CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761196Orig1s000

MULTI-DISCIPLINE REVIEW

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

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	BLA
Application Number(s)	761196
Priority or Standard	Priority
Submit Date(s)	August 7 and September 21, 2020
Received Date(s)	August 7 and September 21, 2020
PDUFA Goal Date	May 21, 2021
Division/Office	DHM2/OOD
Review Completion Date	April 23, 2021
Established Name	Loncastuximab tesirine-lpyl
(Proposed) Trade Name	Zynlonta
Pharmacologic Class	CD19-directed antibody and alkylating agent conjugate
Code name	ADCT-402
Applicant	ADC Therapeutics SA
Formulation(s)	Injection
Dosing Regimen	• 0.15 mg/kg every 3 weeks for 2 cycles • 0.075 mg/kg every 3 weeks for subsequent cycles
Applicant Proposed Indication(s)/Population(s)	Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma including high grade B-cell lymphoma, after at least two prior systemic therapies
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low grade lymphoma, and high-grade B-cell lymphoma

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Jennifer Lee, PharmD, RAC
Pharmacology/Toxicology Reviewer(s)	Natalie Simpson, PhD
Pharmacology/Toxicology Team Leader(s)	Brenda Gehrke, PhD
Office of Clinical Pharmacology Reviewer(s)	Krithika Arun Shetty, PhD Pharmacometrics: Liang Li, PhD OTS/OSIS: Amanda Lewin, PhD
Office of Clinical Pharmacology Team Leader(s)	Ruby Leong, PharmD Pharmacometrics: Lian Ma, PhD OTS/OSIS: Gopa Biswas, PhD
Clinical Reviewer	Candis Morrison, PhD, CRNP
Clinical Team Leader	Nicholas Richardson, DO, MPH
Statistical Reviewer	Jay Zhao, PhD
Statistical Team Leader	Yu-te Wu, PhD
Associate Director for Labeling (ADL) (acting)	Elizabeth Everhart, MSN, ACNP
Cross-Disciplinary Team Leader	Nicholas Richardson, DO, MPH
Deputy Division Director (DHOT)	Haleh Saber, PhD, MS
Division Director (OCP)	Brian Booth, PhD
Division Director (OB)	Thomas Gwise, PhD
Division Director (OOD)	Nicole Gormley, MD
Office Director (or designated signatory authority)	Marc Theoret, MD

OTS: Office of Translational Sciences
OSIS: Office of Study Integrity and Surveillance
DHOT: Division of Hematology Oncology Toxicology
OCP: Office of Clinical Pharmacology
OB: Office of Biostatistics
OOD: Office of Oncologic Diseases

Additional Reviewers of Application

OPQ/OBP	ATL: Bazarragchaa Damdinsuren, MD, PhD Reviewer: Massod Rahimi, PhD Labeling: James Barlow, RPh
OPRO	Regulatory Business Process Manager: Anita Brown
OPMA	Facility Team Leader: Zhong Li, PhD Micro Team Leader for Drug Substance (DS) and Drug Product (DP): Candace Gomez-Broughton, PhD

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	Primary DS Micro and Facility Reviewer: Bo Chi, PhD Primary DP Micro and Facility Reviewer: Amy Devlin, PhD
ONDP	DS Branch Chief and Secondary Assessor for Drug-Linker: Ali Al Hakim, PhD DS Assessor for Drug-Linker: Rohit Tiwari, PhD
OPDP	Nisha Patel, PharmD, RAC Team Leader: Susannah O'Donnell
OSI	Reviewer: Anthony Orencia, MD, FACP Team Leader: Min Lu, MD, MPH Branch Chief: Kassa Ayalew, MD, MPH
OSE	Safety Regulatory Project Manager: Neil Vora, PharmD, MBA, PMP
OSE/DMEPA	Reviewers: Maximilian Straka, PharmD, FISMP; Carlos M. Mena-Grillasca, BS Pharm Team Leaders: Hina Mehta, PharmD DMEPA Deputy Director: Danielle Harris, PharmD
PLT	Reviewer: Ruth Mayrosh, PharmD Team Leader: Barbara Fuller, RN, MSN, CWOCN Associate Director for Patient Labeling: LaShawn Griffiths, MSHS-PH, BSN, RN
IRT for Cardiac Safety Studies	Raman K. Baweja, PhD, Nan Zheng, PhD; Janell E. Chen, PhD; Dalong Huang, PhD; Christine E. Garnett, PharmD

ATL: Application Technical Lead
OPQ=Office of Pharmaceutical Quality
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
PLT=Patient Labeling Team
IRT= Interdisciplinary Review Team

Glossary

Abbreviation	Definition
ABW	adjusted body weight
ADA	antidrug antibody
ADaM	Analysis Data Model
ADC	antibody-drug conjugate
ADCT	ADC Therapeutics
ADME	absorption, distribution, metabolism, and excretion
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
AUC_{inf}	area under the serum concentration-time curve from time 0 to infinity
AUC_{tau}	area under the concentration-time curve from time zero to the end of the dosing interval
BLA	Biologics License Application
BMI	body mass index
B-NHL	B-cell non-Hodgkin lymphoma
BOR	best overall response
BRA	Benefit-Risk Assessment
CAR-T	chimeric antigen receptor T-cell
C_{avg}	average serum concentration
CD19	human cluster of differentiation 19
CDISC	Integrated Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulations
C_{max}	maximum serum concentration
CMC	Chemistry, Manufacturing, and Controls
COA	clinical outcome assessment
CR	complete response
CRF	case report form
CRO	clinical research organization
CRR	complete response rate
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events

Abbreviation	Definition
CYP	cytochrome P450
DHAP	cisplatin, cytarabine, dexamethasone
DHAX	dexamethasone, cytarabine, oxaliplatin
DLBCL	diffuse large B-cell lymphoma
DMF	Drug Master File
DOR	duration of response
ECG	electrocardiogram
ECLIA	electro-chemiluminescence immunoassay
ECOG	Eastern Cooperative Oncology Group
EQ-5D-5L	European Quality of Life (EuroQol)-5 Dimensions-5 Levels
EOT	end of treatment
FACT-G	Functional Assessment of Cancer Therapy-General
FACT-Lym	Functional Assessment of Cancer Therapy-Lymphoma
FDA	Food and Drug Administration
FL	follicular lymphoma
GCP	Good Clinical Practice
GDP	gemcitabine, dexamethasone, cisplatin
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
HD	high-dose (chemotherapy)
HNSTD	highest non-severely toxic dose
HRQoL	health-related quality of life
IC50	half maximal inhibitory concentration
ICE	ifosfamide, carboplatin, etoposide
ICH	International Council for Harmonization
IgG1	immunoglobulin G1
IND	Investigational New Drug
ISS	integrated summary of safety
IV	intravenous(ly)
LFT	liver function test
LymS	Lymphoma Subscale
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NDA	New Drug Application
NHL	non-Hodgkin lymphoma
NME	new molecular entity
NOS	not otherwise specified
OPQ	Office of Pharmaceutical Quality
ORR	overall response rate

Abbreviation	Definition
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigations
PBD	pyrrolobenzodiazepine
PDUFA	Prescription Drug User Fee Act
PFS	progression-free survival
P-gp	permeability-glycoprotein
PI	prescribing information
PK	pharmacokinetic(s)
PMC	postmarketing commitment
PMR	postmarketing requirement
PPI	patient package insert
PR	partial response
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
Q3W	every 3 weeks
QTc	corrected QT
QTcB	QT corrected by Bazett's formula
QTcF	corrected QT (Fridericia's correction)
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
REMS	risk evaluation and mitigation strategy
RFS	relapse-free survival
SAE	serious adverse event
SAP	statistical analysis plan
SCT	stem cell transplant
SMQ	Standardized MedDRA Query
TEAE	treatment-emergent adverse event
TOI	FACT-Lym Trial Outcome Index
UK	United Kingdom
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
VAS	visual analog scale

1 Executive Summary

1.1. Product Introduction

Loncastuximab tesirine (ADCT-402) is an antibody-drug conjugate (ADC) consisting of a CD19-directed humanized IgG1 kappa monoclonal antibody conjugated to SG3199, a pyrrolobenzodiazepine (PBD) dimer cytotoxic alkylating agent, through a protease-cleavable valine-alanine linker. SG3199 attached to the linker is designated as SG3249, also known as tesirine. The monoclonal antibody component binds to human CD19, a transmembrane protein expressed on the surface of cells of B-lineage origin. Upon binding to CD19, loncastuximab tesirine is internalized followed by release of SG3199 via proteolytic cleavage. The released SG3199 binds to the DNA minor groove and forms highly cytotoxic DNA interstrand crosslinks, subsequently inducing cell death.

The recommended dose of loncastuximab tesirine is

- 0.15 mg/kg every 3 weeks for 2 cycles
- 0.075 mg/kg every 3 weeks for subsequent cycles

Loncastuximab tesirine is administered until progressive disease, or unacceptable toxicity.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends accelerated approval of loncastuximab tesirine for:

- Treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low grade lymphoma, and high-grade B-cell lymphoma.

The recommended dose of loncastuximab tesirine is

- 0.15 mg/kg every 3 weeks for 2 cycles
- 0.075 mg/kg every 3 weeks for subsequent cycles administered until progressive disease or unacceptable toxicity

This recommendation is based on the efficacy of loncastuximab tesirine from ADCT-402-201, an open-label, single-arm trial in 145 adult patients with relapsed or refractory large B-cell lymphoma after at least 2 prior systemic regimens. The trial excluded patients with bulky disease and active central nervous system lymphoma. Patients received loncastuximab tesirine 150 µg/kg every 3 weeks for 2 cycles, then 75 µg/kg every 3 weeks for subsequent cycles and received treatment until progressive disease, or unacceptable toxicity. The primary endpoint

was overall response rate (ORR) as assessed by an Independent Review Committee (IRC) using Lugano 2014 criteria.

Of the 145 patients enrolled, the median age was 66 years (range 23 to 94), 59% male, and 94% had an ECOG performance status of 0 to 1. Race was reported in 97% of patients; of these patients, 90% were White, 3% were Black, and 2% were Asian. The diagnosis was DLBCL not otherwise specified (NOS) in 88% (including 20% with DLBCL arising from low grade lymphoma) and high-grade B-cell lymphoma in 8%. The median number of prior therapies was 3 (range 2 to 7), 63% with refractory disease, 17% with prior stem cell transplant, and 9% with prior chimeric antigen receptor (CAR) T-cell therapy.

Among the 145 patients, the median follow-up time was 7.3 months (range 0.3 to 20.2). The ORR per IRC was 48.3% (95% CI 39.9, 56.7), with 24.1% achieving a complete response. The median duration of response (DOR) per Kaplan-Meier was 10.3 months (95% CI 6.9, not evaluable). Notably, of the 70 patients with an objective response, 36% were censored for DOR prior to 3 months.

The ADCT-402-201 trial enrolled patients with relapsed or refractory large B-cell lymphoma after at least 2 prior systemic therapies. In this population, the overall response rate of 48% with associated durability is clinically meaningful. To support accelerated approval, the efficacy data is considered in the context of available therapy for patients with large B-cell lymphoma in the 3rd line setting and beyond. Available therapy includes the chimeric antigen receptor T-cell (CAR-T) therapies, axicabtagene ciloleucel and tisagenlecleucel, with overall response rates of 72% and 50%, respectively, with durability. Additionally, commonly administered regimens include intensive therapy with platinum, etoposide, and/or cytarabine-based combination regimens (ICE, ESHAP, DHAP) with rituximab or less intensive regimens including gemcitabine, gemcitabine-oxaliplatin, or bendamustine, with rituximab. In the 3rd line setting and beyond, these regimens either serve as a bridge to a hematopoietic stem cell transplantation (HSCT) or produce limited responses (response rates of 20-30%). Recently, three agents have received accelerated approval for patients with relapsed or refractory diffuse large B-cell lymphoma including polatuzumab vedotin in combination with bendamustine-rituximab, selinexor, and tafasitamab, with overall response rates of 63%, 29%, and 55%, respectively. In the ADCT-402-201 trial population, 71% of patients had received an intensive salvage regimen, HSCT, or CAR-T therapy. Therefore, the overall response rate of 48% with associated durability for loncastuximab tesirine provides data to support a clinically meaningful benefit in the context of available therapy for patients with relapsed or refractory large B-cell lymphoma after at least 2 prior lines of systemic therapies.

The ADCT-402-201 trial enrolled patients with DLBCL not otherwise specified (NOS) in 88% (including 20% with DLBCL arising from low grade lymphoma) and high-grade B-cell lymphoma in 8%. To support inclusion of the large B-cell lymphoma subtypes enrolled in ADCT-402-201,

specifically patients with high grade B-cell lymphoma, the Applicant provided data from 23 patients with high grade B-cell lymphoma from ADCT-402-101 that demonstrated activity in these patients consistent with the data from the pivotal trial. Thus, the indication for loncastuximab tesirine will reflect the subtypes of large B-cell lymphoma enrolled in the pivotal ADCT-402-201 trial.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

The benefit-risk assessment is favorable for loncastuximab tesirine for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low grade lymphoma, and high-grade B-cell lymphoma.

Efficacy:

Efficacy of loncastuximab tesirine is based on the results from ADCT-402-201, an open-label, multicenter, single-arm trial which included 145 adult patients with relapsed or refractory large B-cell lymphoma after at least 2 prior systemic regimens. Patients received loncastuximab tesirine 150 µg/kg every 3 weeks for 2 cycles, then 75 µg/kg every 3 weeks for subsequent cycles and received treatment until progressive disease, or unacceptable toxicity. The primary endpoint was overall response rate (ORR) as assessed by an Independent Review Committee (IRC) using Lugano 2014 criteria. Among the 145 patients, the median follow-up time was 7.3 months (range 0.3 to 20.2). The ORR per IRC was 48.3% (95% CI 39.9, 56.7), with 24.1% achieving a complete response. The median duration of response (DOR) per Kaplan-Meier was 10.3 months (95% CI 6.9, not evaluable). Notably, of the 70 patients with an objective response, 36% were censored for DOR prior to 3 months.

Safety:

The safety profile of loncastuximab tesirine was supported by analysis of 215 patients administered an initial dose of 150 µg/kg, including the 145 patients from the pivotal trial ADCT-402-201, with relapsed or refractory large B-cell lymphoma.

In 215 patients with relapsed or refractory large B-cell lymphoma, the median duration of treatment was 3 cycles (range 1 to 15) with 30% receiving 5 or more cycles. The most common (≥20%) adverse events, including laboratory abnormalities, were thrombocytopenia, increased gamma-glutamyltransferase, neutropenia, anemia, hyperglycemia, transaminase elevation, fatigue, hypoalbuminemia, rash, edema, nausea, cough, and musculoskeletal pain. Fatal adverse events occurred in 3%, primarily due to infection. Serious adverse events occurred in 40% and Grade 3 or greater adverse events occurred in 73%. The most common serious adverse events included hypercalcemia, infection, and edema or effusion. The most common Grade 3 or greater adverse events included cytopenias, GGT increased, edema or effusion. Adverse events leading

to treatment discontinuation occurred in 19%, most often due to GGT increased, edema, and effusion. Adverse events leading to treatment interruption occurred in 46%, most often due to GGT increased, neutropenia, thrombocytopenia, edema, and rash. The primary safety issues identified with loncastuximab tesirine include serious effusions and edema, myelosuppression, infections, and cutaneous toxicity.

Benefit-Risk:

Loncastuximab tesirine has an overall favorable benefit-risk in patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low grade lymphoma, and high-grade B-cell lymphoma. In the 145 patients from ADCT-402-201, the diagnosis was DLBCL not otherwise specified (NOS) in 88% (including 20% with DLBCL arising from low grade lymphoma) and high-grade B-cell lymphoma in 8%. The median number of prior therapies was 3 (range 2 to 7), 63% with refractory disease, 17% with prior stem cell transplant, and 9% with prior chimeric antigen receptor (CAR) T-cell therapy. However, the majority of patients were White at 90% and only 3% were Black and 2% were Asian, highlighting the limited racial and ethnic distribution of patients. Nevertheless, in this population, the overall response rate of 48% with associated durability and a tolerable safety profile constitutes a meaningful clinical benefit and a favorable benefit-risk. To support accelerated approval, the efficacy data is considered in the context of available therapy for patients with large B-cell lymphoma in the 3rd line setting and beyond. Available therapy includes the chimeric antigen receptor T-cell (CAR-T) therapies, axicabtagene ciloleucel and tisagenlecleucel, with overall response rate of 72% and 50%, respectively, with durability. Although, these therapies have limitations in the general relapsed or refractory large B-cell lymphoma population because of the toxicity profile, the waiting period for CAR-T manufacturing, and restricted availability. Additionally, commonly administered regimens include intensive therapy with platinum, etoposide, and/or cytarabine-based combination regimens (ICE, ESHAP, DHAP) with rituximab or less intensive regimens including gemcitabine, gemcitabine-oxaliplatin, or bendamustine, with rituximab. However, in the 3rd line setting and beyond, these regimens either serve as a bridge to a hematopoietic stem cell transplantation (HSCT) or produce limited responses (response rates 20-30%). Recently, three agents have received accelerated approval for patients with relapsed or refractory diffuse large B-cell lymphoma including polatuzumab vedotin in combination with bendamustine-rituximab, selinexor, and tafasitamab, with overall response rates of 63%, 29%, and 55%, respectively. In the ADCT-402-201 trial population, 71% of patients had received an intensive salvage regimen, HSCT, or CAR-T therapy. Therefore, the overall response rate of 48% with associated durability for loncastuximab tesirine provides data to support a clinically meaningful benefit in the context of available therapy for patients with relapsed or refractory large B-cell lymphoma in the 3rd line setting and beyond.

A notable limitation of the efficacy and safety data include the limited racial and ethnic representation with race reported in 97% of patients in ADCT-402-201; of these patients, 90% were White, 3% were Black, and 2% were Asian. For ethnicity, 9% identified as Hispanic or Latino.

Importantly, the safety data by race and ethnicity demonstrated a trend with a higher proportion of Grade ≥3 adverse events, Grade 3-4 neutropenia, and adverse events leading to dose delays occurring in Black and Hispanic patients compared to White patients, with limited safety data in Asian patients. Therefore, characterization of loncastuximab tesirine in broader racial and ethnic population is warranted and informed a postmarketing requirement.

The ADCT-402-201 trial enrolled patients with DLBCL not otherwise specified (NOS) in 88% (including 20% with DLBCL arising from low grade lymphoma) and high-grade B-cell lymphoma in 8%. To support inclusion of patients with high grade B-cell lymphoma in an indication, the Applicant provided data from 23 patients with high grade B-cell lymphoma from ADCT-402-101 that demonstrated activity in these patients consistent with the data from the pivotal trial. The indication for loncastuximab tesirine will reflect the subtypes of large B-cell lymphoma enrolled in the pivotal ADCT-402-201 trial.

