pola (1.8 mg/kg Q3W up to 6 cycles), as evaluated in POLARIX. It is known that the E-R relationships for biologics with only one dose level might be confounded due to the potential for the extent of disease to impact the PK of a therapeutic antibody. Given that extent of disease may also be related to both safety and efficacy, it is not possible to distinguish between an effect of PK on disease versus an effect of disease on PK (Wang et al. 2017; Dai et al. 2020). Therefore, the positive E-R relationships observed in POLARIX should be interpreted with caution.

The Applicant's References:

Dai HI, Vugmeyster Y, Mangal N. Characterizing Exposure–Response Relationship for Therapeutic Monoclonal Antibodies in Immuno-Oncology and Beyond: Challenges, Perspectives, and Prospects. Clinical Pharmacology & Therapeutics. 2020;108(6):1156-1170.

Wang Y, Booth B, Rahman A, et al. Toward greater insights on pharmacokinetics and exposure–response relationships for therapeutic biologics in oncology drug development. Clinical Pharmacology & Therapeutics. 2017;101(5):582-4.

The FDA's Assessment:

The FDA generally agrees with the Applicant's position regarding E-R analysis for evaluation of overall benefit-risk.

18.4. FDA Grouping of Preferred Terms

Table 54: Grouping of Preferred Terms for FDA Safety Analysis

FDA Grouped PT	Included in Grouping	Not Included
Abdominal pain	All PTs containing "abdominal pain", Abdominal discomfort, Epigastric discomfort	abdominal rigidity
Altered taste	Dysgeusia, Taste disorder, Ageusia	
Anemia	All PTs containing "anaemia", red blood cell decreased, haemoglobin decreased	
Arthralgia	Arthralgia, periarthritis	
Atrial fibrillation or flutter	Atrial fibrillation, Atrial flutter	
Bruising	All PTs containing "bruise," "contusion," or "ecchymosis"	Petechiae, Purpura
Cardiac arrhythmias	High-level group term, "Cardiac arrhythmias", "arrythmia"	
Cardiac failure	All PTs containing "cardiac failure", Cardiomyopathy, Cardiomyopathy failure	Left ventricular dysfunction, cardiac dysfunction
Cellulitis	Cellulitis, All PTs containing "skin infection"	
Chest pain	Chest discomfort, Angina pectoris, chest pain	Non-cardiac chest pain
Colitis (excluding infectious)	Colitis	Necrotizing colitis, neutropenic colitis, Enteritis, enterocolitis viral, Campylobacter colitis Clostridium difficile colitis Cytomegalovirus colitis
Cough	All PTs containing "Cough", upper-airway cough syndrome	Allergic cough
Cytomegalovirus infection	Cytomegalovirus infection reactivation, Cytomegalovirus infection, Cytomegalovirus enteritis	
Diarrhea	Diarrhea	Diarrhoea infectious, colitis
Dizziness	All PTs containing "Dizziness" or "Vertigo"	
Dyspnoea	All PTs containing "Dyspnoea"	