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

- Treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low grade lymphoma, and high-grade B-cell lymphoma.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• DLBCL is fatal if not cured, and patients with relapsed or refractory disease after 2 or more regimens have an especially poor prognosis.	Relapsed or refractory DLBCL is a serious and life-threatening disease.
Current Treatment Options	• Salvage regimens for DLBCL include platinum, etoposide, and/or cytarabine-based combination regimens with rituximab. • Polatuzumab vedotin with bendamustine-rituximab, selinexor, and tafasitamab have accelerated approval.	Patients with relapsed or refractory large B-cell lymphoma have limited treatment options and there is a need for new and effective treatments.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Axicabtagene ciloleucel and tisagenlecleucel have regular approval for relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy.	
Benefit	• ADCT-402-201 is an open-label, multicenter, single-arm trial which included 145 adult patients with relapsed or refractory large B-cell lymphoma after at least 2 prior systemic regimens. • Loncastuximab tesirine was administered at 150 µg/kg every 3 weeks for 2 cycles, then 75 µg/kg every 3 weeks for subsequent cycles and received treatment until progressive disease, or unacceptable toxicity. • Overall response rate per Independent Review Committee was 48.3% (95% CI 39.9, 56.7), with 24.1% achieving a complete response. • Median duration of response (DOR) per Kaplan-Meier was 10.3 months (95% CI 6.9, not evaluable).	Based on overall response rate with durability, loncastuximab tesirine has clinically meaningful activity in patients with relapsed or refractory large B-cell lymphoma after at least 2 prior systemic therapies.
Risk and Risk Management	Of 215 patients with large B-cell lymphoma treated with an initial dose of 150 µg/kg loncastuximab tesirine: • Median duration of treatment was 3 cycles (range 1 to 15). • The most common (≥20%) adverse events, including laboratory abnormalities, were thrombocytopenia, increased gamma-glutamyltransferase, neutropenia, anemia, hyperglycemia, transaminase elevation, fatigue, hypoalbuminemia, rash, edema, nausea, cough, and musculoskeletal pain. • Fatal adverse events occurred in 3%, primarily due to infection.	The safety profile of loncastuximab tesirine is acceptable in the intended patient population. Toxicities were manageable with appropriate treatment interruption, reduction, or discontinuation. The USPI includes warnings and precautions for edema and effusion, myelosuppression, infections, and cutaneous reactions.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Serious adverse events occurred in 40% and Grade 3 or greater adverse events occurred in 73%. • The most common serious adverse events included hypercalcemia, infection, and edema or effusion. • The most common Grade 3 or greater adverse events included cytopenias, GGT increased, edema or effusion. • Adverse events leading to treatment discontinuation occurred in 19%, most often due to GGT increased, edema, and effusion. • Adverse events leading to treatment interruption occurred in 46%, most often due to GGT increased, neutropenia, thrombocytopenia, edema, and rash.	The USPI includes toxicity management for hematologic and non-hematologic toxicities. The safe use of loncastuximab tesirine can be managed through labeling and routine clinical care.

1.4. Patient Experience Data

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

X	The patient experience data that was submitted as part of the application, include:			Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO) – EQ-5D-5L and FACT-Lym questionnaires	**Section 8.1.2**
		□	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.	

Nicholas Richardson, DO, MPH
Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:
Non-Hodgkin lymphoma (NHL) represents a biologically and clinically diverse group of hematologic malignancies arising from precursor and mature B, T, and natural killer cells. It is the seventh most common type of cancer in the United States (US) and accounted for an estimated 4.2% (n=74,200) of new cancer cases in 2019 (Siegel et al 2019). Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHL, and accounts for an estimated 32.5% of NHL (Al-Hamadani et al 2015).

Approximately 25% of DLBCL patients are diagnosed with localized or limited stage disease and typically have a more favorable prognosis; approximately 75% of DLBCL patients present with advanced stage disease, commonly defined as Ann Arbor Stage III and IV or Stage I and II with associated B-symptoms or bulky disease (≥10 cm) (Sehn and Gascoyne 2015). Other difficult to treat disease includes double/triple hit disease and patients who have been heavily treated with two or more lines of prior systemic therapy.

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

2.2. Analysis of Current Treatment Options

In patients with advanced disease, the most commonly used frontline therapy is rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Approximately 60% of DLBCL patients will be cured, with more favorable outcomes seen in patients with limited stage disease. Unfortunately, approximately 10% to 15% of patients exhibit primary refractory disease (nonresponse or relapse within three months of therapy), and an additional 20% to 25% of patients relapse following initial response, usually within the first two years (Sehn and Gascoyne 2015).

Salvage therapy, including high-dose (HD) chemotherapy and autologous stem cell transplant (ASCT), can be effective treatment for DLBCL patients with chemotherapy-sensitive relapse. However, over half of the patients treated in this fashion will not have long-term disease control (Gisselbrecht and Van Den Neste 2018). The prognosis of patients whose disease is refractory to standard salvage chemotherapy, and are therefore not eligible for HD-ASCT, or

who relapse early after HD-ASCT is extremely poor. These patients have a poor response to salvage therapy, with an objective response rate of 26% (complete response [CR] rate [CRR] of 7%) and a median survival of approximately six months (Crump et al 2017). The management of patients with DLBCL who are ineligible for HD-ASCT or who relapse after HD-ASCT is difficult.

Table 1 summarizes more recently Food and Drug Administration (FDA)-approved therapies for relapsed or refractory DLBCL.

Table 1: Applicant-FDA-Approved Therapies for Relapsed or Refractory DLBCL

Product Names	Relevant Indication	Year and Type of Approval[a]	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
CD19-Directed CAR-T Therapies					
Yescarta (axicabtagene ciloleucel) Kymriah (tisagenlecleucel)	Treatment of adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including DLBCL NOS, primary mediastinal large B-cell lymphoma (Yescarta only), high grade B-cell lymphoma, and DLBCL arising from FL.	Yescarta 18 Oct 2017, regular approval Kymriah 01 May 2018, regular approval	The objective response rate or ORR ranged from 50% to 72%, with a CRR ranging from 32% to 51% and a PR rate ranging from 18% to 21%. Median DOR ranged from not estimable to 9.2 months. DOR was short for patients who only achieved a PR (median of 2.1 to 3.4 months).	Substantial toxicity, with 74% to 94% of patients having ADRs of cytokine release syndrome (13% to 23% ≥Grade 3), and 16% to 57% having encephalopathy (11% to 29% ≥Grade 3).	Note: only available at specialized centers and require substantial lead-time for preparation.
Anti-CD79b ADC					
Polivy (polatuzumab vedotin-piiq)	In combination with BR for the treatment of adult patients with relapsed or refractory DLBCL NOS, after at least 2 prior therapies.	10 Jun 2019, accelerated approval	Best ORR was 63%, with a CRR of 50% and a PR rate of 13%. DOR of at least 6 months was observed in 64% of patients and at least 12 months in 48% of patients.	Substantial toxicity. ADRs included peripheral neuropathy in 40% of patients (all grades) and ≥Grade 3 infections in 32%. Febrile neutropenia was reported in 13% of patients (all were ≥Grade 3), and ≥Grade 3 laboratory abnormalities reported as ADRs included neutropenia in 39%, thrombocytopenia in 23%, and anemia in 14%.	Eligible patients were not candidates for HD-ASCT or had experienced prior ASCT treatment failure at study entry, and the study excluded patients who had transformed lymphoma. Although not excluded from the trial, there were no patients enrolled with double hit/triple hit disease.[b]

Product Names	Relevant Indication	Year and Type of Approval[a]	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Nuclear Export Inhibitor					
Selinexor (Xpovio)	Taken orally as a single-agent for the treatment of adult patients with relapsed or refractory diffuse DLBCL NOS, including DLBCL arising from FL, after at least 2 lines of systemic therapy.	22 Jun 2020 accelerated approval	ORR was 29%, with a CRR of 13% and a PR rate of 16%. DOR at 3 months was 56%, at 6 months 38%, and at 12 months 15%.	ADRs included ≥Grade 3 fatigue in 15% of patients. ≥Grade 3 laboratory abnormalities included platelet count decrease (49%), neutrophil count decrease (31%), and hemoglobin decrease (25%).	Eligible patients were not candidates for ASCT, and the study required a minimum of 60 days since last systemic therapy, with a minimum of 98 days in patients with refractory disease (defined as less than PR) to last systemic therapy.
Anti-CD19 Antibody					
Monjuvi (tafasitamab-cxix)	In combination with lenalidomide in patients with relapsed or refractory DLBCL NOS, including DLBCL arising from low grade lymphoma, and who are not eligible for ASCT.	31 Jul 2020 accelerated approval	Best ORR was 55%, with a CRR of 37%, and a PR rate of 18%. DOR was 21.7 months.	Toxicity was substantial, and ≥Grade 3 ADRs included neutropenia (49%), thrombocytopenia (17%), and febrile neutropenia (12%). ≥Grade 3 or higher infections (30%).	Study included DLBCL patients who received 1, but no more than 3 previous systemic regimens. Study excluded patients with primary mediastinal (thymic) large B-cell, primary refractory disease (including patients with relapse within 3 months), double hit/triple hit disease, previous CD19-directed therapy including CAR-T therapy, and prior AlloSCT.[c]

Footnotes for Table 1 appear on next page.

Footnotes for Table 1:
ADC=antibody-drug conjugate; ADR=adverse drug reaction; AlloSCT=allogeneic stem cell transplant; ASCT=autologous stem cell transplant; BR=bendamustine and a rituximab product; CAR-T=chimeric antigen receptor T-cell; CD19=human cluster of differentiation 19; CRR=complete response rate; DLBCL=diffuse large B-cell lymphoma; DOR=duration of response; FDA=Food and Drug Administration; FL= follicular lymphoma; HD=high-dose; NOS= not otherwise specified; ORR=overall response rate; PR=partial response rate; USPI=United States Prescribing Information
a www.fda.gov (accessed 21 Oct 2020)
b Sehn et al 2020
c www.ClinicalTrials.gov, NCT02399085 (accessed 01 Nov 2020); Monjuvi Multi-Discipline Review (see https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/761163Orig1s000MultidisciplineR.pdf; accessed 12 Oct 2020)
Source: Kymriah USPI 2018; Monjuvi USPI 2020; Polivy USPI 2019; Xpovio USPI 2020; Yescarta USPI 2020; also see footnotes a, b, and c

The Applicant's Position:
There have been a number of treatments for relapsed or refractory DLBCL patients approved in recent years, however, there remains an unmet medical need. With the exception of the chimeric antigen receptor T-cell (CAR-T) therapies, all have received accelerated approval (polatuzumab vedotin-piiq [in combination with bendamustine and a rituximab product (BR), selinexor, and tafasitamab-cxix [in combination with lenalidomide]). All have substantial toxicities, and over half of patients will not have a durable response. In addition, patients with high risk characteristics such as primary refractory disease and double hit/triple hit disease have been excluded from the studies for one or more of these new therapies. The patient population used in the pivotal ADCT-402-201 study was more inclusive and therefore more representative of the relapsed/refractory population with respect to the types of patients eligible to enroll (e.g., allowed inclusion of patients who were candidates for ASCT, patients with primary refractory disease, double/triple hit disease, transformed disease, or previous receipt of CAR-T therapy). There remains an unmet medical need for treatments for patients with relapsed or refractory DLBCL.

The FDA's Assessment:
The FDA disagrees with the Applicant's characterization of the recently approved agents, including axicabtagene ciloleucel, tisagenlecleucel, polatuzumab vedotin, selinexor, and tafasitamab, for patients with relapsed or refractory large B-cell lymphoma. For each agent, the FDA determined that the data supporting approval demonstrated substantial evidence of effectiveness along with a favorable benefit-risk evaluation for the indicated population as described in the U.S. Prescribing information. Therefore, the characterization regarding substantial toxicities and limited durable responses doesn't provide the appropriate context for the associated benefit and the risks with each agent and the population. Additionally, FDA disagrees with the statement that the population in ADCT-402-201 is more inclusive and thus more representative of patients with relapsed or refractory large B-cell lymphoma. For the approved agents listed, the eligible and enrolled patients are taken in the context of the efficacy and safety data for the respective agents and ultimately informed the indicated population, which was determined to be applicable to a U.S. patient population. The FDA acknowledges that the ADCT-402-201 study enrolled patients with high-risk features as noted above. The FDA agrees there remains an unmet need for patients with relapsed or refractory large B-cell lymphoma and that new treatments are needed.

3 Regulatory Background

3.1. US Regulatory Actions and Marketing History

The Applicant's Position:
Loncastuximab tesirine is not currently marketed in the US.

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

3.2. Summary of Presubmission/Submission Regulatory Activity

Key regulatory interactions were as follows:

- **End of Phase 1 Meeting**: An End of Phase 1 meeting was held on 28 Mar 2018, at which the Phase 2 study design was discussed. It was agreed that the Phase 2 study population did not need to be restricted to transplant ineligible patients. A recommended patient population, which was used in the study, was one that had failed at least two prior lines of multi-agent systemic therapy.

- **Orphan Drug Designation**: Orphan drug designation was granted 08 Jun 2017 for treatment of DLBCL.

- **Pediatric Study Plan**: A request for a waiver in the age group 0 to 12 months and a request for deferral in the age group 1 to 17 years was submitted in an Initial Pediatric Study Plan in Feb 2020; following FDA review, an Agreed Initial Pediatric Study Plan was submitted to the Agency on 27 Jul 2020, in which FDA's recommendations on the initial plan were incorporated.

- **Confirmatory Phase 3 Study**: ADC Therapeutics (ADCT) has initiated a confirmatory Phase 3 study of loncastuximab tesirine in patients with DLBCL and the study was discussed at a Type C meeting with the FDA on 29 Jan 2020.

- **PreBLA Meeting**: ADCT discussed the content and presentation of data for a Biologics License Application (BLA) with the FDA on 17 Apr 2020.

- **BLA Submitted and Request for Priority Review:** ADCT submitted the Initial BLA and a request for priority review designation on 21 Sep 2020. The Chemistry, Manufacturing, and Controls (CMC) information for the BLA was submitted as a presubmission on 7 Aug 2020.

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

APPEARS THIS WAY ON ORIGINAL

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

4.1. Office of Scientific Investigations (OSI)

Clinical site inspections were requested for two clinical sites in the U.S. with the highest accrual for Study ADCT-402-201, along with inspection of the Applicant, ADC Therapeutics, Inc. The clinical sites included 1) Site 7 – University Hospitals Cleveland Medical Center (Dr. Caimi, MD, Cleveland, OH), which enrolled 10 patients and 2) Site 6 – Washington University School of Medicine (Dr. Kahl, MD, St. Louis, MO), which enrolled 7 patients. Based on the clinical site inspections, the study data from the clinical sites were considered reliable. Additionally, the Applicant was inspected concerning its oversight of ADCT-402-201. Based on the inspection, the Applicant's oversight of the clinical trial and the quality of conducting the study were determined to be adequate. The audited study data submitted to the Agency was deemed acceptable in support of the BLA application, in compliance with Good Clinical Practice.

4.2. Product Quality

Loncastuximab tesirine-lpyl (ADCT-402) is an antibody-drug conjugate comprised of a recombinant humanized IgG1κ monoclonal antibody (mAb) against human CD19 conjugated through interchain cysteines to pyrrolobenzodiazepine (PBD) dimer molecules via a protease-cleavable Val-Ala dipeptide-containing linker by thiol-maleimide chemistry. The loncastuximab tesirine-lpyl manufacturing process (b) (4) (b) (4).

Loncastuximab tesirine-lpyl drug product is supplied as a sterile, preservative-free, white to off-white lyophilized cake or powder in a single-dose vial for intravenous use after reconstitution and further dilution. Each vial contains 10 mg loncastuximab tesirine-lpyl, L-histidine (2.8 mg), L-histidine monohydrochloride (4.6 mg), sucrose (119.8 mg), and polysorbate 20 (0.4 mg). After reconstitution with 2.2 mL of Sterile Water for Injection, USP, the resulting concentration is 5 mg/mL with a pH of 6.0.

The recommended dose of loncastuximab tesirine-lpyl is 0.15 mg/kg every 3 weeks for 2 cycles followed by 0.075 mg/kg every 3 weeks for subsequent cycles.

The Office of Pharmaceutical Quality (OPQ) assessment of loncastuximab tesirine-lpyl manufacturing has identified that the methodologies and process used for mAb intermediate, drug linker intermediate, drug substance and drug product manufacturing, release and stability testing are robust and sufficiently controlled to result in a consistent and safe product. The mAb

intermediate manufacturing process is robust for inactivation and removal of adventitious agents. All facilities use for the manufacture and quality control testing were found to be acceptable for the proposed operations.

The immunogenicity assays were determined to be sufficiently sensitive to detect anti-drug antibodies (ADA) in the presence of loncastuximab tesirine-lpyl at plasma concentrations. Anti-drug antibodies were not characterized or assessed for neutralizing activity as the characterization and neutralizing antibody (NAb) assays were not submitted with the application. The review team concluded that a validated NAb was not necessary for approval as no patients were found to have treatment-emergent ADAs in ADCT-402-201. Although, as a validated NAb assay may be required for future clinical Nab assessment, a postmarketing commitment was issued (Section 13).

The Office of Pharmaceutical Quality recommends approval of loncastuximab tesirine-lpyl manufactured by ADC Therapeutics SA for human use under the conditions specified in the package insert. The data submitted support the conclusion that the manufacture of loncastuximab tesirine-lpyl is well-controlled and leads to a product that is pure and potent.

- Manufacturing location:
  - Monoclonal Antibody Intermediate: (b) (4)
  - Drug Linker Intermediate: (b) (4)
  - Drug Substance: (b) (4)
  - Drug Product: (b) (4)
- Fill size and dosage form: 10 mg, for injection, lyophilized powder in a single-dose vial
- Dating period:
  - Monoclonal Antibody Intermediate: (b) (4)
  - Drug Linker Intermediate: (b) (4)
  - Drug Substance: (b) (4) months when stored at (b) (4)
  - Drug Product: 24 months when stored at 5 ± 3°C
  - For packaged products: Not packaged
  - Stability Option:
    - We have approved the stability protocols in your license application for the purpose of extending the expiration dating of your antibody intermediate, drug linker intermediate, drug substance and drug product under 21 CFR 601.12.
- Exempt from lot release: Yes
  - Rationale: specified product

    Note: Loncastuximab tesirine-lpyl is exempted from lot release per FR 95-29960.

4.3. Clinical Microbiology

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

4.4. Devices and Companion Diagnostic Issues

Not applicable

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Loncastuximab tesirine (designated as ADCT-402 or RB4v1.2-SG3249) is an antibody-drug conjugate (ADC) with an established pharmacologic class (EPC) of CD19-directed antibody and alkylating agent conjugate. The humanized antibody component (RB4v1.2) of loncastuximab tesirine is an IgG1 kappa isotype. The antibody is conjugated (at the inter-chain cysteine residues) to a protease cleavable valine-alanine linker-payload designated as SG3249 (tesirine). SG3249 contains the payload SG3199, a pyrrolobenzodiazepine (PBD) dimer cytotoxic agent, a para-aminobenzoic acid (PABA) moiety, and a malemide polyethylene glycol (PEG) moiety. Loncastuximab tesirine has an average drug/antibody ratio (DAR) of approximately 2.3, purified from a distribution of drug load species with DAR values ranging from 0 to 6. PBDs are a class of naturally occurring antibiotics found in Streptomyces spp. PBD monomers bind in the DNA minor groove and form a single covalent aminal linkage to the exocyclic N2 amino group of guanine within purine-guanine-purine sequences. PBD dimers, obtained by joining two PBD monomers together via an appropriate polymethylene tether, have the ability to produce two covalent bonds forming highly cytotoxic DNA interstrand cross-links.[1] Cluster of differentiation (CD) 19 is a type I transmembrane glycoprotein belonging to the immunoglobulin Ig super family expressed on all types of B-lymphocytes except plasma cells, including leukemias and lymphomas of B-cell origin.[2,3]

Loncastuximab tesirine binds to cell surface CD19 and is internalized. Once inside the cell, the cytotoxic drug (SG3199) is released, forming DNA crosslinks and leading to cell death. The submitted pharmacology studies suggest CD19 binding and expression is an important determinant for the cytotoxic activity of loncastuximab tesirine.

The monoclonal antibody (mAb) component of loncastuximab tesirine, RB4v1.2, is selective for human CD19 and not cross-reactive with CD19 from any nonclinical species. The cynomolgus monkey was selected by the Applicant as the species for the nonclinical safety evaluation of loncastuximab tesirine, based on several considerations, including: (i) the greater predictivity of pharmacokinetic (PK) parameters obtained in this species for humans, (ii) the potential for reduced immunogenicity in this species compared to other nonclinical species, (iii) the observation that the skin is a target organ for toxicity with ADCs containing PBD warheads in

[1] John A. Hartley (2020): Antibody-drug conjugates (ADCs) delivering pyrrolobenzodiazepine (PBD) dimers for cancer therapy, Expert Opinion on Biological Therapy, DOI: 10.1080/14712598.2020.1776255
[2] Carter, R. H. and R. A. Barrington (2004). "Signaling by the CD19/CD21 complex on B cells." Curr Dir Autoimmun 7: 4-32.
[3] Tedder, T. F. (2009). "CD19: a promising B cell target for rheumatoid arthritis." Nat Rev Rheumatol 5(10): 572-577.

cynomolgus monkeys, which has translational value for humans. The Applicant submitted single- and repeat-dose toxicity studies evaluating the toxicities of SG3199 alone in rats or dogs.

No stand-alone safety pharmacology studies were conducted. Safety pharmacology assessments were incorporated into the GLP-compliant general toxicology studies in Sprague Dawley rats and cynomolgus monkeys. In the 13-week monkey study, slightly prolonged PR interval and increases in systolic, diastolic, and mean arterial pressures were observed in monkeys treated with loncastuximab tesirine on Day 78 compared to predose; however, the increases were within the range of animal variability. These trends are noted because there are pericardial effusions and a potential for cardiac toxicity observed in patients.

Proteolytic cleavage at the valine-alanine linker releases the inactive PABA cytotoxic agent moiety; the PABA group is self-immolative, resulting in the release of the active SG3199 cytotoxic agent. The fate of the maleimide-polyethylene glycol 8 (PEG8) moiety attached to the antibody has not been defined and likely remains attached until the antibody is catabolized. Loncastuximab tesirine was cleared slowly in animals with the half-life ranging from 8 to 17 days in monkeys. Exposures to loncastuximab tesirine generally increased dose proportionally with an increase in dose level. There were no major differences in plasma exposure between males and females and no evidence of accumulation with repeated dosing. Maximal serum concentrations were generally reached within 1.5 hours of dosing. Plasma concentrations were overall comparable between loncastuximab tesirine and the monoclonal antibody component, and the level of deconjugated SG3199 was below the lower limit of quantitation at most timepoints and dose levels in the 13-week repeat-dose study in monkeys. Plasma stability studies combined with the toxicokinetic data in monkeys suggest the ADC is stable and, when free, SG3199 is highly protein bound in rat, cynomolgus monkey and human plasma (approximately 97%, 93%, and 94%, respectively). [3H]-SG3199 distribution was rapid and widespread with the majority of tissues reaching maximum radioactivity at 2 hours post dose, the first sampling time point. There was no apparent distribution of SG3199 to melanin-containing tissues or the brain or spinal cord. Linear clearance profiles for loncastuximab tesirine were noted across the dose range studied (0.075-0.9 mg/kg), indicative of a lack of target-mediated drug disposition (TMDD) and consistent with the lack of cross-reactivity of RB4v1.2 to cynomolgus monkey CD19.

Loncastuximab tesirine-related toxicities were seen in the kidneys, liver, lungs, male reproductive organs, organs of the hematopoietic system, gastrointestinal tract, skin, salivary gland, and urinary bladder. Inappetence, body weight loss, and immunosuppression were dose limiting with the ADC in rats and skin toxicity (lesions) was dose limiting with the ADC in monkeys. Liver toxicity (jaundice) in rats and inappetence and body weight loss in Beagle dogs were dose limiting for SG3199. Decreased prothrombin time, increased platelets and fibrinogen, and hemorrhage were observed mainly in monkeys after repeated doses with

loncastuximab tesirine, although some minor changes in coagulation parameters were observed in rats following repeated doses of SG3199. Toxicity findings were generally reversible at tolerated doses, except for black spots on the skin and the effects on male reproductive organs. Also present during recovery at low incidence were organ hemorrhages and edema and myocardial degeneration. Some monkeys with these histopathological findings also displayed changes in hematology and clinical pathology parameters associated with inflammation. Treatment of monkeys with loncastuximab tesirine resulted in pro-inflammatory responses as indicated by increases in the white blood cells (WBCs) and/or differentials, increased fibrinogen, and histopathology observations (multi-organ inflammation, particularly the lung, kidney, or injection site). Pro-inflammatory findings with loncastuximab tesirine are consistent with findings in a meta-analysis of PBD-containing ADCs.[4] Of note, several of the findings with loncastuximab tesirine were observed in studies conducted with the free payload in pilot or GLP toxicology studies (Studies 527812, 527037, 527042 and 525532; data not presented in this review).

Reproductive and developmental toxicology studies were not conducted since cytotoxic (i.e. genotoxic) drugs that affect actively dividing cells, such as loncastuximab tesirine, are expected to be embryo/feto toxic and teratogenic. This position is consistent with the ICH S9 guidance.

The payload, SG3199, was genotoxic in GLP in vitro studies (in vitro micronucleus assay and the chromosome aberration assay in human lymphocytes from whole blood). A GLP bacterial reverse mutation assay (Ames test) was also conducted; however, mutagenicity could not be assessed due to cytotoxicity at all concentrations tested. In pharmacology studies and other toxicity studies, the Applicant demonstrated that SG3199 crosslinks DNA and causes double strand breaks. The results of these studies indicate that loncastuximab tesirine will cause chromosomal damage; therefore, the wait times for contraception will be T1/2 (half-life) + three months for males and 5 x T1/2 + six months for females after the last dose. The genotoxic risk for loncastuximab tesirine will be included in the labeling.

Fertility studies have not been conducted with loncastuximab tesirine. Results from repeat-dose toxicity studies with intravenous administration of loncastuximab tesirine in cynomolgus monkeys indicate the potential for impaired male reproductive function and fertility. Administration of loncastuximab tesirine to cynomolgus monkeys every 3 weeks at 0.6 mg/kg for a total of 2 doses, or every 3 weeks at 0.3 mg/kg for 13 weeks resulted in adverse findings that included decreased weight and/or size of the testes and epididymis, atrophy of the seminiferous tubules, germ cell degeneration, and/or reduced sperm content. The dose of 0.3 mg/kg in animals results in an exposure (AUC) that is approximately 3 times the exposure at the maximum recommended human recommended dose [MRHD] of 0.15 mg/kg. Findings were not

[4] Saber H, Simpson N, Ricks TK, et al. An FDA oncology analysis of toxicities associated with PBD-containing antibody-drug conjugates. Regul Toxicol Pharm. 2019;107:104429.

reversible at the end of the 12-week recovery period following 4 or 13 weeks of dosing. The animal:human safety margin was determined from a human exposure (AUC) of 26,518 day.ng/mL (or 636 hr.µg/mL) at the maximum recommended human dose (MRHD) of 0.15 mg/kg every 3 weeks and the Day 43 AUC from the 13-week general toxicology study in monkeys was 1830 hr*µg/mL at 0.3 mg/kg.

Additionally, a GLP tissue cross-reactivity study showed antigen-specific staining (membranous-to-cytoplasmic) of loncastuximab tesirine in mononuclear and/or stellate cells within the majority of human tissue specimens. The histological localization of the positive cells was interpreted as being specific to the binding of loncastuximab tesirine to CD19 expressed on the surface of B-lymphocytes and cells of follicular dendritic lineage, and no off-target binding was identified.

SG3199 is photoreactive and exposure to visible light, UVA or UVB radiation enhance its ability to mediate DNA crosslinking and double-stranded breaks, which may represent a contributory underlying mechanism to the epidermal hyperpigmentation and hyperkeratosis observed upon IV administration of loncastuximab tesirine in vivo.

In summary, loncastuximab tesirine causes cell death primarily driven by the payload SG3199. The toxicities observed in animals have generally been observed in patients. However, inflammatory responses (e.g. those seen in the lung and kidney) observed in animals have not been observed in patients or are of low incidence such that a cause-effect relationship has been difficult to establish. These toxicities are included in Section 13.2 of the label to provide additional information on potential ADC-related toxicities. Potential reproductive toxicities based on the mechanism of action and genotoxicity will also be communicated in the product labeling. There are no nonclinical issues to preclude approval of loncastuximab tesirine for the proposed indication.

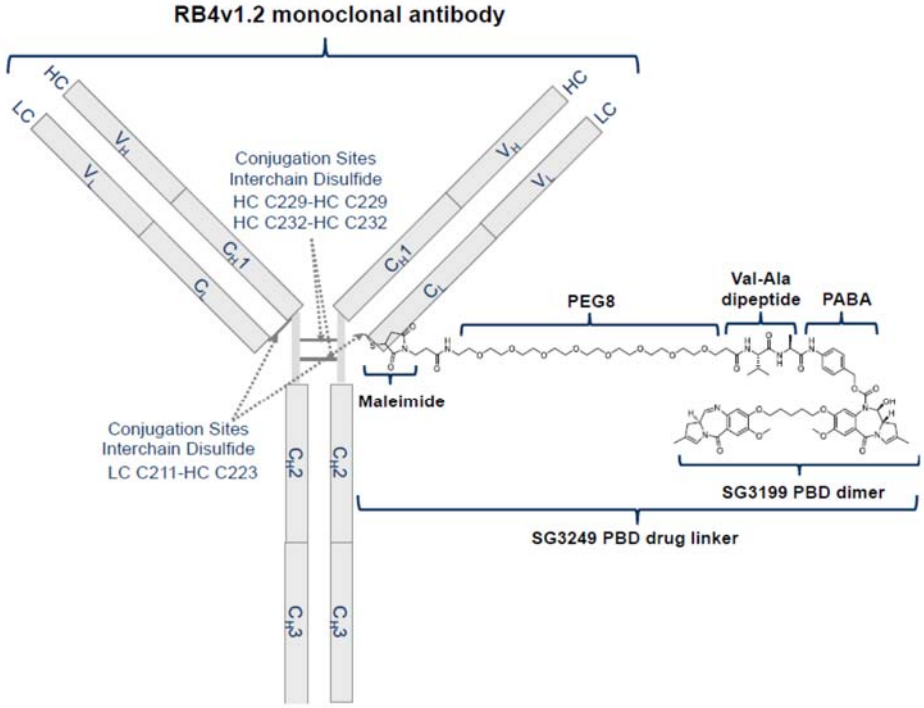
5.2. Referenced New Drug Applications (NDAs), BLAs, Drug Master Files (DMFs)

The Applicant's Position:
Not applicable.

5.3. Pharmacology

Diagram of Loncastuximab Tesirine with RB4v1.2 antibody, SG3249 PBD drug linker, and SG3199 PBD Components

(Figure taken from the Applicant's Drug Substance Summary)



Note: Schematic above illustrates conjugation to one of the interchain cysteine conjugation sites. ADCT-402 has an average DAR of approximately 2.3 and consists of a distribution of drug load species with DAR values ranging from 0 – 6.

Primary Pharmacology

Some of the mechanism of action studies were conducted using the antibody component (RB4v1.2) of loncastuximab tesirine (ADCT-402). In Study No. ADCT-402_R_009_R, the Applicant demonstrated that RB4v1.2 and ADCT-402 had comparable binding to CD19 using a competitive Ramos cell-based binding assay. Binding of RB4v1.2 to a panel of CD19 positive (Daudi, Ramos, DOHH-2, GRANTA-519, NAMALWA, SU-DHL-4, MEC-2, NALM-6) and CD19 negative (i.e., CD19 levels below the threshold of detection; SUP-T1, KM-H2) human leukemia and lymphoma cell lines was determined using flow cytometry (Study No. SIR041). The EC50s for binding to the CD19 positive cell lines ranged from 197 pM in Ramos Burkitt lymphoma cells to 665 pM in B-cell leukemia MEC-2 cells and there was no binding to the CD19 negative cells. The apparent KD for binding to CD19 positive cell lines ranged from 206 pM in Ramos cells to 757 and 790 pM in MEC-2 and B-cell lymphoma SU-DHL-4 cells, respectively.

Results from flow cytometry demonstrated that ADCT-402 bound to CD19 positive human Ramos cells and that neither ADCT-402 nor an isotype control ADC (with the same linker-payload as ADCT-402) bound to cynomolgus monkey peripheral blood mononuclear cells (PBMCs), despite confirmed CD19 expression on these cells (Study No. SIR039). Thus, binding of ADCT-402 to CD19 was not expected in the cynomolgus monkey toxicology studies.

The cytotoxicity of the payload (SG3199), ADCT-402, or the isotype control ADC against the panel of cell lines mentioned above was determined following 5 days of incubation using the cell viability (MTS) assay (Study No. SIR041). The IC50 values for SG3199 ranged between 17 pM for Acute lymphoblastic leukemia (ALL) NALM-6 cells and 361 pM for KM-H2 Hodgkin's lymphoma cells. For ADCT-402, the IC50 values for CD19 positive cells ranged from 0.07 pM in GRANTA-519 B-cell lymphoma cells to 13 pM in MEC-2 cells; the IC50 values for the CD19 negative cells were a log higher and the IC50s for the isotype control ADC were 30-fold higher than the CD19 positive cells. This data was also presented in a publication for which the Applicant has the right of reference that mentions there is a weak, yet significant negative correlation between the IC50 for cytotoxicity and the number of CD19 sites/cell and that GRANTA-519 and NALM-6 cells lines were most sensitive to both SG3199 and ADCT-402.[5]

Of note, at the highest concentration of ADCT-402 tested (67 nM), some cell lines appeared to retain resistant populations of cells, as evidenced by less than 90% total cell killing in these cell lines. ADCT-402 cytotoxic activity was 87% in GRANTA-519, 76% in MEC-2, 85% in KM-H2, and 83% in SU-DHL-4 cells. ADCT-402 cytotoxic activity reached >90% in the other tested cell lines. While the B-cell lymphoma GRANTA-519 cell line was one of the most sensitive CD19 positive cell lines to ADCT-402, this cell line had the highest level of heterogeneity of CD19 expression (approximately 2- to 3-fold greater than other CD19 positive cell lines) and lowest mean CD19 density (sites/cell). The B-cell lymphoma SU-DHL-4 cell line also had a lower mean CD19 density compared to other CD19 positive cell lines, but did not display a high level of heterogeneity of CD19 expression. Binding of RB4v1.2 to SU-DHL-4 cells was the lowest (highest KD) of all the CD19 positive cell lines and, in cytotoxicity assays, was also one of the least sensitive of the CD19 positive cell lines to ADCT-402 and SG3199. Overall, this data supports CD19 binding and expression is an important determinant for the cytotoxic activity of loncastuximab tesirine. The Applicant also determined whether ADCT-402 could kill CD19 negative cells in the presence of CD19 positive cells (aka, the bystander effect). The cytotoxicity of ADCT-402 and the isotype control ADC was measured by separately counting viable unlabeled effector cells (CD19 positive GRANTA-519 and Daudi cells or CD19 negative SUP-T1 and KM-H2 cells) and CFSE-labeled CD19 negative target cells (SUP-T1 or KM-H2) in 1:1 mixed co-cultures exposed for 4 days to serial dilutions of ADCT-402. ADCT-402, when in the presence of CD19 positive cells, is more active at killing CD19 negative cells than the isotype control ADC

[5] Zammarchi F, Corbett S, Adams L, et al. ADCT-402, a pyrrolobenzodiazepine dimer-containing antibody-drug conjugate targeting CD-19 expressing malignancies. Blood. 2018;131:1094–1105.

(up to 37-fold). ADCT-402, when in the presence of CD19 negative cells, is only 5-fold or less more active at killing CD19 negative cells than the isotype ADC control. There appears to be a small bystander effect, however, the Applicant noted that the ADCT-402 potency did not correlate statistically with the bystander potency (Study No. SIR041).

The ability of ADCT-402 to induce DNA crosslinking was determined in Ramos cells using a Comet assay. The cross-links formed were concentration dependent. The peak of cross-linking induced by ADCT-402 occurred around 12 hours after the two-hour exposure and persisted for up to 36 hours post-treatment, while the free payload SG3199 reached the same maximal cross-links during the two-hour incubation period. This likely reflects the time it takes for ADCT-402 to be trafficked to and processed in the lysosome and for the released payload, SG3199, to travel into the nucleus. In contrast, the isotype control ADC did not produce cross-links under identical conditions (Study Nos. ADCT402_R_018_R and UCL-ADCT-001). Immunofluorescence microscopy was used to detect internalization and co-localization of ADCT-402 with the lysosomal marker, lysosome associated membrane protein 1 (LAMP-1). CD19 expressing Ramos cells exposed to 2 µg/mL ADCT-402 (1 hour at 4°C) showed cell surface binding. When these cells were incubated at 37°C with ADCT-402, some ADCT-402 was still localized at the cell membrane after 1 hour, but there was also evidence of internalization and co-localization with lysosomes. This co-localization increased at 2 and 4 hours. No evidence of residual ADC staining was evident at 24 hours, suggesting complete lysosomal degradation.[5]

The in vivo activity of ADCT-402 was evaluated in immunodeficient mice subcutaneously (SC) xenografted with the CD19 positive human Ramos or Daudi Burkitt's lymphoma cell lines or with the CD19 positive human DLBCL cell line, WSU-DLCL2 (Study No. ADCT-402_R_007_R). In this study, ADCT-402 is referred to as RB4v1.2-SG3249 and batches SPADC2704.02/.04/.10 were used. In different trials using the Ramos model, 6/10 and 9/10 mice were tumor free following a single intravenous (IV) dose of 1 mg/kg ADCT-402, but no anti-tumor effects were observed at 0.3 mg/kg. In the Daudi xenograft model, 7/10 mice were tumor free following administration of a single IV dose of 0.3 mg/kg ADCT-402. No mice were tumor free following single IV doses up to 1 mg/kg in the WSU-DLCL2 xenograft model; however, there was a dose-dependent delay in tumor growth and a significant increase in the number of animals that were alive at the end of the study in mice administered 1 mg/kg ADCT-402 compared to phosphate buffered saline (PBS) vehicle control.

In a different study report (Study No. Ramos-e222) assessing anti-tumor activity in the SC Ramos model, 5/10 and 10/10 mice were tumor free following single IV doses of 0.66 and 1 mg/kg ADCT-402 (referred to as SPADC2704.10), respectively. ADCT-402 administered as a single IV dose of 1 mg/kg was more effective (as determined by a larger number of mice that were tumor free) compared to the fractionated regimens (0.33 mg/kg IV weekly for 2 to 3 weeks or every 4 days (3 doses total)). Also in this study report, ADCT-402 (single IV dose of 1

mg/kg) and two other CD19-targeted ADCs, RB4v1.2-DM4 (DAR~3.3) and hBU12-vc-PAB-MMAF (DAR~4.2), were compared side by side. Ten out of 10 animals (100%) treated with ADCT-402 were tumor free with zero animals tumor free with higher and more frequent doses of the comparator ADCs. The Applicant noted that the difference in the ADCs' activity was not due to differential target binding of the two anti-CD19 antibodies (RB41.2 and hBU12), as both ADCs showed similar binding kinetics.

In a disseminated Ramos xenograft model, ADCT-402 (referred to as 20141126-ADC) was administered as a single 1 mg/kg IV dose or fractionated IV doses of 0.33 mg/kg every 4 days (3 doses total). Following administration of single or fractionated doses, ≥80% of mice were still alive on Day 91 compared to 0% alive on Day 19 in PBS vehicle controls (Study No. Ramos-e224).

In a disseminated pre-B ALL NALM-6 xenograft model, ADCT-402 (referred to as Batch Lot. 20141126) was administered as a single 1 mg/kg IV dose or fractionated IV doses of 0.33 mg/kg every 4 days (3 doses total). Following administration of single or fractionated doses, 10/10 and 8/10 mice, respectively, were still alive on Day 90 compared to 0% alive on Day 21 in PBS vehicle controls (Study No. MV13135).

In a different study report (Study No. WSU-DLCL2-e242) assessing the WSU-DLCL2 mouse xenograft models, more mice were tumor free (7/10) when ADCT-402 (referred to as C075/083-011) was administered at single IV doses of 0.25 or 5 mg/kg on Day 10 in combination with intraperitoneal (IP) gemcitabine (every 3 days for 4 doses) than with either agent alone (0/10 mice tumor free). When 0.25 or 0.5 mg/kg ADCT-402 was administered as a single IV dose alone or on Day 1 in combination with 10 mg/kg intraperitoneal (IP) rituximab (every 4 days for 4 total doses), tumor regression was not affected, however, about 2 times more mice treated with the combination were alive on Day 62 of the study compared to either treatment administered alone.

Secondary Pharmacology

The Applicant's Position:
No formal secondary pharmacodynamic studies were conducted with loncastuximab tesirine or the SG3199 cytotoxic warhead. Potential off-target binding of loncastuximab tesirine was evaluated in a Good Laboratory Practice (GLP)-compliant human tissue cross-reactivity study in which specific, membranous-to-cytoplasmic staining was observed in mononuclear and/or stellate cells within the majority of human tissue specimens. Within the lymphoreticular, neuronal, and the majority of other tissues, these were scattered and individualized positive mononuclear and/or stellate cells located throughout the parenchyma with variable staining intensity. The histological localization of the positive cells was interpreted as being specific to

the binding of loncastuximab tesirine to human cluster of differentiation 19 (CD19) expressed on the surface of B-lymphocytes and cells of follicular dendritic lineage, and no off-target binding was identified.