FDA Grouped PT	Included in Grouping	Not Included
Edema	Face oedema, Swelling face, oedema peripheral, Fluid retention, Pulmonary oedema, peripheral swelling, swelling,	Localized sites of edema (e.g. Localized oedema, Oedema mouth, oedema mucosal, testicular oedema, Periorbital oedema, joint swelling, angioedema, laryngeal oedema, lymphedema, muscle oedema, pharyngeal oedema, catheter site oedema, eyelid oedema)
Fatigue	Asthenia, Fatigue	lethargy
Febrile neutropenia	Febrile neutropenia, Neutropenic sepsis, Febrile bone marrow aplasia, Neutropenic infection * Note: Neutropenic sepsis is counted under both the "febrile neutropenia" and "sepsis" PTs	
Gastroenteritis	Gastroenteritis and specific types (e.g. campylobacter, viral), Enteritis,	Enteritis infectious, Gastroenteritis radiation, Gastritis, Duodenitis, gastrointestinal viral infection, gastrointestinal candidiasis,
Gastrointestinal hemorrhage	All PTs containing "Gastrointestinal hemorrhage", anal haemorrhage, , Hematochezia, Hematemesis, Large intestinal hemorrhage, Melena, Hemorrhoidal hemorrhage, Rectal hemorrhage, Upper gastrointestinal haemorrhage	
Headache	All PTs containing "headache", Migraine, Ophthalmic migraine, head discomfort	
Intracranial hemorrhage	Subdural hematoma, Cerebral hemorrhage	
Hepatitis	hepatitis B	FDA's "Transaminase elevation" grouping, PTs containing "Hepatic failure", Hepatic encephalopathy
Herpesvirus infection	High-level group term, "Herpes viral infection", "herpes zoster", "herpes simplex", "herpes", oral herpes, genital herpes, herpes simplex reactivation	
Hyperbilirubinemia	Blood bilirubin increased, Hyperbilirubinemia	
Hyperglycemia	Hyperglycemia, blood glucose increased	
Hypersensitivity	Hypersensitivity, Drug Hypersensitivity, Urticaria, Angioedema	
Hypertension	Hypertension, Blood pressure increased, systolic hypertension	

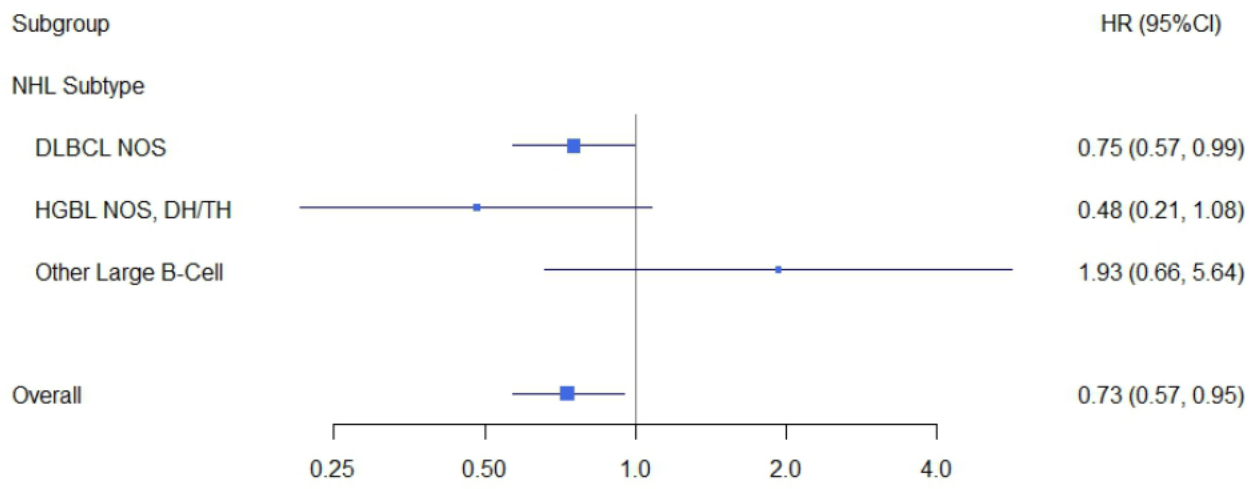
FDA Grouped PT	Included in Grouping	Not Included
Hypotension	Hypotension, Orthostatic hypotension, blood pressure decreased	
Interstitial lung disease	SMQ broad – Interstitial lung disease, pneumonitis, Acute respiratory distress syndrome	
Leukocytosis [a]	White blood cell increased	
Mucositis	Stomatitis, Mucosal inflammation, Mouth ulceration, Tongue ulceration, Aphthous ulcer, Oropharyngeal pain, Oral pain, Odynophagia, [Oral mucosal erythema, Aphthous stomatitis, Oral discomfort, Oropharyngeal discomfort	
Musculoskeletal pain	Back pain, Musculoskeletal chest pain, Musculoskeletal pain, Neck pain, Myalgia, Bone pain, spinal pain	Arthralgia, Pain in extremity joint stiffness, Musculoskeletal stiffness, arthritis and terms including arthritis, pain, non-cardiac chest pain, pain (breast, catheter site, ear, flank, gingival, groin, infusion site, lymph node, jaw, skin, pleuritic, procedural, pelvic, sinus, oesophageal, oral, oropharyngeal, urinary tract)
Myocardial ischemia or infarction	Acute myocardial infarction, Myocardial infarction,	
Nausea	Nausea	
Neutropenia	Neutropenia, Neutrophil count decreased	Febrile neutropenia, white blood cell count decreased
Peripheral neuropathy	Broad SMQ for peripheral neuropathy excluding muscle weakness and gait disturbance. polyneuropathy, peripheral sensory neuropathy, neuropathy peripheral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, neuralgia, dysaesthesia, oral dysaesthesia, Paraesthesia, Hypoaesthesia, Peroneal nerve palsy, Hypotonia, Hyporeflexia, Neuromyopathy, Paraesthesia ear, Hyperaesthesia,	Skin burning sensation , neurological symptoms, Post herpetic neuralgia, ileus paralytic, paralysis recurrent laryngeal nerve,
Pneumonia	All PTs containing "pneumonia", including within another word (e.g. atypical pneumonia, viral, pneumocystis jirovecii pneumonia), Bronchopulmonary aspergillosis, Lower respiratory infection, All PTs containing "lower respiratory infection" and its variants	