The FDA's Assessment:

FDA concurs with the Applicant's assessment, but does not concur with the placement of this assessment. Tissue cross-reactivity studies are not secondary pharmacology studies and results should be described under Other Toxicology studies, consistent with placement of tissue cross-reactivity studies in the EDR. FDA notes that the staining reported above was observed at ADCT-402 concentrations ≥ 1 µg/mL.

Safety Pharmacology

The Applicant's Position:

Consistent with International Council for Harmonization (ICH) S6(R1), no stand-alone safety pharmacology studies were conducted with loncastuximab tesirine, and safety pharmacology endpoints were evaluated as part of the GLP-compliant 4- and/or 13-week repeat-dose toxicity studies in cynomolgus monkeys. Parameters evaluated included cardiovascular endpoints (8-lead electrocardiogram (ECG) [heart rate, RR-, PR-, QRS-, QT-, and QT corrected by Bazett's formula [QTcB]-interval] and blood pressure), respiratory rate, and neurobehavioral assessments (general assessment of sensorimotor function and a standard observation battery [modified Irwin]). No loncastuximab tesirine-related effects were noted on any endpoint studied.

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment. No evaluation for hERG inhibition was submitted for the ADC or SG3199. There was large variability in the individual ECG data in monkeys, but overall any observed changes in cardiovascular parameters assessed as part of the GLP toxicology studies in monkeys were not considered adverse or ADC-related.

5.4. Absorption, Distribution, Metabolism, and Excretion (ADME)/Pharmacokinetics (PK)

The Applicant's Position:

No formal ADME studies were conducted with loncastuximab tesirine. The SG3199 cytotoxic warhead was highly protein bound in rat, cynomolgus monkey, and human plasma. Tissue distribution of [3H]-SG3199 upon intravenous (IV) administration to pigmented and non-pigmented rats was rapid and widespread, with radioactivity in the majority of tissues peaking at 0.5 h postdose, without specific distribution to melanin-containing tissues. SG3199 acted as an inhibitor of transport mediated via BCRP, OATP1B1, OAT1, OAT3, OCT2, OCT1, MATE1, MATE2-K, and BSEP, but not via permeability-glycoprotein (P-gp) or OATP1B3, and

acted as a substrate for P-gp, but not for BCRP, OATP1B1, OATP1B3, or OCT1. The observed half maximal inhibitory concentrations (IC50) for transporter inhibition were well above the observed clinical exposures to SG3199, and therefore of limited concern. Metabolism studies showed that rat and cynomolgus monkey hepatocyte metabolite profiles most closely matched the human hepatocyte metabolite profile, whereas rat microsome metabolite profile most closely matched the human liver microsome metabolite profile. Furthermore, SG3199 was not a potent inhibitor of cytochrome P450 (CYP) enzymes, with CYP3A4/5 and non-CYP-mediated processes potentially involved in its metabolism. Following a single IV dose of [^{3}H]-SG3199 the main route of excretion of total radioactivity was via the feces/biliary route with minor urinary excretion.

In GLP-compliant repeat-dose toxicity studies in cynomolgus monkeys, loncastuximab tesirine exhibited linear PK without evidence of target-mediated clearance (consistent with the antibody component of the ADC being selective for human CD19) or substantial deconjugation (similar total antibody and antibody-drug conjugate [ADC] exposures, with short-lived, low level exposure to free SG3199), and a half-life ranging from ~8-17 days. Based on the PK parameters determined in the pivotal toxicology study, maximum serum concentration (C_{max})- and area under the concentration-time curve from time zero to the end of the dosing interval (AUC_{tau})-based exposure margins relative to a 150 µg/kg loncastuximab tesirine clinical dose were approximately 3- and 45-fold, respectively. With regard to SG3199, PK parameters could not be accurately determined in a GLP-compliant 4-week repeat-dose toxicity study in the rat, but available data following dosing on Day 1 indicated a half-life ranging from ~8.6-41 min, with clearance values >1000 mL/h/kg.

The FDA's Assessment:

Overall, the FDA concurs with the Applicant's assessment. Plasma stability studies were also conducted. The results support the stability of ADCT-402 in cynomolgus monkey or human plasma at 37°C for up to 7 days. The studies also showed that SG3199 binds to serum proteins, possibly serum albumin (Study Nos. SIR040 and VS-01009). Additionally, in an excretion study in rats, excretion was determined to be rapid, with most radioactivity (83.5 ± 5.8%) recovered 24 hours post dose (Study No. 197683). More details regarding the toxicokinetics of the payload when administered IV daily for 28 days to rats and the ADC when administered IV every 3 weeks (q3w) to monkeys for 4 or 13 weeks are provided below.

Rat 4-week payload only study with daily IV administration

SG3199

	C0 (pg/mL)				AUC_{0-t} (pg*h/mL)			
(µg/kg/day)	Day 1		Day 28		Day 1		Day 28	
	Male	Female	Male	Female	Male	Female	Male	Female
0.1	522	572	749	467	85.1	96.5	137	ND
0.5	1510	2390	2890	2640	326	447	941	652

	C0 (pg/mL)				AUC_{0-t} (pg*h/mL)			
(µg/kg/day)	Day 1		Day 28		Day 1		Day 28	
	Male	Female	Male	Female	Male	Female	Male	Female
1	4100	4170	ND	ND	950	920	ND	ND

ND = Not determined. C0 = the theoretical concentration at time zero after intravenous bolus dosing; assumed to be Cmax.

- The very rapid clearance of SG3199 hampered accurate determination of toxicokinetic (TK) parameters. Based on the available data following dosing on Day 1, systemic exposure to SG3199 increased with dose, without evidence of sex-related difference in exposure, and no evidence of accumulation.
- The mean half-life ranged from 0.143 to 0.690 hours (8 to 41 minutes), with a longer mean half-life observed with higher SG3199 doses.
- Mean clearance on Day 1 ranged from 1040 to 1520 mL/h/kg; on Day 28, mean clearance could only be determined in 0.5 µg/kg/day females at 728 mL/h/kg.

Monkey 4-week ADC study with q3w IV administration

Dose ADC	0.3 mg/kg				0.6 mg/kg			
Analyte	TAb		ADC		TAb		ADC	
Day	Day 1	Day 22	Day 1	Day 22	Day 1	Day 22	Day 1	Day 22
C_{max} (µg/mL)	7.21	8.79	7.19	8.21	15.75	17.4	14.55	15.5
AUC (hr* µg/mL)	981	1280	ND	ND	2000	2375	ND	ND

ND = not determined; TAb = total antibody; values are sex-averaged; On Day 1, AUC = 0-504 and on Day 22 AUC = 0-t

- Plasma concentrations for the conjugate and total antibody were comparable. Only plasma concentrations determined using methods to detect the antibody were used in the determination/presentation of other TK parameters (AUC, Cl, Vz, Tmax, and T1/2).
- Clearance of the total antibody was comparable to values in the 13-week study and much lower than hepatic blood flow and the glomerular filtration rate, with no trend relating to dose level or sex.
- There was no accumulation of the total antibody.
- As expected, the observed volume of distribution indicated distribution of the ADC (measured as total antibody) was minimal (blood and lymphatic space mainly), irrespective of dose level or sex.
- The TK profile is consistent with the lack of any target mediated drug clearance or the generation of any anti-drug antibodies in this study.
- There was evidence of some separation between the total RB4v1.2 mAb and ADCT-402 conjugate concentration-time curves beginning on Day 42 at 0.3 mg/kg and Day 71 at 0.6 mg/kg, which may suggest low-level shedding of SG3199.
- Antibodies against ADCT-402 were detected in 2 monkeys, one at 0.3 and one at 0.6 mg/kg, with evidence of accelerated drug clearance in the monkey at 0.3 mg/kg.

Dose ADC	0.3 mg/kg				0.6 mg/kg			
Analyte	SG3199				SG3199			
Day	Day 1		Day 22		Day 1		Day 22	
Sex	M	F	M	F	M	F	M	F
C_{max} (pg/mL)	55.9	53.3	14.6	10.1	204	117	111	102

M = male; F = female

- Most animals at both dose levels of the ADC were exposed to SG3199 at five minutes (0.08 h) after the end of the first infusion.
- Serum concentrations had dropped to below the lower limit of quantification between 8 and 120 hours post dose at 0.3 mg/kg, and between 72 and 216 hours post dose at 0.6 mg/kg, with the exception of one male, which still had a measurable concentration at 336 hours post dose.
- On Day 1, the Tmax of SG3199 was between 0.58 and 1.5 hours (measured at the start of infusion) at 0.3 and 0.6 mg/kg, respectively. On Day 22, Tmax was 0.58 hours for both doses.
- The exposure (Cmax) of SG3199 was approximately less than 2% the exposure for the ADC.

Monkey 13-week ADC study with q3w IV administration

ADC

	Cmax (µg/mL)			AUC_{0-t} (hr* µg/mL)			Cl (mL/h/kg)	
Day	Day 1	Day 43	Day 85	Day 1	Day 43	Day 85	Day 1	Day 43
0.075	2.26	2.80	3.08	256	506	221	0.308	0.163
0.15	4.40	5.35	5.00	496	959	388	0.293	0.154
0.3	10.87	10.6	9.31	996	1830	617	0.248	0.186

- On Days 1 and 43, the mean sex-averaged half-life for the ADC ranged from 207 to 231 hours (or 8.6 to 9.6 days).
- No sex differences were observed, with dose proportional exposure (Cmax and AUC) and no ADC accumulation over the dosing period.
- Median Tmax values for conjugated ADCT-402 ranged from 0.583 to 1.50 hours from the start of infusion on Days 1 and 85 and was 1.50 hours from the start of infusion on Day 43.
- ADC concentrations were measurable up to 168 hours from the end of infusion on Day 85.
- From 1583 serum samples, a selection of 530 samples were analyzed by LC-MS/MS to detect the concentration of SG3199 in plasma. From the bioanalysis, 530 valid results were obtained. For the samples, the concentrations of SG3199 ranged from approximately <25.0 pg/mL to 40 pg/mL in the monkeys.

- A total of 8 samples from 7 animals scored positive in the ADA screening assay. In the confirmation assay, 7 samples from 7 animals were confirmed positive for anti-ADCT-402 antibodies. Note: 5 of the 7 confirmed positive titers were taken from pretest (Day -6) samples and 2 of the 7 were from animals on Day 85 (one female each at 0.075 and 0.15 mg/kg). The exposure to conjugated ADCT-402 was notably lower compared to the profiles of other animals in the respective dosing groups, therefore, the data for these two animals was excluded from descriptive statistics.

5.5. Toxicology

5.5.1. General Toxicology

The Applicant's Position:
No pharmacologically relevant nonclinical species for safety evaluation—as defined in ICH S6(R1)—exists for loncastuximab tesirine, due its antibody component being selective for human CD19. The cynomolgus monkey was selected as nonclinical species for safety evaluation of loncastuximab tesirine, given the greater predictive value of PK data generated in this species for humans, potential for reduced impact of antidrug antibody (ADA) formation on drug exposure, and the proven utility of 1/6th highest non-severely toxic dose (HNSTD) for setting clinical starting doses with ADCs. Furthermore, toxicities that are known class effects associated with pyrrolobenzodiazepine dimer (PBD) warheads (eg, skin toxicity) are observed in this species. Importantly, on-target (ie, CD19-mediated) toxicity cannot be evaluated in this or any other nonclinical species; however, a considerable body of data on the nonclinical and clinical safety of CD19- and CD20-specific B-cell-depleting agents exists.

In repeat-dose toxicity studies in cynomolgus monkeys, loncastuximab tesirine exhibited a safety profile consistent with SG3199-mediated effects on the skin (epidermal hyperpigmentation with hyperplasia/hyperkeratosis), bone marrow (hypocellularity associated with regenerative anemia), kidney (nephropathy—degeneration and hyperplasia/hypertrophy of distal tubules and collecting ducts, mainly in the cortico-medullary junction) and testis (testicular atrophy with reduced spermatogenesis). The majority of these findings were considered to be reversible, although (full) reversibility was not always demonstrated in the context of completed studies. The nonclinical toxicity of SG3199 was predominantly evaluated in the rat, with the toxicity profile characterized by myelosuppression, increased liver enzymes/liver toxicity, and inflammation of the gastrointestinal tract with epithelial degeneration.

The FDA's Assessment:
FDA generally concurs with the Applicant's assessment. More details regarding the toxicities associated with the payload and ADC are provided below. Overall, the toxicities of the ADC appear payload driven.

The Applicant submitted single-dose and repeat-dose general toxicology studies in which Sprague Dawley rats or Beagle dogs were dosed with the payload (SG3199) only. In the studies submitted, liver toxicity (jaundice) was dose limiting in rats. In dogs, the dose limiting toxicities were inappetence and body weight loss. Toxicity to the hematopoietic system (e.g., reduced red blood cells (RBCs), WBCs, and platelets in the periphery; decreased hematopoiesis or lymphoid depletion in the bone marrow), liver toxicity (elevated liver enzymes, jaundice, and/or, hepatocyte hypertrophy, bile duct hyperplasia, periportal fibrosis and pigment deposits in the liver), kidney toxicity (elevations in blood urea nitrogen (BUN) or electrolyte imbalances) and gastrointestinal tract changes were observed in both species. Hyperkeratosis of the skin and ulceration and atrophy of squamous epithelium in the esophagus were observed only in dogs.

The non-GLP 7-day repeat-dose toxicology study in rats (Study No. 525548) was used to support the proposed specifications of not more than (NMT) (b) (4) free SG3199 per mL of the ADC. Male rats (n=3/group) were administered SG3199 intravenously over 15 to 30 seconds daily for 7 days at doses of 0 (5% (v/v) N,N-dimethylacetamide (DMA)), 0.1, 0.3, 1, and 3 µg/kg/day. There was reduced body weight gain at doses ≤ 1 µg/kg/day, but not body weight loss as observed at 3 µg/kg/day. There were no apparent test article-related microscopic findings at ≤ 1 µg/kg/day. At 3 µg/kg/day SG3199, microscopic findings of severe decreased hematopoiesis in the bone marrow (femur and sternum), mild necrosis with inflammation at the injection site, minimal alveolar focal inflammation of the lung, and moderate to marked atrophy of the thymus were observed.

The Applicant conducted GLP 4-week and 13-week repeat-dose general toxicology studies in which cynomolgus monkeys were dosed with the ADC, followed by a 12-week recovery period. In the 4-week study (Study No. 8303115), monkeys were administered IV doses of the ADC over 30 minutes at doses of 0 (b) (4), 0.3, and 0.6 mg/kg q3w (2 doses). There were no unscheduled mortalities. At 0.6 mg/kg, increased vascularization of the eye was observed in one recovery male. Statistically significant and transient increases in platelets were observed at doses ≥ 0.3 mg/kg on Days 14 and 20. Two-fold (100%) increases in liver enzymes (AST, GLDH) were observed at 0.6 mg/kg compared to controls. At 0.6 mg/kg in males, urine specific gravity dropped on Days 20 and 28 and on Day 20, there were 2-fold increases in urine creatinine compared to controls. Microscopic findings of increased subcutaneous fat and fat in the serosa of the gallbladder were also observed at 0.6 mg/kg.

The majority of the toxicities observed in the 4-week study were also observed in the 13-week study, with progression of some findings to lower doses with longer periods of dosing. For example, the incidence of black spots that correlated microscopically with epidermal hyperpigmentation observed at 0.6 mg/kg q3w in the 4-week study was comparable to the incidence at the 0.3 mg/kg dose in the 13-week study. Statistically significant decreases in hematocrit and hemoglobin were observed only at 0.6 mg/kg in the 4-week study and were observed at ≥ 0.15 mg/kg on Day 92 of the 13-week study. Creatinine elevations in the 4-week study were only observed at 0.6 mg/kg and during the recovery phase; in the 13-week study they were observed during the main study phase in females at doses ≥ 0.15 mg/kg. Microscopic findings of nephropathy (characterized by tubular degeneration and dilation) were observed at 0.6 mg/kg in the 4-week study and are observed at doses ≥ 0.075 mg/kg in the 13-week study. In one 0.6 mg/kg female, slight fibrosis (pleural/subpleural) of the lungs was observed only in the recovery phase in the 4-week study; in the 13-week study, minimal to moderate fibrosis (pleural/ subpleural) of the lungs was observed at doses ≥ 0.15 mg/kg during the dosing phase. In the 13-week study, multifocal edema, alveolar hemorrhage, acute inflammation, and necrosis were observed in the lung, but were not present or were reduced in severity by the end of the 12-week recovery phase. Also, adverse findings in male reproductive organs were present at 0.6 mg/kg only in the 4-week study and at all doses (≥ 0.075 mg/kg) in the 13-week study.

The results from the 13-week general toxicology study in cynomolgus monkeys are presented below.

ADCT-402 13-week intravenous infusion toxicity study in sexually mature cynomolgus monkey with a 12-week recovery phase [Study No. 8374716]

Key Study Findings

- Toxicities were observed in the bone marrow (decreased cellularity), kidney (nephropathy), skin (black discoloration, epidermal hyperpigmentation and hyperplasia), male reproductive organs (depletion/degeneration of the germ cells in the testis and reduced sperm in the epididymis), lung (fibrosis) likely secondary to inflammation, salivary gland (degranulation), urinary bladder (vacuolation), and gastrointestinal tract (inflammation and in some cases, hemorrhage).
- Multiorgan inflammation/edema/mononuclear cell infiltration/congestion and hemorrhages were observed.
- In the pituitary, basophil hypertrophy was noted in males at 0.3 mg/kg, indicative of changes in hormonal homeostasis.

- No fresh corpus luteum was observed in one 0.3 mg/kg female and congestion of the myometrium in the uterus/cervix was observed in one female each at 0.075 and 0.3 mg/kg.
- In general, toxicities were reversible over the 12-week recovery period. Black spots on the skin and male reproductive organ toxicity were still present at the end of the recovery period and did not show a clear trend in reversibility.
- Two recovery males had organ hemorrhages and/or edema that were not present in terminal animals, some of which appear associated with inflammation.
- Myocardial degeneration was observed in control and in ADCT-402 treated monkeys. Macroscopic correlates and correlating heart weight increases were only observed in ADC-402 treated monkeys during the recovery phase. The toxicological significance of these observations is uncertain.

Conducting laboratory and location: (b) (4)

GLP compliance: **Yes**

Methods

Dose and Frequency of Dosing:	0 (vehicle), 0.075, 0.15, 0.3 mg/kg, once every 3 weeks for 3 months (Days 1, 22, 43, 64, and 85)
Route of Administration:	30-minute IV infusion
Formulation/Vehicle:	(b) (4) (b) (4)
Species/Strain:	Cynomolgus monkeys
Number/Sex/Group:	Main study – 3/sex/group; Recovery – 2/sex/group
Age:	47 to 88 months old
Satellite Groups/Unique Design:	None
Deviation from Study Protocol Affecting Interpretation of Results:	None; however, concentrations of the low dose dosing solution were regarded as below the limit of detection. Therefore, the determined concentrations could not be regarded as valid and the correct dilution could only be assumed.

Observations and Results: changes from control (13-week monkey toxicology study)

Parameters	Major findings
Mortality	All animals survived until their scheduled sacrifice on Day 92 (Week 13) of the dosing phase or Day 85 (Week 12) of the recovery phase.

<table>
<tr><td>Clinical Signs</td><td>Black spots and/or skin discoloration were observed from Day 78 onwards in 2 of 5 females administered 0.075 mg/kg and from Day 22 onwards in 1 of 5 males administered 0.075 mg/kg. Black spots were also observed on Day 29 onwards in all females administered 0.15 mg/kg (not reversible in the 2 recovery females), and 0 of 5 males administered 0.15 mg/kg.