FDA Grouped PT	Included in Grouping	Not Included
Rash	All PTs containing "rash", all PTs containing "dermatitis, dermatitis acneiform, allergic, exfoliative, exfoliative generalized" except as noted, Drug eruption, Erythema multiforme, Toxic skin eruption,	All PTs containing "Eczema", All PTs containing erythema, seborrheic dermatitis, rosacea, skin exfoliation, Actinic keratosis, Folliculitis, Urticaria, Lichen planus, Herpes dermatitis, bullous hemorrhagic dermatosis
Renal insufficiency	All PTs containing "renal failure" , Acute kidney injury, Blood creatinine increase, Blood creatine increase, Renal impairment, Chronic kidney disease.	Renal tubular acidosis, renal tubular dysfunction, renal tubular necrosis
Respiratory tract infection	Respiratory tract infection, Influenza A virus test positive, influenza, Influenza like illness, coronavirus infection, coronavirus test positive, respiratory tract congestion,	Upper respiratory tract infection, Lower respiratory tract infection [b]
Sepsis	All PTs containing "Bacteraemia" or "Sepsis", including within another word (e.g. urosepsis) * Note: Neutropenic sepsis is counted under both the "febrile neutropenia" and "sepsis" PTs	Bacterial infection, Septic shock , bacterial pyelopenphritis, bacterial vulvovaginitis, bacteriuria, infections (all types)
Second primary malignancy	PTs including "cancer, "carcinoma, neoplasm", Hodgkin's disease, melanoma	
Supraventricular tachycardia	High-level term, "Supraventricular arrhythmias"	
Thrombocytopenia	Thrombocytopenia, Platelet count decreased	Immune thrombocytopenic purpura
Thrombosis or thromboembolism	All PTs containing "thrombosis" except as noted, Peripheral embolism, Pulmonary embolism, embolism	Superficial thrombosis, Embolic cerebral infarction
Transaminase elevation	Alanine aminotransferase increased, Aspartate aminotransferase increased, hepatic enzyme abnormal,Transaminase increased, Hepatic enzyme increased, liver function test increased, transaminase increased	PTs under FDA's "Hepatitis" grouping, PTs containing "hepatic failure", Hepatic function abnormal
Upper respiratory tract infection	All PTs containing "upper respiratory tract infection," "sinusitis," "laryngitis, or "pharyngitis," including within another word (e.g. nasopharyngitis), all PTs containing "rhinitis" except as noted, Rhinovirus infection	Rhinitis allergic , sinus congestion
Urinary tract infection	All PTs containing "cystitis" or "urinary tract infection", Pyelonephritis, Kidney infection	
Ventricular arrhythmia	High-level term, "Ventricular arrhythmias and cardiac arrest", ventricular tachycardia	

18.5. Efficacy Results by NHL Subgroup

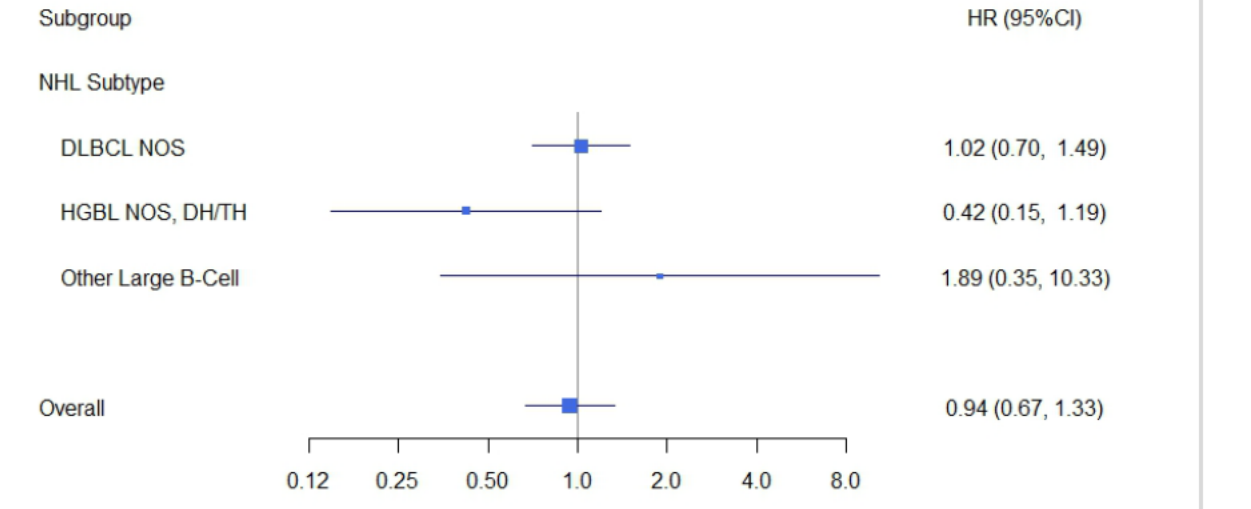
The FDA's assessment:
To assess the consistency of the treatment effect in POLARIX, FDA conducted exploratory, unadjusted analyses of PFS and OS by lymphoma subgroup: DLBCL NOS (n=740), HGBL (n=93), and other large B-cell lymphomas (n=46). The results suggest heterogeneity in the treatment effect.

Figure 43: Forest Plot of PFS by Histologic Subgroup



Source: FDA analysis

Figure 44: Forest Plot of OS by Histologic Subgroup



Source: FDA analysis. CCOD 6/15/2022.