Dark/black spots were found on extremities (leg and/or arms) from Day 22 onwards in all males administered 0.3 mg/kg and from Day 29 onwards in all females administered 0.3 mg/kg; later on, spots or blackened skin were also observed on the trunk and the head/face of single animals. Discoloration was reversible by Recovery Day 64 in males but not in females.</td></tr>
<tr><td>Body Weights</td><td>0.3 mg/kg (males only): The group mean body weight decreased from pre dose to Day 91 (-0.3 kg). While 4 of 5 animals in this group lost body weight, this decrease mainly reflects the change in two terminal males (-0.3 kg and -0.9 kg from pre dose to Day 91). Although these two animals were not selected to undergo recovery, the selected recovery animals gained body weight from Day 91 of the dosing phase until the end of the recovery phase. Treatment with up to 0.3 mg/kg ADCT-402 had no effect on food consumption.</td></tr>
<tr><td>Ophthalmoscopy</td><td>Findings such as opacity, pigmented dots, compaction, drusen, myelinated nerve fiber, spider web structure, and epipapillary membrane were considered incidental as they were infrequent, were found in both test item-treated animals and controls, lacked a dose response, or were comparable with observations typically noted in this laboratory animal species.</td></tr>
<tr><td>ECG and Blood Pressure</td><td>0.15 mg/kg (one recovery female): slightly prolonged PR interval (+7 ms) was observed on Day 78 of the recovery phase compared to pre dose.
0.3 mg/kg (one recovery male and one recovery female): prolonged PR interval (+32 ms; +16 ms) was observed on Day 78 of the recovery phase compared to pre dose.

These animals had histopathologic findings of myocardial degeneration in the heart. The females also showed increases in systolic, diastolic, and mean arterial pressures on Day 78 of recovery compared to pre dose, but the absolute values were within the normal range.</td></tr>
<tr><td>Hematology</td><td>Percent changes compared to the control.
<table>
<tr><th></th><th></th><th colspan="4">Males</th><th colspan="4">Females</th></tr>
<tr><th>Dose (mg/kg/q3w)</th><th>Day</th><th>0</th><th>0.075</th><th>0.15</th><th>0.3</th><th>0</th><th>0.075</th><th>0.15</th><th>0.3</th></tr>
<tr><td>Hematocrit %</td><td>92</td><td>49</td><td>-5</td><td>-11***</td><td>-18***</td><td>42</td><td>8</td><td>1</td><td>-12</td></tr>
<tr><td>Reticulocytes 10^12/L</td><td>92</td><td>0.1</td><td>-4</td><td>-38*</td><td>-73***</td><td>0.1</td><td>34</td><td>-51</td><td>-63*</td></tr>
<tr><td>Erythrocytes 10^12/L</td><td>92</td><td>7.2</td><td>-4</td><td>-16***</td><td>-23***</td><td>6.4</td><td>9</td><td>-2</td><td>-18*</td></tr>
<tr><td>Monocytes 10^9/L</td><td>92</td><td>0.7</td><td>10</td><td>40</td><td>104</td><td>0.6</td><td>4</td><td>25</td><td>88*</td></tr>
<tr><td>Eosinophils 10^9/L</td><td>92</td><td>0.5</td><td>-62</td><td>-72</td><td>-80</td><td>0.3</td><td>-52*</td><td>-63**</td><td>-63**</td></tr>
<tr><td>Hemoglobin mmol/L</td><td>92</td><td>9.0</td><td>-2</td><td>-11**</td><td>-17***</td><td>7.8</td><td>6</td><td>0</td><td>-11</td></tr>
<tr><td>M:E Ratio</td><td>92</td><td>2.2</td><td>-11</td><td>19</td><td>475</td><td>1.8</td><td>-9</td><td>28</td><td>126</td></tr>
</table>
M = myeloid; E = erythroid; *p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001

Findings reversed or demonstrated a trend in reversibility by the end of the recovery phase.
Sporadic elevations in WBCs and neutrophils compared to pretest were observed mainly in 0.3 mg/kg females are were reversible in 1 out of 2 recovery females.
</td></tr>
<tr><td>Coagulation</td><td>Percent changes compared to the control.</td></tr>
</table>

	Males					Females			
Dose (mg/kg/q3w)	**Day**	**0**	**0.075**	**0.15**	**0.3**	**0**	**0.075**	**0.15**	**0.3**
Fibrinogen g/L	92	2.3	6	14	56*	2.0	10	9	36***

*p ≤ 0.05; ***p ≤ 0.001

- A statistically significant decrease in prothrombin time (-10% compared to control) was observed at 0.3 mg/kg on Days 36 and 78 (males only) and at 0.15 and 0.3 mg/kg on Day 57.
- Increases in mean APTT (up to +18% compared to pretest) were observed mainly at 0.3 mg/kg and later in the dosing phase. The magnitude of change was more pronounced when compared to pretest vs. control values.
- Findings reversed by the end of the recovery phase.

Clinical Chemistry

Percent changes compared to the control.

	Males					Females			
Dose (mg/kg/q3w)	**Day**	**0**	**0.075**	**0.15**	**0.3**	**0**	**0.075**	**0.15**	**0.3**
Creatinine µmol/L	92	298	0	16	18	70	8	24**	36***

**p ≤ 0.01; ***p ≤ 0.001

- Findings demonstrated reversibility.
- In one male administered 0.3 mg/kg, blood urea nitrogen (BUN) was increased approximately 2-fold on Day 92.
- Creatine kinase was increased in males at all dose levels (including control) on Day 92, which is considered a result of the intramuscular ketamine injections being administered on Day 91 for the scheduled ophthalmoscopy examinations.
- Decreases in mean albumin (up to -19% compared to pretest) were observed mainly at 0.3 mg/kg and later in the dosing phase. The magnitude of change was more pronounced in individual monkeys and when comparing mean ADCT-402-treated high dose values to pretest vs. vehicle control values.
- Increases of about +20% compared to pretest in globulin were observed as early as Day 15 of dosing in some individual males and females at 0.3 mg/kg.
- C-reactive protein levels were not measured.

Urinalysis

Unremarkable.

Gross Pathology

		Males				Females			
Dose (mg/kg/q3w)		**0**	**0.075**	**0.15**	**0.3**	**0**	**0.075**	**0.15**	**0.3**
Number of Animals Examined (Terminal/Recovery)		3/2	3/2	3/2	3/2	3/2	3/2	3/2	3/2
TESTIS	Abnormal consistency				3/1	NA	NA	NA	NA
	Abnormal shape				2/1	NA	NA	NA	NA
	Decreased size			0/1	2/1	NA	NA	NA	NA
	Discoloration, pale				3/0	NA	NA	NA	NA
EPIDIDYMIS	Abnormal consistency				2/0	NA	NA	NA	NA
	Abnormal shape				2/0	NA	NA	NA	NA
	Decreased size				2/0	NA	NA	NA	NA
	Discoloration, pale				2/0	NA	NA	NA	NA

	LUNG	Abnormal consistency				1/0				
		Abnormal shape				1/0				
		Adhesion with diaphragm				2/0				
		Adhesion with lobe				1/0				
		Adhesion with pleura			1/0	1/0				
		Discoloration, red				0/1				
	BRAIN	Discoloration, dark				0/1				
	HEART	Abnormal consistency				0/1			0/1	0/1
		Discoloration, pale				1/1				
		Discolored focus				0/1				
		Increased size								0/1
	SKIN/SUBCUTIS	Discoloration, black, grey or brown				3/0				3/0
		Discolored focus, brown								1/0
	GLAND, LACRIMAL	Discoloration, dark				0/1				
	GLAND, PITUITARY	Discoloration, red				0/1				
	GLAND, SALIVARY, SUBMANDIBULAR	Discoloration, dark				0/1				
		Enlargement				0/1				
	GLAND, THYROID	Enlargement				1/0				1/1
	KIDNEY	Abnormal surface				0/1				0/1
		Congestion/Congestion of vessels		0/1		0/1				
		Discoloration, pale					1/0			2/1
		Discolored focus, red								0/1
		Increased size				1/0				
	LARGE INTESTINE, CECUM	Discoloration, dark, red	0/1			1/2				
	LARGE INTESTINE, COLON	Discoloration, grey				1/0				
	LIVER	Increased size				1/1				
	LYMPH NODE, MESENTERIC	Decreased size				1/0				
	SITE, INJECTION	Discoloration, black, grey				3/0				3/0
	SPLEEN	Enlargement			1/0	2/2				1/0
	STOMACH	Discoloration, red				0/1				
	UTERUS/CERVIX	Discoloration	NA	NA	NA	NA		0/1	1/0	1/2
	OVARY	Decreased size	NA	NA	NA	NA				1/0

Blank cells = finding not present in group or not toxicologically significant; NA = organ not present in sex.

- Black, brown, or grey discoloration or brown discolored foci in the skin were observed on the arms, legs, head, injection site, and/or trunk of all animals at the

high dose of 0.3 mg/kg and correlated microscopically with epidermal hyperpigmentation.

- Increased size or pale discoloration of the kidneys correlated microscopically with nephropathy.
- Bilateral abnormal shape, soft consistency, pale discoloration, and/or decreased size of the testis and epididymis were noted in all males at the high dose of 0.3 mg/kg and correlated microscopically with depletion/degeneration of the germ cells and reduced sperm in the lumen, respectively.
- Male reproductive findings did not appear reversible. Kidney findings appeared to progress at the macro-, but not microscopic level. Discolorations in many organs, mainly in one male, appeared in the recovery phase that were not present in other animals during the dosing phase.
- During the recovery phase, general pale discoloration, firm consistency of the left atrium, and/or increased size of the heart were observed in animals administered 0.15 or 0.3 mg/kg and correlated microscopically with myocardial degeneration.

Organ Weights

Percent changes compared to the control.

		Males				Females			
Dose (mg/kg/q3w)		**0**	**0.075**	**0.15**	**0.3**	**0**	**0.075**	**0.15**	**0.3**
Number of Animals Examined		**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**
Organ/Tissue	**Test**								
EPIDIDYMIS	Organ to BW (%)	0.1	-25	-19	-33	NA	NA	NA	NA
	Organ to BrW (%)	10	-50	-33	-46*	NA	NA	NA	NA
	Weight (g)	8	-51	-40	-50*	NA	NA	NA	NA
GLAND, PROSTATE	Organ to BW (%)	0.1	-1	-6	-14	NA	NA	NA	NA
	Organ to BrW (%)	7	-32	-23	-29	NA	NA	NA	NA
	Weight (g)	5	-33	-31	-33	NA	NA	NA	NA
GLAND, SEMINAL VESICLE	Organ to BW (%)	0.2	-53	-55	-58	NA	NA	NA	NA
	Organ to BrW (%)	18	-69	-63	-64	NA	NA	NA	NA
	Weight (g)	14	-69*	-66*	-66*	NA	NA	NA	NA
KIDNEY	Organ to BW (%)	0.3	18	-1	64*	0.4	-23	-9	5
	Organ to BrW (%)	34	-25	-20	32**	27	-2	-24	-15
	Weight (g)	26	-28	-28*	22	16	19	-15	-1
LUNG	Organ to BW (%)	0.4	18	13	37	0.4	-24	18	15
	Organ to BrW (%)	38	-25	-11	33	30	-5	-1	-7
	Weight (g)	28	-28	-20	27	17	15	10	9
TESTIS	Organ to BW (%)	0.7	-50	-46	-72**	NA	NA	NA	NA
	Organ to BrW (%)	77	-66	-56	-78**	NA	NA	NA	NA
	Weight (g)	59	-67	-61	-79**	NA	NA	NA	NA

BW = body weight; BrW = brain weight; *p ≤ 0.05; **p ≤ 0.01

- Thymus weights were decreased at all doses, but did not display a clear dose-response.

- Decreased testis weight correlated microscopically with germ cell degeneration/ depletion at 0.3 mg/kg.
- Decreased epididymis weight correlated microscopically with the absence of spermatids (severe reduced sperm) in the tubules at 0.3 mg/kg.
- Increased kidney weights in males at 0.3 mg/kg correlated with nephropathy.
- Increase lung weights in males at 0.3 mg/kg correlated with severe inflammation during dosing and alveolar hemorrhage during recovery.
- Organ weight changes in the epididymis, testis, and lungs were not reversible.
- During recovery, absolute and relative heart organ weights were increased in one female each administered 0.15 mg/kg or 0.3 mg/kg, compared to concurrent controls, and correlated microscopically with myocardial degeneration.

Histopathology

			Males				Females			
Dose (mg/kg/q3w)			**0**	**0.075**	**0.15**	**0.3**	**0**	**0.075**	**0.15**	**0.3**
Number of Animals Examined (Terminal/Recovery)			**3/2**	**3/2**	**3/2**	**3/2**	**3/2**	**3/2**	**3/2**	**3/2**
Organ/Tissue	**Finding**									
SKIN/ SUBCUTIS	Edema, focal	MOD								2/0
	Hemorrhage, focal	MIN								1/0
	Hemorrhage, focal and multifocal	MILD				1/0				2/0
	Hyperpigmentation, epidermis, multifocal	MOD				3/0				3/0
	Inflammation, acute, focal	MILD								1/0
LUNG	Edema, multifocal	MOD				0/1*				
		SEV				1/0				
	Fibrosis, perivascular, multifocal	MIN				1/0				
	Fibrosis, pleural/ subpleural, focal and multifocal	MIN			0/1					
		MILD			1/0	0/1+				
		MOD				1/0				
		MARK				1/0				
	Hemorrhage, multifocal, alveoli	MOD				0/1*				
	Infiltrate, mononuclear cells, multifocal, focal and multifocal	MIN		0/1		1/0		1/0		0/1
	Inflammation, acute, multifocal	SEV				1/0				
	Necrosis, multifocal	MOD				1/0				

	GLAND, PROSTATE	Cell debris, lumen, focal and multifocal	MIN		0/1	2/1		NA	NA	NA	NA
			MILD				2/0	NA	NA	NA	NA
		Degeneration, epithelium, focal and multifocal	MIN		0/1	2/0		NA	NA	NA	NA
			MILD			0/1*	2/0	NA	NA	NA	NA
		Infiltrate, mononuclear cells, focal and multifocal	MIN		0/1	2/1*		NA	NA	NA	NA
			MILD				2/0	NA	NA	NA	NA
	HEART	Degeneration, myocardium, multifocal, left ventricle	MILD		0/1						
			MOD	2/0			0/1*			0/1	0/1
		Epithelial squamous plaque, focal and multifocal	MIN		1/0			1/0			0/1
			MILD				1/0				
		Hemorrhage, multifocal, left ventricle	MILD				0/1*				
		Hyperplasia, epicardium, focal left atrium	MIN				0/1*				
		Infiltrate, mononuclear cells, multifocal	MIN	1/0		0/1	3/1*	0/1	1/0	0/1	0/2
			MILD				0/1+				
		Neurons, epicardium, focal left atrium	MILD				0/1*				
	SITE, INJECTION	Edema, focal	MIN					0/1	1/0		
		Edema, focal and multifocal	MILD	0/1			2/0				
		Hemorrhage, focal and multifocal	MIN				1/0				1/1
		Hyperpigmentation, epidermis	MIN		2/0	1/2	0/1+		3/0	2/1	0/1
			MILD			2/0					2/0
			MOD				3/0				1/1
		Hyperplasia, epidermis	MIN							0/1	0/1
			MILD							0/1	0/1

	GLAND, SALIVARY, SUBMANDIB-ULAR	Degeneration, acinar cell	MOD				1/0				
		Degranulation, multifocal	MIN								0/1
			MILD			0/1	0/1+				1/0
			MOD				1/0				
		Infiltrate, mononuclear cells, focal and multifocal	MIN	1/1	1/1	1/1	2/1+	1/1			0/1
		Pigment, unilateral	MILD				0/1+				
	KIDNEY	Nephropathy, bilateral	MIN		1/1	2/2			1/1	2/2	
			MILD			1/0	0/1+				1/1
			MOD				1/1*				2/1
			MARK				2/0				
	LARGE INTESTINE, CECUM	Hemorrhage, ileocecal valve	MILD				0/1*				
			MOD				0/1*				
		Hyperplasia, GALT (gut associated lymphoid tissue), ileocecal valve	MILD				0/1*				
		Inflammation, subacute, ileocecal valve	MILD				0/1+				
	MUSCLE, SKELETAL	Degeneration, focal myofibers	MIN				0/1+				
		Edema, focal	MILD				0/1+				

		Hemorrhage, focal	MILD				0/1+				
	TESTIS	Depletion/degeneration, germ cells, bilateral	MIN		1/0	1/0		NA	NA	NA	NA
			MILD		0/1	1/1		NA	NA	NA	NA
			MOD				0/1*	NA	NA	NA	NA
			SEV			0/1	3/1+	NA	NA	NA	NA
		Infiltrate, mononuclear cells, bilateral	MIN	0/1			1/0	NA	NA	NA	NA
	TONGUE	Degeneration, muscle, multifocal	MILD				0/1+				
		Edema	MILD				0/1+				
		Inflammation, subacute, multifocal	MIN				0/1+				
	BONE MARROW, STERNUM	Hypocellularity, bone marrow	MIN				3/0				
	EPIDIDYMIS	Infiltrate, mononuclear cells, multifocal	MIN			1/1	0/1*	NA	NA	NA	NA
		Reduced sperm, lumen, bilateral	MOD				1/0	NA	NA	NA	NA
			MARK				1/0	NA	NA	NA	NA
			SEV			0/1	1/1+	NA	NA	NA	NA
	GLAND, MAMMARY	Cyst, focal; nipple, submucosa	MOD				0/1*				
	GLAND, PITUITARY	Cyst, focal and multifocal	MIN	1/0	0/1	1/0		0/1		1/0	0/1
			MOD								1/0
		Hypertrophy, basophils, multifocal, pars distalis (anterior)	MILD				2/0				
		Pigment, meninges	MILD				0/1+				
	LYMPH NODE, MANDIBULAR	Decreased lymphocytes	MILD				1/0				
	OVARY	No fresh corpus luteum		NA	NA	NA	NA				1/0
	PANCREAS	Degranulation, acini	MILD				1/0				
		Infiltrate, mononuclear cells, focal and multifocal	MIN		1/0	1/0	1/0				
	SPLEEN	Increased cellularity, red pulp	MILD				1/0				
	STOMACH	Congestion, mucosa, fundus	MILD				0/1*				

	Inflammation, acute	MILD				1/0					
	Inflammation, chronic	MIN					1/1	0/1			
		MILD				1/0					
URINARY BLADDER	Infiltrate, mononuclear cells, multifocal	MILD				1/0					
	Vacuolation, urothelium	MILD				1/0					
UTERUS/CERVIX	Congestion, myometrium	MILD	NA	NA	NA	NA		0/1		0/1	

Blank cells = finding not present in group or not toxicologically significant; * = findings were in the same recovery high dose male; + = findings were in the same recovery high dose male; NA = organ not present in sex.

- The tubular nephropathy in the kidney was present in the distal portion of the nephron (distal tubules and collecting ducts) and was characterized by one or more of the following changes: tubular degeneration, regeneration, basophilia, disorganization in the medullary rays, corticomedullary junction and papilla, tubular dilation in the cortex, tubular cellular hypertrophy/atypia in the papilla, edema/extracellular matrix deposition in the corticomedullary junction and medullary rays, hyaline material in the tubules, and variable inflammation and/or fibrosis. These renal changes correlated with slightly increased serum creatinine values in one male and two females administered 0.3 mg/kg.
- In the testis, minimal to slight depletion/degeneration of germ cells was present in one male administered 0.075 mg/kg and two males administered 0.15 mg/kg. This finding consisted of bilateral atrophy of seminiferous tubules, with multifocally reduced height of germinal epithelium, disorganized spermatogenesis, germ cell degeneration, and some tubules with Sertoli cells only. In all animals administered 0.3 mg/kg, severe depletion/degeneration of germ cells was noted and characterized by tubules with Sertoli cells only and complete absence of mature spermatozoa in the lumen. However, given the presence of spermatogonia in all males, the Applicant noted that adverse effects on male reproductive organs are expected to reverse with time.
- Hypocellularity in the bone marrow was characterized by a reduction of erythropoietic cells, with a normal number of myeloid cells and megakaryocytes, and correlated with hematology data.
- Although lung fibrosis can be seen as a common spontaneous finding in the cynomolgus monkey, both the incidence and severity observed in the current study are higher than typically seen. In addition to the marked pleural fibrosis seen in the lung of one 0.3 mg/kg male, there was also severe acute inflammation (alveolar neutrophils, lymphocytes and macrophages), with edema and necrosis. This correlated with increased lung weight and semi-firm consistency with abnormal shaped lobes and adhesions at necropsy. This animal was thin, had decreased albumin, increased globulin and fibrinogen relative to pretest, consistent with inflammatory response.
- Myocardial degeneration of the heart was characterized by myocyte degeneration, vacuolation, swelling of nuclei, and interstitial edema in terminal control and recovery ADCT-402 treated monkeys. One 0.3 mg/kg recovery male with this finding also had swelling (eyelids, face or extremities) as well as changes in clinical

	chemistry parameters (compared to pretest) consistent with inflammatory response. This male also had lung hemorrhage, but no apparent inflammatory cell reaction or erythrophagocytosis was associated with the hemorrhage. In this animal, hemorrhage was also noted in the cecum (moderate, ileocecal valve), which correlated macroscopically with dark discoloration of the ileocecal valve, and heart (slight, left atrium).
Other evaluations (bone marrow smear, immunogenicity)	**0.3 mg/kg:** bone marrow smears revealed a decreased percentage of maturing erythroid cells (EMAT) with a corresponding decrease in percentage total erythroid cells (MERT), an increased percentage of myeloid maturing cells (MMAT) with a corresponding increase in percentage of total myeloid cells (MMYT), and rarely, increased % myeloid proliferating cells (MYPR). The combination of increased % myeloid cells and % erythroid cells resulted in minimally to markedly increased myeloid:erythroid (M:E) ratios. ADA: See Section 5.4.