Table 55: Results of PFS and OS by NHL Subgroups

NHL Subtype	Parameter	Pola + R-CHP	R-CHOP
Overall	**N**	440	439
	PFS		
	1-year rate (95% CI)	83.9% (80.4, 87.4)	79.8% (75.9, 83.6)
	diff	4.1% (-1.1, 9.3)	
	2-year rate (95% CI)	76.7% (72.7, 80.8)	70.2% (65.8, 74.6)
	diff	6.5% (0.5, 12.5)	
	HR (95% CI)	**0.73 (0.57, 0.95)**	
	OS		
	1-year rate (95% CI)	92.2% (89.7, 94.7)	94.6% (92.5, 96.8)
	diff	-2.5% (-5.8, 0.8)	
	2-year rate (95% CI)	88.7% (85.7, 91.7)	88.7% (85.7, 91.7)
	diff	-0.01% (-4.3, 4.2)	
	HR (95% CI)	**0.94 (0.67, 1.33)**	
DLBCL NOS	**N**	373	367
	PFS		
	1-year rate (95% CI)	84.0% (80.3, 87.8)	81.0% (76.9, 85.1)
	diff	3.0% (-2.6, 8.6)	
	2-year rate (95% CI)	77.3% (72.9, 81.7)	70.9% (66.1, 75.6)
	diff	6.4% (-0.03, 12.9)	
	HR (95% CI)	**0.75 (0.57, 0.99)**	
	OS		
	1-year rate (95% CI)	91.9% (89.1, 94.6)	95.5% (93.4, 97.7)
	diff	-3.7% (-7.2, -0.2)	
	2-year rate (95% CI)	88.0% (84.7, 91.3)	89.6% (86.4, 92.8)
	diff	-1.6% (-6.2, 3.0)	
	HR (95% CI)	**1.02 (0.70, 1.49)**	
HGBL (NOS or DH/TH)	**N**	43	50
	PFS		
	1-year rate (95% CI)	86.1% (75.7, 96.4)	67.4% (53.8, 81.1)
	diff	18.6% (1.5, 35.7)	
	2-year rate (95% CI)	81.4% (69.8, 93.0)	62.7% (48.5, 76.9)
	diff	18.7% (0.4, 37.0)	
	HR (95% CI)	**0.48 (0.21, 1.08)**	
	OS		
	1-year rate (95% CI)	95.2% (88.8, 100)	85.4% (75.3, 95.4)
	diff	9.9% (-2.0, 21.8)	
	2-year rate (95% CI)	95.2% (88.8, 100)	81.1% (69.9, 92.2)
	diff	14.2% (1.3, 27.0)	
	HR (95% CI)	**0.42 (0.15, 1.19)**	

NHL Subtype	Parameter	Pola + R-CHP	R-CHOP
Other LBCL [a]	**N**	24	22
	PFS		
	1-year rate (95% CI)	78.4% (61.6, 95.2)	85.7% (70.8, 100)
	diff	-7.3% (-29.8, 15.2)	
	2-year rate (95% CI)	58.4% (37.2, 79.6)	76.2% (58.0, 94.4)
	diff	-17.8% (-45.8, 10.2)	
	HR (95% CI)	**1.93 (0.66, 5.64)**	
	OS		
	1-year rate (95% CI)	91.7% (80.6, 100)	100% (100, 100)
	diff	-8.3% (-19.4, 2.7)	
	2-year rate (95% CI)	87.5% (74.3, 100)	90.9% (78.9, 100)
	diff	-3.4% (-21.3, 14.5)	
	HR (95% CI)	**1.89 (0.35, 10.33)**	

[a] T-cell/histiocyte-rich LBCL (n=28) and EBV+ DLBCL (n=18)
Source: Applicant response to 2/22/2023 IR. OS based on the 6/15/2022 CCOD.
Note: Some numbers vary slightly from the ODAC briefing document due to a difference in statistical program.

[sBLA 761121/008 Polivy (polatuzumab vedotin)]				

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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Clinical Pharmacology Team Leader				☑ Approved
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Division Director DHMII (Clinical)	Nicole Gormley, MD	OOD/DHMII	Sections: All	**Select one:** ☐ Authored ☑ Approved
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DCPI = Division of Cancer Pharmacology I		
DPM = Division of Pharmacometrics		
OB = Office of Biostatistics		
DBIX = Division of Biometrics IX		
OOD = Office of Oncologic Diseases		
DHM2 = Division of Hematologic Malignancies II		

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