Abbreviations: ADA = Anti-drug antibodies; TK = Toxicokinetic; MIN = minimal; MOD = moderate; MARK = marked; SEV = severe.

5.5.2. Genetic Toxicology

The Applicant's Position:
Genotoxicity of SG3199 was evaluated in two in vitro assays in human lymphocytes, a micronucleus assay, and a chromosome aberration assay. Consistent with its mode of action (covalent DNA crosslinking agent), SG3199 was found to be clastogenic in both assays.

The FDA's Assessment:
FDA concurs that SG3199 was clastogenic in both the in vitro micronucleus assay and the chromosome aberration assay in human lymphocytes from whole blood. FDA also notes that clastogenicity was observed in the presence and absence of metabolic activation (S9 mix). In the chromosome aberration assay, statistically significant and concentration-dependent increases in chromosomal aberrations were observed and were comprised mainly of broken segments (gaps or breaks) of one or both chromatids that are aligned or unaligned; a single, usually circular, part of a chromatid lacking a centromere; an exchange(s) between two or more chromosomes resulting in the formation of a tri- or more-armed configuration; and miscellaneous aberrations. Some aberrations exceeded the positive control range. A GLP bacterial reverse mutation assay (Ames test) was also submitted; however, mutagenicity could not be assessed due to cytotoxicity at all concentrations tested (≥ (b) (4) plate and above using plate incorporation method in TA98, TA100, TA1535, TA1537 and TA102 Salmonella typhimurium strains and at 0.01 or 0.1 mg/mL and above in strain TA98 using a 'treat and plate' method). Of note, based on its mechanism of action and results described in 5.3 and 5.5.5, SG3199 is expected to damage DNA and be mutagenic.

5.5.3. Carcinogenicity

The Applicant's Position:
In accordance with ICH S9, ICH S6(R1) and ICH S1A, no carcinogenicity studies were conducted with loncastuximab tesirine or SG3199 given the genotoxic mode of action of SG3199 (see Section 5.5.2) and the intended clinical use in patients with advanced cancer.

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

5.5.4. Reproductive and Developmental Toxicology

The Applicant's Position:
Given that SG3199 is a potent genotoxicant, in accordance with ICH S9 and ICH S6(R1), no reproductive and developmental toxicity studies were conducted with loncastuximab tesirine, and, based on the mode of action of SG3199, reproductive and developmental toxicity is expected. With regard to fertility, the potential for effects of loncastuximab tesirine on male and female fertility was assessed in the pivotal repeat-dose toxicity study in sexually mature cynomolgus monkeys by evaluation of the reproductive tract (organ weights and histopathological evaluation) as outlined in ICH S6(R1). In males, marked testicular toxicity (testicular atrophy with reduced spermatogenesis) was observed, while there were no effects on the female reproductive organs.

The FDA's Assessment:
FDA concurs with the Applicant's assessment but notes that there was no fresh corpus luteum in one high dose female at 0.3 mg/kg in the 13-week monkey study. The relationship of this finding to loncastuximab tesirine is uncertain due to the low incidence in the 13-week monkey study and the lack of the finding at higher doses in other studies. Therefore, at this time, this finding and a potential for loncastuximab tesirine to impair female reproductive function is not included in labeling.

5.5.5. Other Toxicology Studies

The Applicant's Position:
Based on findings in cynomolgus monkeys (skin discoloration/black skin, correlating with epidermal hyperpigmentation) and humans (skin rash), SG3199 is considered to be a photosensitizing agent. This is corroborated by preclinical data indicating that the ultraviolet-visible light absorption characteristics of SG3199 exceed the threshold of concern for potential photoreactivity as described in ICH S10, and by in vitro studies demonstrating that ultraviolet and/or visible light enhance the intrinsic ability of SG3199 to mediate DNA crosslinking and double strand DNA breaks.

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

Natalie Simpson, PhD
Primary Reviewer

Brenda Gehrke, PhD
Pharmacology/Toxicology Team Leader

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

Loncastuximab tesirine is an antibody drug conjugate consisting of a CD19-targeted monoclonal antibody bound to the DNA crosslinking pyrrolobenzodiazepine (PBD) dimer, cytotoxic drug, SG3199, via a protease-cleavable valine-alanine linker. The Applicant is seeking accelerated approval of loncastuximab tesirine for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma including high grade B-cell lymphoma, after at least two prior systemic therapies.

The proposed dosing regimen of loncastuximab tesirine is 150 µg/kg for the first two cycles (once every three weeks, Q3W), then 75 µg/kg Q3W, as a 30 min IV infusion. This dosing regimen was evaluated in a phase 2, single-arm Study ADCT-402-201 (Study 201) and showed evidence of efficacy with an acceptable safety profile. In Study 201, the observed ORR was 48.3% (95% CI: 39.9- 56.7%) with a CRR of 24.1% (95% CI: 17.4- 31.9%).

The clinical pharmacology review focused on the appropriateness of the proposed dosing regimen for the general patient population, dosing recommendations for patients with mild hepatic impairment (HI) and instructions for concomitant use of strong CYP3A inhibitors. Two postmarketing requirements, one regarding dosing recommendations for patients with moderate to severe HI, the other regarding clinical data from an adequate representation of U.S. racial and ethnic minority patients with large B-cell lymphoma, have been identified as detailed in Section 6.1.2.

6.1.1. Recommendations

The Office of Clinical Pharmacology recommends the approval of BLA 76196 from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Primary evidence of the effectiveness of loncastuximab tesirine in the proposed indication is derived from in Study 201. The observed ORR by independent central review (primary endpoint) was 48.3% (95% CI: 39.9- 56.7%). Best overall responses included 35 patients (24.1%) with a complete response and 35 patients (24.1%) with a partial response. Median duration of response

	(DOR) per Kaplan-Meier was 10.3 months (95% CI 6.9, not evaluable).
General dosing instructions	The proposed recommended dosing regimen of loncastuximab tesirine is 150 µg/kg Q3W for the first two cycles, then 75 µg/kg Q3W, as a 30 min IV infusion. The dose for patients with a body mass index (BMI) ≥ 35 kg/m^2 is calculated based on an adjusted body weight (ABW) as follows: ABW in kg=35 kg/m^2×(height in meters)^2 Dose to administer (mg)= (b) (4)
Dosing in patient subgroups (intrinsic and extrinsic factors)	• No dose adjustment is needed for patients with mild hepatic impairment (NCI-ODWG criteria). Dosing recommendations cannot be made for patients with moderate and severe hepatic impairment. • No dose adjustment is needed for patients with mild or moderate renal impairment (CLcr ≥ 30 mL/min). There is limited data in patients with severe renal impairment (CLcr < 30 mL/min). • No loncastuximab tesirine dose adjustment is needed when used concomitantly with CYP3A inhibitors.
Labeling	The clinical pharmacology review team has specific content and formatting change recommendations for the product labeling. Key modifications to the label made by the FDA include the addition of Section 8.6 hepatic Impairment, addition of statements regarding E-R relationships in Section 12.2, and the format and content in Section 12.3.
Bridge between the to-be-marketed and clinical trial formulations	In Study 201, 35/145 (24.1%) patients received a frozen liquid formulation and 110/145 (75.9%) received the to-be-marketed lyophilized formulation. Analysis of data from Study 201 indicated no clinically relevant difference in the ADC exposure, safety and efficacy of the two formulations. PK data for the unconjugated payload is limited, precluding a comparison of exposure between the two formulations for this moiety.

6.1.2. Post-Marketing Requirements and Commitments

PMC or PMR	Rationale	Key Consideration and Design Features
PMR	Hepatic impairment may increase the exposure of unconjugated SG3199	An open-label, non-randomized, dose-escalation trial should be

	and increase risk of drug toxicity. There is currently insufficient data in patients with moderate or severe hepatic impairment to assess the impact on PK. Additional information is required to determine safe dosing of loncastuximab tesirine in patients with moderate or severe hepatic impairment.	conducted to determine a safe an appropriate dosing regimen of loncastuximab tesirine in patients with moderate and severe hepatic impairment, according to the National Cancer Institute Organ Dysfunction Working Group criteria. Safety and pharmacokinetic information for loncastuximab tesirine and SG3199 should be collected to determine the appropriate starting dose dosing regimen of loncastuximab tesirine for this population.
PMR	The pivotal study ADCT-402-201 enrolled 145 adult patients with large B-cell lymphoma of which, 90% (n=130) were White, 3% (n=5) were Black, 2% (n=3) were Asian, and 5% (n=7) were Other. Of those, 9% (n=13) of patients identified as Hispanic or Latino. The population PK analysis for Studies ADCT-402-101 and ADCT-402-201 included 294 (90%) White, 16 (5%) Black, 6 (2%) Asian and 10 (3%) grouped as Other races. There are insufficient PK data from the limited number of patients in Asian and other racial subgroups to inform the need of dose adjustment for these specific patient populations. This is a concern as significant exposure–response relationships with both safety and efficacy have been identified for loncastuximab tesirine. Additionally, safety data from Study 201, demonstrated that a higher proportion of Grade ≥3 adverse events, Grade 3-4 neutropenia, and	An integrated final report should be submitted containing data from clinical trials to further characterize the exposure of loncastuximab tesirine monotherapy and in combination with immunochemotherapy, the increased risk of severe and serious adverse events, including severe neutropenia, and efficacy among U.S. racial and ethnic minority patients with large B-cell lymphoma. The population pharmacokinetic and exposure-response analyses for both efficacy and safety should be updated.

	TEAEs leading to dose delays (primarily neutropenia) occurred in Black and Hispanic patients compared to White patients, with limited safety data in Asian patients. Therefore, data from an adequate representation of U.S. racial and ethnic minority patients with large B-cell lymphoma is needed to further characterize the PK, PD, safety and tolerability, and efficacy of loncastuximab tesirine in these patients.	

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:

Pharmacokinetics

Serum concentrations of PBD-conjugated antibody and total antibody measured in Phase 1 and 2 studies of 328 patients with relapsed or refractory B-cell non-Hodgkin lymphoma (B-NHL) formed the basis for an integrated population PK analysis. Data were well described using a two-compartment model with common linear- and time-dependent clearance components for conjugated antibody and total antibody, and deconjugation clearance for conjugated antibody. With initial doses of 150 µg/kg every three weeks (Q3W) x2, steady state occurred fairly rapidly relative to the 75 µg/kg Q3W steady state condition, and was associated with minimal accumulation for the subsequent doses of 75 µg/kg Q3W. SG3199 levels were predominantly below the lower limit of quantification for most patients and time points which precluded any robust characterization.

Distribution: Apparent volume of distribution of conjugated antibody was 4.24 L.

Metabolism: The antibody moiety is thought to be processed via normal protein catabolic processes. CYP3A4/5 is potentially involved in metabolism of SG3199.

Elimination: For the typical patient, linear clearance was 0.218 L/day and the time-dependent clearance component approaches 0 by ~15 weeks. The estimated half-life of conjugated antibody was 14.6 days (Cycle 1) and 20.6 days (Cycle 5). SG3199 is eliminated predominantly

into the feces.

Immunogenicity: No evidence of an impact of immunogenicity on PK exposure, safety, or efficacy was observed.

Pharmacodynamics

Exposure-response Analysis for Efficacy: For patients with DLBCL in studies ADCT-402-101 and ADCT-402-201, the conjugated antibody average serum concentration (C_{avg}) during Cycle 1 was significantly associated with overall response and with overall survival (OS).

Exposure-response Analyses for Safety:
For all patients in studies ADCT-402-101 and ADCT-402-201, treatment-emergent adverse event (TEAE) categories of skin and nail reactions, edema-effusion, fatigue, pain, liver function test (LFT) abnormalities, gamma-glutamyl transferase (GGT) increased, and platelet decreased- and neutrophil decreased-related toxicities were evaluated for relationship to exposure. C_{avg} in Cycle 1 was significantly associated with Grade ≥2 increased GGT, LFT abnormalities, skin and nail reactions, and pain.

The effect of conjugated antibody in serum on change from baseline (Δ) corrected QT (Fridericia's correction) (QTcF) was evaluated in ADCT-402-201. No large changes in mean Δ corrected QT (QTc) intervals (ie, >20 ms) were detected following loncastuximab treatment with 150 µg/kg.

The Applicant's Position:
The PK and pharmacometric assessments presented provide a thorough description of loncastuximab tesirine disposition for patients with relapsed or refractory DLBCL.

The FDA's Assessment:
FDA generally agrees with the Applicant's description of the known clinical pharmacology properties of loncastuximab tesirine in the overall B-NHL patient population.
Immunogenicity of loncastuximab tesirine does not appear to be a major concern as the incidence of treatment-emergent anti-drug antibodies (ADA) is low. At the proposed dosing regimen in Study 201, no patients developed treatment emergent ADA (see section 6.3.1). Due to the low incidence treatment emergent ADA against loncastuximab tesirine at the proposed dosage, the impact of immunogenicity on PK, safety and efficacy is not fully characterized.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:
For patients with relapsed or refractory DLBCL, it is proposed that loncastuximab tesirine be administered IV over 30 min on Day 1 of each cycle (every 3 weeks) as 150 µg/kg Q3W x2, then 75 µg/kg Q3W thereafter. PK analysis indicates that administration of loncastuximab tesirine 150 µg/kg Q3W x2, followed by a 50% dose reduction to 75 µg/kg Q3W thereafter maintains constant exposure to conjugated antibody for the duration of the dosing interval, as evidenced by the moderate accumulation index value in study ADCT-402-201 of 1.65 by Cycle 2. From study 402-101, at the 200 µg/kg dose, the frequency of TEAEs was higher and probability of a dose modification increased sharply relative to 150 µg/kg.

The Applicant's Position:
For patients with relapsed or refractory DLBCL, loncastuximab tesirine administered as 150 µg/kg Q3W x2, then 75 µg/kg Q3W thereafter is supported by the PK analyses, and exposure-response analyses for safety and efficacy.

The FDA's Assessment:
FDA agrees with the Applicant's position that the proposed dosing regimen is acceptable for the general patient population. The dose selection was based on safety and efficacy information in Study 101 over the dose range of 15 to 200 µg/kg as described in Section 6.3.2.2. The initial 150 µg/kg dose was selected as adverse events increased at the higher dose level of 200 ug/kg, and as clinical responses were observed at the 150 µg/kg dose level. The planned dose reduction to 75 ug/kg was instituted to mitigate cumulative toxicities without impacting clinical response.

6.2.2.2. Therapeutic Individualization

Data:
Determinants contributing to loncastuximab tesirine exposure variability were assessed in the population PK analysis and included factors of age, race, sex, baseline body weight, baseline laboratory measurements, baseline disease characteristics, ADA response, formulation, and selected concomitant agents. None of the factors tested had a clinically relevant effect on loncastuximab tesirine exposure.

The Applicant's Position:
No dose adjustments are recommended based on patient intrinsic or extrinsic factors. There were insufficient numbers of patients with severe or greater renal impairment and moderate or greater hepatic impairment to draw definitive conclusions.

The FDA's Assessment:
No therapeutic individualization is needed for age (20-94 years), sex, body weight (42.1 to 160.5 kg), ECOG status (0 to 2) or baseline albumin (17 to 52 g/L). No dose adjustment is needed in mild hepatic impairment (total bilirubin ≤ upper limit of normal (ULN) and AST > ULN, or total bilirubin >1 to 1.5 × ULN and any AST), or in mild or moderate renal impairment (CLcr ≥ 30 mL/min). There was insufficient data in patients with severe renal impairment or with end-stage renal disease. There was insufficient information regarding the effects of race and ethnicity on the PK, safety and efficacy of loncastuximab tesirine. There was insufficient data to assess the effect on loncastuximab tesirine PK in patients with moderate or severe hepatic impairment . Two PMRs have been identified to address these issues as detailed in Section 6.1.2.

6.2.2.3. Outstanding Issues

The Applicant's Position:
No outstanding issues are anticipated.

The FDA's Assessment:
FDA does not agree with the Applicant's position. There is insufficient information regarding the effects of race or ethnicity on the PK, safety and efficacy of loncastuximab tesirine. There was insufficient loncastuximab tesirine data available in patients with moderate (n=1) or severe (n=0) hepatic impairment. As such, 2 PMRs will be issued.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:
Overview of Loncastuximab Tesirine Clinical Pharmacology Characteristics

Chemical Structure
Loncastuximab tesirine is a human CD19-targeted ADC, consisting of a humanized immunoglobulin G1 (IgG1) kappa monoclonal antibody specific for human CD19, conjugated to SG3199, a PBD dimer cytotoxic drug, through a protease-cleavable valine-alanine linker. SG3199 attached to the linker is designated as SG3249, also known as tesirine.

Mechanism of Action
The monoclonal antibody binds to human CD19. The small molecule cytotoxin, PBD dimer (SG3199), is a DNA crosslinking agent conjugated to the antibody via a protease-cleavable

linker. Upon binding CD19, loncastuximab tesirine is internalized and the linker is cleaved by lysosomal proteases to enable release of the PBD dimer which then binds to the DNA minor groove and forms highly cytotoxic DNA interstrand crosslinks, subsequently inducing cell cycle arrest and cell death.

Bioanalytical Methods
The concentrations of conjugated antibody and total antibody of loncastuximab tesirine in serum were measured using separate validated electro-chemiluminescence immunoassays (ECLIAs). SG3199 concentrations were measured using a validated liquid chromatography-tandem mass spectrometric assay. Screening, confirmation, and titration of anti-loncastuximab tesirine ADAs were performed using a validated bridging ECLIA platform (MesoScale Discovery technology).

Dose Proportionality
Assessment was performed using a power model based on linear regression with log-transformed values of conjugated antibody area under the serum concentration-time curve from time 0 to infinity (AUC_{inf}), AUC_{tau}, and C_{max} during Cycles 1 and 2. Exposure was generally proportional to loncastuximab tesirine from 15-200 µg/kg. Given high variability of conjugated antibody C_{max} in Cycle 1, the proportionality of exposure for this metric could not be shown for doses ≤90 µg/kg.

Accumulation
Following the 150 µg/kg dose Q3W, accumulation indices by Cycle 2 were 1.65 for conjugated antibody, and 2.07 for total antibody. Exposures to SG3199 were predominantly below the lower limit of quantification for most patients and time points.

Absorption
Loncastuximab tesirine was administered as an IV infusion, thus no bioavailability studies were performed. The time to maximum concentration was typically close to end of infusion or shortly after end of infusion.

Distribution
Conjugated antibody has an apparent volume of distribution of 4.24 L. In human plasma, SG3199 is highly (~94%) protein bound.

Metabolism
The antibody moiety is thought to be processed via normal protein catabolic processes. CYP3A4/5 is potentially involved in the metabolism of SG3199.

Elimination
Linear clearance of conjugated antibody and total antibody was 0.218 L/day (from population PK analysis for typical patient) and falls within range of monoclonal antibody clearance. SG3199 is eliminated mainly via feces and biliary route (95.5%). The estimated typical half-life of loncastuximab tesirine PBD-conjugated antibody was 14.6 days at Cycle 1, and 20.6 days by Cycle 5.

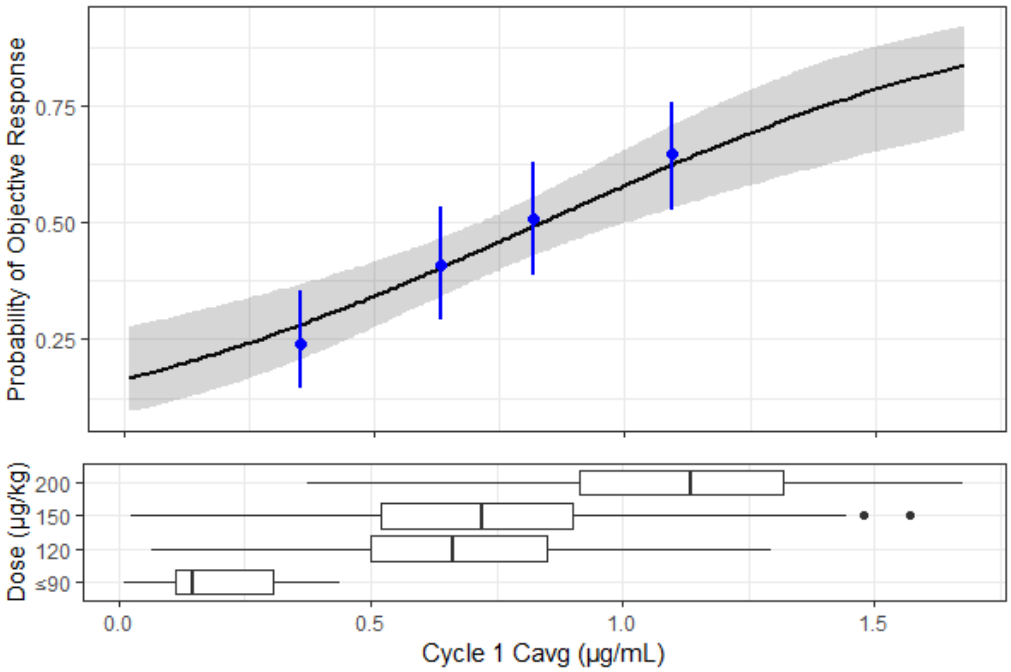
Immunogenicity
Loncastuximab tesirine did not exert a clinically relevant ADA induction effect. Of 328 patients tested for ADA to loncastuximab tesirine, seven (2.13%) exhibited confirmed positive ADA occurring at any time. One patient (0.305%) exhibited a confirmed positive ADA response postdose only, with a very low $\log_2$ titer (<1). Differences in PK, safety, and efficacy between ADA-positive and ADA-negative subgroups were not considered clinically relevant.

Population Pharmacokinetic Assessment
Loncastuximab tesirine conjugated antibody and total antibody PK was well described by a two-compartment model with parallel linear and time-dependent clearance pathways. The impact of age, race, sex, baseline body weight, baseline laboratory measurements, baseline disease characteristics, ADA, formulation, and selected concomitant agents on the PK of loncastuximab tesirine were evaluated. Notable statistically significant factors were body weight, sex, Eastern Cooperative Oncology Group (ECOG), and albumin on linear clearance; body weight and sex on central volume of distribution, disease subtype and albumin on time-dependent clearance, and sex on time-dependent clearance rate constant. However, simulation of exposures from the 150 µg/kg Q3W x2 regimen followed by 75 µg/kg Q3W thereafter indicated no dose adjustments were warranted, either because exposure differences were not clinically relevant or because of increased safety concern for patients with relapsed or refractory DLBCL that higher doses would portend.

Characterization of SG3199 disposition was infeasible due to the limited number of observations above the lower limit of quantification of the assay.

Exposure-response Assessment for Efficacy
For overall response rate (ORR), a significant relationship between conjugated antibody C_{avg} during Cycle 1 and overall response was identified ($p<0.001$) (Figure 1).

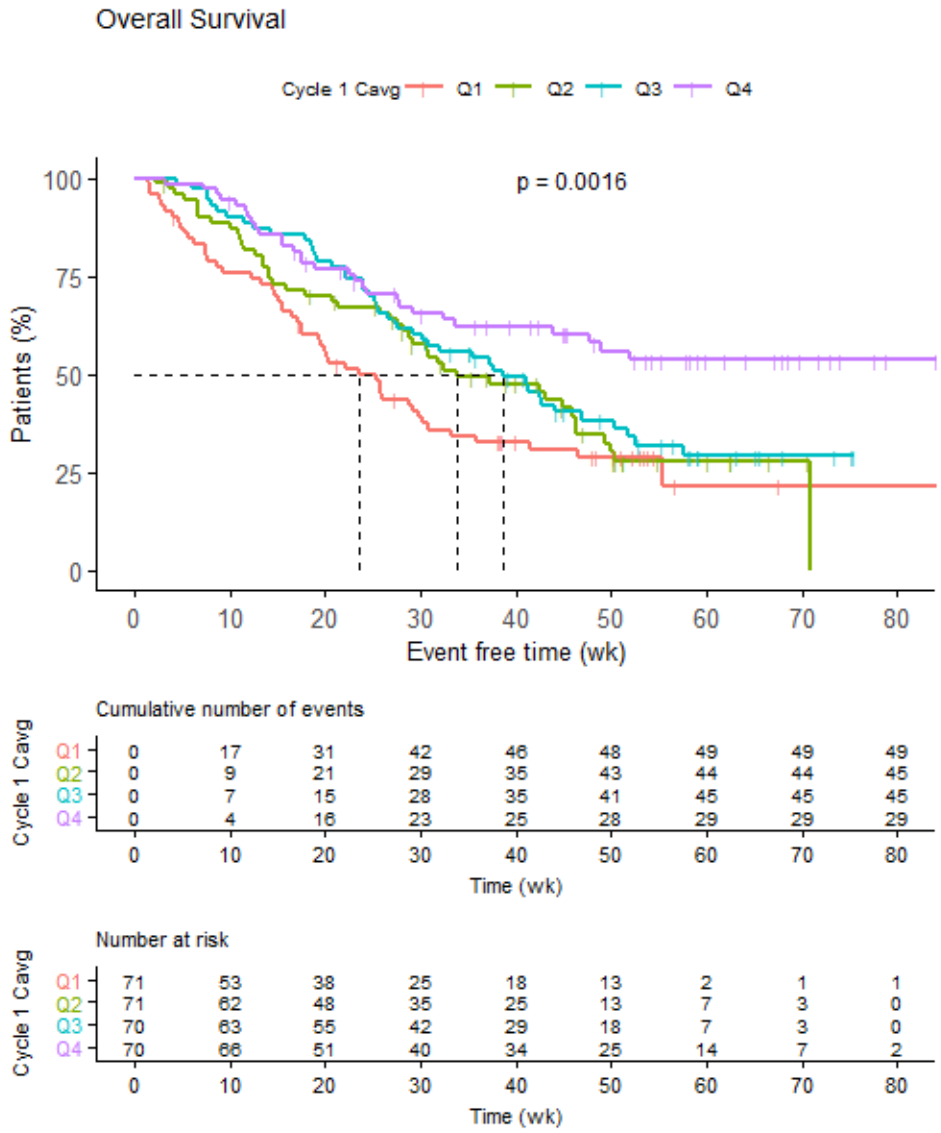
Figure 1: Applicant-Observed and Model-Predicted Overall Response Rate from the Logistic Regression Base Model by PBD-Conjugated Antibody Cycle 1 C_{avg} and the Distribution of PBD-Conjugated Antibody Cycle 1 C_{avg} by Dose Levels in DLBCL Patients



C_{avg}=average serum concentration; DLBCL=diffuse large B-cell lymphoma; PBD=pyrrolobenzodiazepine
Note: The solid blue circles (vertical line segments) represent the mean (95% CI, Clopper-Pearson method) overall response rate (ORR) for each quartile of Cycle 1 C_{avg}. The solid black line and shaded grey area represent the predicted ORR (95% CI) from a univariate logistic regression using individual patient level Cycle 1 C_{avg}. The exposure ranges for Cycle 1 C_{avg} were: 1st quartile (0.0120 to 0.504 µg/mL), 2nd quartile (0.506 to 0.723 µg/mL), 3rd quartile (0.727 to 0.941 µg/mL), and 4th quartile (0.943 to 1.68 µg/mL).

For OS, increasing exposures of conjugated antibody Cycle 1 C_{avg} were associated with longer OS (log rank test p=0.0016) (Figure 2). Median survival for patients with C_{avg} in highest exposure was not estimated since quartiles did not cross 50% survival cutoff.

Figure 2: Applicant-Kaplan-Meier Survival Curves (p<0.05) for Overall Survival by C_{avg} of PBD-Conjugated Antibody in Cycle 1 of DLBCL Patients in Studies ADCT-402-101 and ADCT-402-201



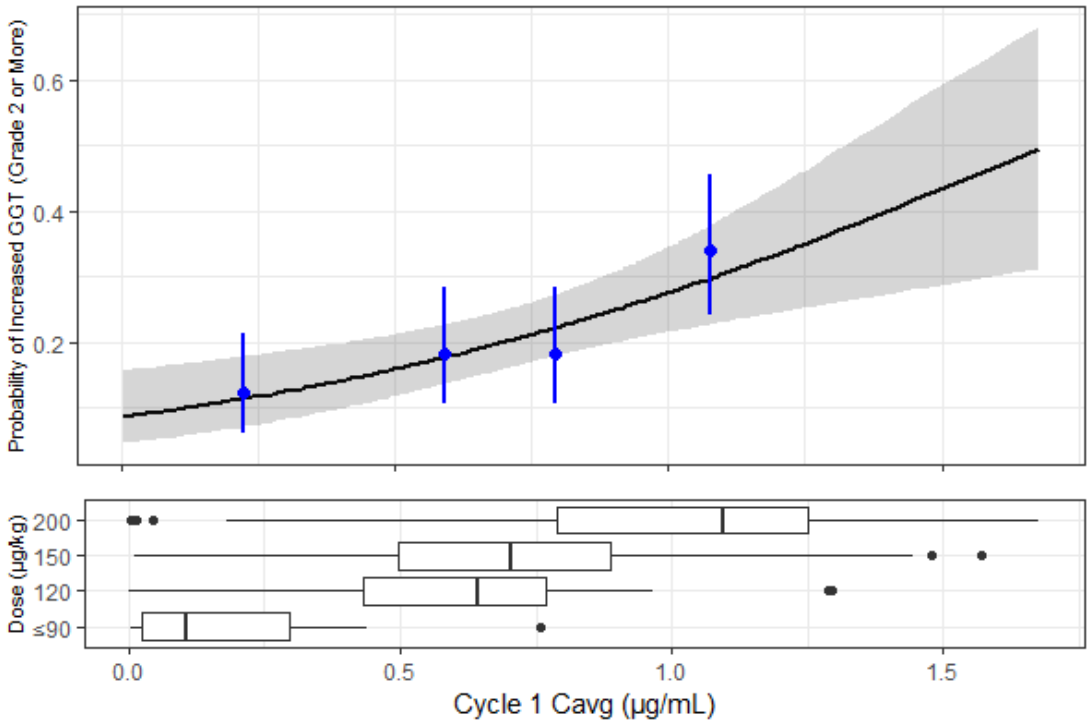
C_{avg}=average serum concentration; DLBCL=diffuse large B-cell lymphoma; PBD=pyrrolobenzodiazepine
Note: The solid lines represent the Kaplan-Meier survival curves for quartile groups of PBD-conjugated antibody exposure. Right-censoring is indicated by the vertical ticks on the survival curves. Median event-free times (mEFT), if reached, are indicated with black dashed lines. Log rank test was used to test for significant differences between Kaplan-Meier curves (p<0.05).

Exposure-response Assessment for Safety

TEAEs included skin and nail reactions, edema-effusion, fatigue, pain, LFT abnormalities, GGT

increased, neutrophil decreased, and platelet decreased-related toxicities. Grade ≥2 TEAEs were investigated for the correlation with the exposure to loncastuximab tesirine. For skin and nail reactions, LFT abnormalities, GGT increased (Figure 3), and pain, significant relationships ($p<0.05$) were observed for exposure.

Figure 3: Applicant-Observed and Predicted Probability of GGT Increased (Grade ≥2) From the Logistic Regression Base Model by Cycle 1 C_{avg} and the Distribution of Cycle 1 C_{avg} by Dose Levels in All Patients



p-value=0.000669

C_{avg}=average serum concentration; GGT=gamma-glutamyl transferase
Note: The solid blue circles (vertical line segments) represent the mean (95% CI, Clopper-Pearson method) probability of GGT increased (Grade ≥2) each quartile of Cycle 1 C_{avg}. The solid black line and shaded grey area represent the predicted probability (95% CI) of increased GGT (Grade ≥2) from a univariate logistic regression using individual patient level Cycle 1 C_{avg}. The quartile ranges for Cycle 1 C_{avg} were: 1st quartile (0.0120 to 0.462 µg/mL), 2nd quartile (0.463 to 0.700 µg/mL), 3rd quartile (0.702 to 0.918 µg/mL), and 4th quartile (0.919 to 1.68 µg/mL).

Exposure-response Assessment for Immunogenicity

Safety signals detected in the ADA-positive subgroup (which included seven patients with confirmed positive ADA anytime) were no worse than those in the ADA-negative subgroup.

ORR differences between the ADA-positive subgroup (which included seven patients with confirmed positive ADA anytime) and ADA-negative patients indicated that no definitive relationship was apparent.

Exposure-response Assessment for QT

The relationship between PBD-conjugated antibody serum concentrations and ΔQTcF were investigated using a linear mixed-effect modeling approach, with ΔQTcF as the dependent variable, and serum concentration of PBD-conjugated antibody as the explanatory variate. The estimated slope of the PBD-conjugated antibody serum concentration-QTc relationship was nearly flat. The effect on ΔQTcF for the 150 µg/kg dose was predicted to be 4.45 ms (90% CI: 3.02 to 5.89) and 4.74 ms (90% CI: 3.28 to 6.21) at geometric mean peak PBD-conjugated antibody concentrations in Cycle 1 and Cycle 2, respectively. For SG3199, given the very limited exposure and minimal time points with detectable SG3199 concentration in serum, the concentration-QTc analysis was not considered relevant.

The Applicant's Position:

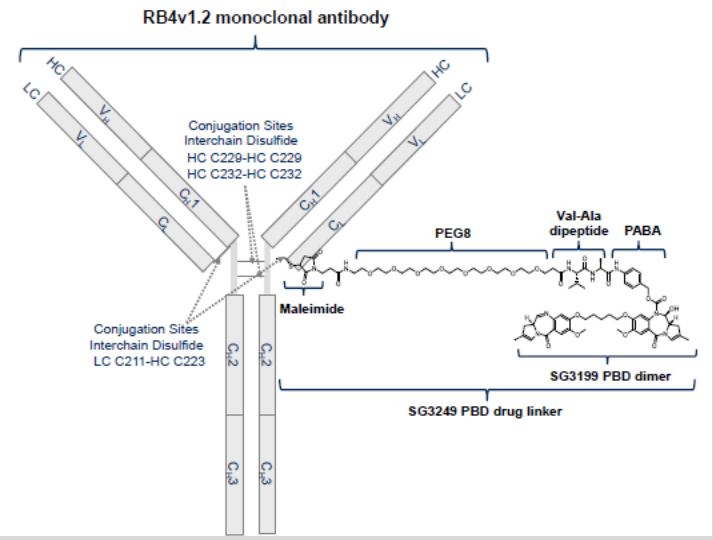
Loncastuximab tesirine is a drug with no relevant liability for drug interactions, and limited clinically relevant effects from intrinsic or extrinsic factors of variability. Its disposition was well characterized by a two-compartment model with linear and time-dependent components of clearance. Significant relationships of exposure to safety and efficacy were established. Assessment of the PK, safety, and efficacy support the safe and effective use of loncastuximab tesirine in patients with relapsed or refractory DLBCL.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. An overview of loncastuximab tesirine pharmacology and pharmacokinetic characteristics based on the FDA's assessment are presented below.

General Pharmacology and Pharmacokinetic Characteristics

PHYSICOCHEMICAL PROPERTIES	
Chemical structure and molecular weight	Loncastuximab tesirine is an antibody drug conjugate consisting of a CD19-targeted humanized IgG1κ monoclonal antibody (rB4v1.2) bound to the DNA crosslinking PBD dimer cytotoxic drug SG3199, via a protease-cleavable valine-alanine linker. The average drug-to-antibody ratio is approximately 2.3. The molecular weight of Loncastuximab tesirine is approximately 150 kDa.

	 *(Source: 2.3.S Drug substance summary)*
PHARMACOLOGY	
Mechanism of action	The monoclonal antibody component binds to human CD19, a transmembrane protein expressed on the surface of cells of B-lineage origin. The small molecule component is SG3199, a PBD dimer and alkylating agent. Upon binding to CD19, loncastuximab tesirine is internalized followed by release of SG3199 via proteolytic cleavage. The released SG3199 binds to the DNA minor groove and forms highly cytotoxic DNA inter-strand crosslinks, subsequently inducing cell death.
QT/QTc prolongation	Based on the FDA QT IRT's analysis, at the maximum recommended therapeutic dose of 150 µg/kg during Cycle 1 and Cycle 2, loncastuximab tesirine did not cause large mean increases (i.e., > 20 msec) in the QTc interval (Source: FDA QT IRT review).
GENERAL INFORMATION	
Bioanalytical assay	Loncastuximab tesirine (SG3199-conjugated antibody concentration), total antibody (total unconjugated and conjugated antibody concentration) and unconjugated (free) SG3199 were measured in Study 101 and Study 201. Loncastuximab tesirine and total antibody concentrations were measured using validated electro-chemiluminescence immunoassays (ECLIAs). Unconjugated SG3199 concentrations were measured using a validated LC-MS/MS method. (See Section 19.4 for additional information). The LC-MS/MS assay employed for determining serum unconjugated SG3199 levels is a free assay, and any protein-bound SG3199 is not detected.

<table>
<tr><td>Patient PK vs. healthy subject PK</td><td>Loncastuximab tesirine PK has not been evaluated in healthy subjects.</td></tr>
<tr><td>Steady-state exposure at the proposed dosing regimen</td><td>The exposures of loncastuximab tesirine in patients with DLBCL at the approved recommended dosage in Cycle 1, Cycle 2 and at steady state based on population PK analysis are as follows:
<table>
<tr><th>Time</th><th>C_{max} (ng/mL)</th><th>AUC_{tau} (day.ng/mL)</th></tr>
<tr><td>Cycle 1</td><td>3028 (39.9%)</td><td>17,478 (66.5%)</td></tr>
<tr><td>Cycle 2</td><td>3563 (35.3%)</td><td>26,518 (54.1%)</td></tr>
<tr><td>Steady state</td><td>2173 (32.1%)</td><td>20,663 (38.2%)</td></tr>
</table>
Unconjugated SG3199 serum concentrations were below the limit of quantitation in the majority of clinical samples.</td></tr>
<tr><td>Maximum tolerated dose or exposure</td><td>In the phase 1 Study 101, loncastuximab tesirine was evaluated over the dosage range of 15 µg/kg to 200 µg/kg Q3W to Q6W[1] in patients with B-NHL including DLBCL. The loncastuximab tesirine MTD was not reached in this study.</td></tr>
<tr><td>Dose proportionality</td><td>Loncastuximab tesirine undergoes both linear and time-dependent clearance. The FDA conducted power analyses of loncastuximab tesirine PK parameters after a single dose in the subset of patients with DLBCL in Study 101, over the dose ranges of 15 to 200 µg/kg and 120 to 200 µg/kg (there were a limited number of patients with DLBCL in the 15-90 µg/kg dose range). The Cmax and AUClast of loncastuximab tesirine appears to increase in an approximately dose proportional manner from 15 to 200 µg/kg. However, the confidence intervals for AUClast and AUCinf were wide in the 120 to 200 µg/kg dose range as detailed in the table below, precluding a conclusion of dose linearity in this range.
<table>
<tr><th>Analyte</th><th>PK parameters (Cycle 1)</th><th>Slope Estimate (90% CI)</th></tr>
<tr><td rowspan="3">Loncastuximab tesirine (120 to 200 µg/kg)</td><td>Cmax</td><td>1.03 (0.69, 1.37)</td></tr>
<tr><td>AUClast</td><td>1.30 (0.52, 2.08)</td></tr>
<tr><td>AUCinf</td><td>1.98 (-0.1, 4.05)</td></tr>
<tr><td rowspan="2">Total antibody (120 to 200 µg/kg)</td><td>Cmax</td><td>1.04 (0.66, 1.42)</td></tr>
<tr><td>AUClast</td><td>1.25 (0.44, 2.06)</td></tr>
</table>
Source: Reviewer's analysis</td></tr>
<tr><td>Accumulation</td><td>At the proposed dosing regimen, the accumulation ratio of loncastuximab tesirine by Cycle 2 was 1.4 based on AUClast and 1.2 based on Cmax in patients with DLBCL. Loncastuximab tesirine steady</td></tr>
</table>

	state Cmax following 75 µg/kg Q3W was 28.2% lower than the Cmax after the first dose at 150 µg/kg. The time to reach steady state was 210 days.
Variability	The inter-subject variability (CV%) in steady state loncastuximab tesirine AUCtau and Cmax was 38.2% and 32.1%, respectively.
Immunogenicity	Please see the Office of Pharmaceutical Quality (OPQ) review regarding the bioanalytical performance of the ADA assays. A neutralizing antibody assay has not been developed. OPQ will issue a PMC for the development of a validated nAb assay, as part of this PMC, Applicant has been asked to adequately bank serum samples from ongoing and future trials to evaluate neutralizing potential of any samples that test ADA positive. In Study 201, 134 patients treated at the proposed dosage had immunogenicity assessment at baseline and at least one time point post-dose. No patient developed treatment-emergent ADA against loncastuximab tesirine. One patient tested positive for ADA against loncastuximab tesirine at baseline only. In Study 101, 130 patients with DLBCL had an immunogenicity assessment at baseline and at least one time point post dose. Three patients tested positive for ADA at baseline only. One patient tested positive at baseline (titer = 1) and on treatment (titer <1). One (0.8%) patient, dosed at 120 µg/kg, developed treatment emergent ADA. Due the limited number of patients who were positive for ADA during treatment with loncastuximab tesirine, the impact of ADA on the PK, safety and efficacy of loncastuximab tesirine is not fully characterized. However, the immunogenicity of loncastuximab tesirine does not appear to be a significant clinically-relevant concern overall, as the incidence of treatment-emergent ADA at the proposed dosing regimen is low.
ABSORPTION	
Bioavailability	Complete as loncastuximab tesirine is administered via IV infusion
TMAX	Close to end of infusion
DISTRIBUTION	
Volume of distribution (Vd)	Population PK-derived geometric mean (CV%) steady-state volume of distribution of loncastuximab tesirine in patients with DLBCL is 7.11 L (26.6%).
Plasma protein	The human plasma protein binding of the payload SG3199 is 94%[2].The

binding and blood-to-plasma distribution	blood-to-plasma ratio of SG3199 has not been determined.
ELIMINATION	
Terminal elimination half-life and clearance	The geometric mean (CV%) of loncastuximab tesirine clearance decreased with time from 0.499 L/day (89.3%) after a single dose to 0.275 L/day (38.2%) at steady state in patients with DLBCL. The mean (SD) half-life of loncastuximab tesirine was 14.0 (6.78) days in Cycle 1 and 20.8 (7.06) days at steady state in patients with DLBCL.
Metabolism	The monoclonal antibody portion of loncastuximab tesirine is expected to be metabolized into small peptides and individual amino acids by catabolic pathways. In vitro, SG3199 is metabolized by CYP3A4/5.
Excretion	After IV administration of [^{3}H]-SG3199 to rats, total radioactivity was excreted mainly via feces and biliary route (97.5±3.0%), with minor urinary excretion of radioactivity (3.8±0.3%). No mass-balance studies were conducted in human subjects.
Drug interaction liability	No clinical drug-drug interaction studies have been conducted with loncastuximab tesirine. In vitro: • SG3199 is a substrate of CYP3A4/5 but not of other major CYP enzymes • SG3199 is a substrate of P-gp, but not a substrate of BCRP, OATP1B1, or OCT1[3] • SG3199 is not a direct or time-dependent inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C19, CYP2D6, CYP3A4/5 and CYP2E1. Minimal inhibitory effects were observed on CYP2C8 (<30%) and CYP2C9 (<15%) at 0.5 µg/mL (0.85 µM), which is orders of magnitude higher than the clinically relevant unconjugated SG3199 serum exposure (geomean Cmax in Study 201 ~84 pM) • No CYP induction experiments have been conducted. The potential for SG3199-mediated CYP induction is expected to be low at the clinically relevant unconjugated (free) serum exposures • SG3199 does not inhibit P-gp or OATP1B3. The clinical serum exposure of unconjugated SG3199 is orders of magnitude below the IC_{50}s for inhibition of BCRP, OATP1B1, OAT1, OAT3, OCT2, OCT1, MATE1, MATE2-K, and BSEP

[1] Regimens evaluated in Study 101: 15, 30, 60, 90, 120, 150, 200 µg/kg Q3W IV, 120 µg/kg Q3W for 2 cycles then 60 µg/kg Q6W beginning 6 weeks after Cycle 2, 150 µg/kg Q3W for 2 cycles then 60 µg/kg Q6W beginning 6 weeks after Cycle 2, 150 µg/kg Q3W for 3 cycles then 75 µg/kg Q3W, 200 µg/kg Q6W for 2 cycles then 60 µg/kg Q6W beginning 6 weeks after Cycle 2 and 200 µg/kg Q6W in Cycle 1 then 60 µg/kg Q6W beginning 6 weeks after Cycle 1

[2]Experimental limitations include low radiochemical purity, instability and volatility (tritium exchange) of [^{3}H]-SG3199.
[3] Results of OATP1B3 experiment are inconclusive

6.3.2. Clinical Pharmacology Questions

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

Data:
With increasing exposures to loncastuximab tesirine as measured by conjugated antibody, statistically significant ($p<0.05$) increases in ORR and OS (as well as progression-free survival [PFS], not previously discussed) were observed. Modeling provided good prediction to observed median OS over time.

The Applicant's Position:
The clinical pharmacology data provide a profile of exposure and associated relationship to efficacy that support the effectiveness of loncastuximab tesirine in relapsed or refractory DLBCL. Significant and meaningful ORR and ability to characterize the exposure-response relationships for efficacy and safety in these patients provide a sound quantitative basis of support for loncastuximab tesirine behavior.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment that the clinical pharmacology program provides supportive evidence of efficacy.

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

Data:
PK analysis indicates that administration of loncastuximab tesirine 150 µg/kg Q3W x2, followed by a 50% dose reduction to 75 µg/kg Q3W thereafter maintains constant exposure to conjugated antibody for the duration of the dosing interval, as evidenced by the moderate accumulation index value in study ADCT-402-201 of 1.65 by Cycle 2. From study 402-101, at the 200 µg/kg dose, the frequency of Grade 3 and higher TEAEs was higher and the probability of a dose modification increased sharply after the second dose. Reduction of the dose following Cycle 2 was supported by the observation that median time to tumor response was 43 days, approximately equivalent to two cycles of treatment. Significant associations of exposure to TEAEs, particularly for increased GGT, LFT abnormalities, skin and nail effects, and pain, were established.

The Applicant's Position:
The use of an induction regimen of 150 µg/kg Q3W x2, followed by a 50% dose reduction to 75 µg/kg Q3W thereafter is considered appropriate. It provides rapid achievement of steady-state exposure relative to the 75 µg/kg steady-state condition, maximizes objective response for the majority of patients who respond, and can mitigate cumulative toxicities that higher initial doses or continued treatment at 150 µg/kg Q3W would otherwise yield.

The FDA's Assessment:
FDA agrees that the proposed dosing regimen of 150 µg/kg Q3W x2 followed by 75 µg/kg Q3W is acceptable for the general patient population. The proposed dosing regimen is supported by safety and efficacy data in the pivotal Study 201, safety, activity and PK data in Study 101 and the exposure-response relationships of loncastuximab tesirine with regards to safety and efficacy.

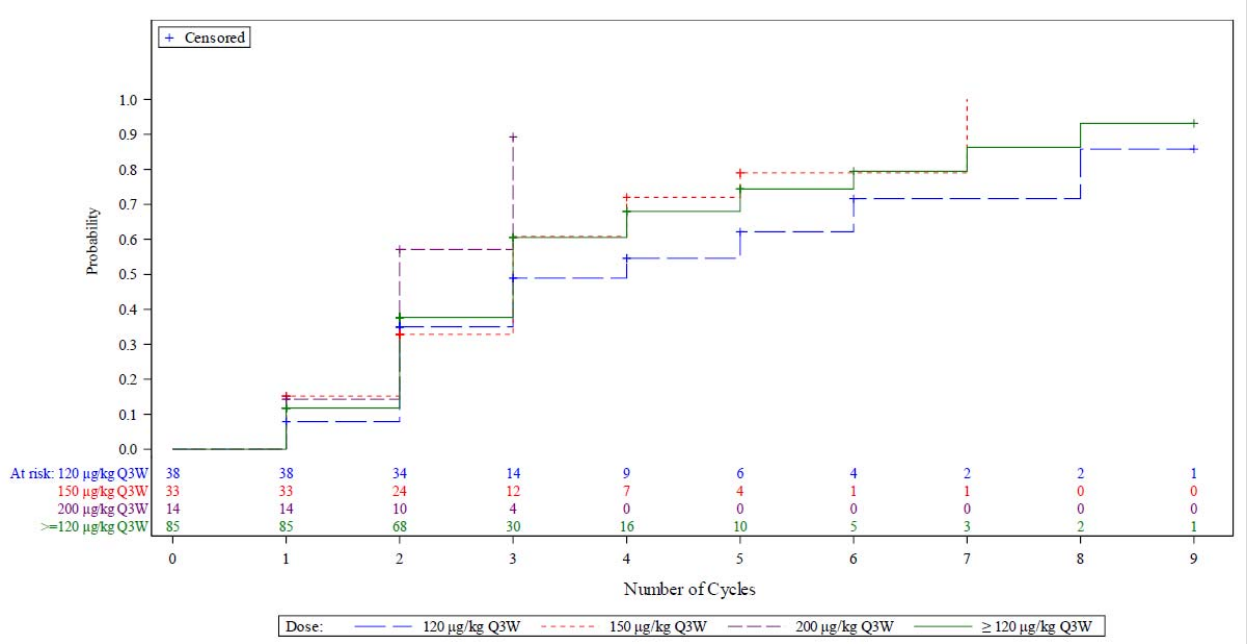
Dosing regimens ranging from 15 to 200 mg Q3W IV were evaluated in a B-HNL patient population (n=183; including 139 patients with DLBCL) in the phase 1 Study 101. As a limited number of patients were enrolled at dosage levels ≤ 90 µg/kg Q3W (n=17; 10 DLBCL patients), assessment was focused on regimens ≥120 µg/kg.

In order to mitigate cumulative toxicities, and as the risk of AEs leading to dose modifications increased after the second or third dose at dose levels ≥ 120 µg/kg (Figure 4), additional dosing regimens with planned dose reductions were evaluated in Study 101. These included:

- 120 µg/kg Q3W x 2 then 60 µg/kg Q6W,
- 150 µg/kg Q3W x 2 then 60 µg/kg Q6W,
- 150 µg/kg Q3W x 3 then 75 µg/kg Q3W,
- 200 µg/kg Q6W x 2 then 60 µg/kg Q6W and
- 200 µg/kg Q6W in Cycle 1 then 60 µg/kg Q6W.

Dose-response relationships, as summarized in the tables below, were observed with select safety findings and anti-tumor activity. The ORR in patients with DLBCL was numerically higher at the 200 µg/kg Q3W regimen than at the 120 and 150 µg/kg Q3W dosing regimens (Table 3). However, at the 200 µg/kg dose level adverse events including grade≥3 thrombocytopenia, neutropenia and edema/effusion (Table 2) were unacceptable. Therefore, the next highest dose level, 150 ug/kg was selected. The timing of the planned dose reduction in Cycle 3 was supported by a median time to first response in DLBCL patients treated at 150 µg/kg in Study 101 of 42 days.

Figure 4: Kaplan-Meier Plot of Time to First AE Leading to Dose Modification in Patients Receiving 120 µg/kg Q3W, 150 µg/kg Q3W, 200 µg/kg Q3W Dosing Regimens Throughout Study 101



Source: Applicant's analysis in response to an FDA IR

Table 2: Summary of Adverse Events by Dosing Regimen in Study 201

	120 µg/kg Q3W (N=38)	150 µg/kg Q3W (N=33)	200 µg/kg Q3W (N=14)
Patients with any grade 3 or higher TEAE	28 (73.7)	28 (84.8)	12 (85.7)
Patients with any TEAE related to ADCT-402	35 (92.1)	27 (81.8)	14 (100)
Patients with any serious TEAE	17 (44.7)	18 (54.5)	6 (42.9)
Patients with any TEAE leading to ADCT-402 dose reduction	5 (13.2)	2 (6.1)	1 (7.1)
Patients with any TEAE leading to ADCT-402 dose delay	17 (44.7)	16 (48.5)	8 (57.1)
Patients with any TEAE leading to ADCT-402 withdrawal	9 (23.7)	8 (24.2)	4 (28.6)
Select common AEs; Grade ≥3			
Thrombocytopenia	5 (13.2)	2 (6.1)	3 (21.4)

Neutropenia	5 (13.2)	2 (6.1)	3 (21.4)
Anemia	4 (10.5)	6 (18.2)	3 (21.4)
GGT Inc	9 (23.7)	8 (24.2)	2 (14.3)
ALT increase	2 (5.3)	2 (6.1)	1 (7.1)
AST increase	1 (2.6)	1 (3.0)	1 (7.1)
Edema or effusion	3 (7.9)	3 (9.1)	3 (21.4)

120, 150 or 200 mg Q3W: Dose given every 3 weeks (per cycle) throughout treatment duration
Source: Applicant's response to an FDA IR

Table 3: Response Rates in Patients with Diffuse Large B-cell Lymphoma by Dosing Regimen in Study 101

	120 µg/kg Q3W (N=31)	**150 µg/kg Q3W (N=23)**	**200 µg/kg Q3W (N=11)**
ORR (CR + PR) [n, (%)]	13 (41.9)	10 (43.5)	7 (63.6)
95% CI for ORR	(24.5, 60.9)	(23.2, 65.5)	(30.8, 89.1)
Complete response [n, (%)]	6 (19.4)	5 (21.7)	6 (54.5)

120, 150 or 200 mg Q3W: Dose given every 3 weeks (per cycle) throughout treatment duration
Source: Applicant's response to an FDA IR

Efficacy at the proposed dosing regimen in the DLBCL indication was demonstrated in Study 201. The primary endpoint in Study 201 was ORR according to the 2014 Lugano classification by independent central review. The observed ORR in Study 201 was 48.3% (95% CI: 39.9- 56.7%) with a median DoR of 10.3 (6.9, NE). Best overall responses included 35 patients (24.1%) with CR and 35 patients (24.1%) with PR. Additional information regarding the efficacy in Study 201 is provided in Section 8.1.2. The median time to first response in Study 201 at the proposed dosing regimen was 41 days, close to that observed in Study 101. Efficacy at the proposed regimen in Study 201 does not appear to be compromised relative to DLBCL patients in Study 101 (n=23) treated at 150 µg/kg throughout the treatment duration, who had an ORR of 43.5% (95% CI: 23.2, 65.5) and a median DoR of 4.04 (1.2, NE) with a CRR of 21.7% (Source: Applicant's analysis in response to an FDA IR).

The rates of TEAEs leading to dose modifications at the proposed dosing regimen in Study 201 are summarized in Table 4, which appear to be similar to those observed at the 150 µg/kg Q3W regimen in Study 101, based on a cross-study comparison. However, the overall tolerability of the proposed dosing regimen was acceptable, as a high mean (SD) relative dose intensity of 94.2 (10.3)% was maintained at the proposed dose in Study 201. Ninety one percent of patients achieved relative dose intensity ≥ 80% and 78.6% achieved relative dose intensity ≥ 90%.

Table 4: Adverse Events Leading to Dose Modifications at the Proposed Dosing Regimen in Study 201

N	**145 (%)**
Patients with any TEAE leading to ADCT-402 reduction	11 (7.6)

Patients with dose reductions due to TEAE in C1 or C2	5 (3.4)
Patients with dose reductions due to TEAE in ≥ C3	6 (4.1)
Patients with any TEAE leading to ADCT-402 delay	74 (51.0)
Patients with any TEAE leading to ADCT-402 withdrawal	34 (23.4)
Mean (SD) relative dose intensity	94.2 (10.3)%
Abbreviations: C, cycle; TEAE, treatment emergent adverse event	

Source: Study 201 CSR and reviewer's analysis

Based on a cross-study comparison summarized inTable 1Table 5, the FDA noted that the '150 µg/kg Q3W for 2 cycles then 60 µg/kg Q6W beginning 6 weeks after Cycle 2' regimen showed a trend towards lower Grade ≥3 TEAEs (62.5% vs 72.4%), SAEs (25% vs 39.3%) and TEAEs leading to dose reduction (0 vs 7.6%), delay (37.5% vs 51%) or withdrawal (12.5 vs 23.4) relative to the proposed dosing regimen. Efficacy appears to be maintained at the 150 Q3W x 2 then 60 µg/kg Q6W, with the ORR in patients with DLBCL being 57.1% vs 48.3%. However, the interpretation is limited by the small number of patients with DLBCL (n=14) in the '150 µg/kg Q3W for 2 cycles then 60 µg/kg Q6W beginning 6 weeks after Cycle 2' arm in Study 101.

Table 5: Cross Study Comparison of the 150 µg/kg Q3W x 2 then 60 µg/kg Q6W Regimen in Study 101 and the 150 µg/kg Q3W x 2 then 75 µg/kg Q3W Regimen in Study 201

	Study 101 150 µg/kg Q3W x 2 then 60 µg/kg Q6W	Study 201 150 µg/kg Q3W x 2 then 75 µg/kg Q3W
Safety	**N=16**	**N=145**
Patients with any grade 3 or higher TEAE	10 (62.5)	105 (72.4)
Patients with any TEAE related to ADCT-402	15 (93.8)	117 (80.7)
Patients with any serious TEAE	4 (25.0)	57 (39.3)
Patients with any TEAE leading to ADCT-402 dose reduction	0 (0)	11 (7.6)
Patients with any TEAE leading to ADCT-402 dose delay	6 (37.5)	74 (51.0)
Patients with any TEAE leading to ADCT-402 withdrawal	2 (12.5)	34 (23.4)
Efficacy	**N=14**	**N=145**
ORR (CR + PR) [n, (%)]	8 (57.1)	70 (48.3)
95% CI for ORR	(28.9, 82.3)	(39.9, 56.7)
Complete response [n, (%)]	4 (28.6)	35 (24.1)

150 µg/kg Q3W x 2: 150 µg/kg Q3W for 2 cycles then 60 µg/kg Q6W beginning 6 weeks after Cycle 2

The Applicant evaluated exposure-response relationships of loncastuximab tesirine with efficacy and safety endpoints to further support the proposed dosing regimen. Exposure-

efficacy analyses were conducted in patients with R/R DLBCL (N=284), while exposure-safety analyses included all patients with R/R NHL and DLBCL (N=328) from both Studies 101 and 201. Applicant's analysis reported that higher loncastuximab tesirine Cavg during Cycle 1 was significantly associated with higher ORR (Figure 1), longer OS (Figure 2), and higher risk of Grade ≥2 increased GGT (Figure 3).

The reviewer's independent analysis confirmed Applicant's results, and also identified that higher loncastuximab tesirine C1 Cavg was associated with increasing probability of other adverse events, including Grade≥2 LFT abnormalities (Figure 26), skin and nail abnormalities (Figure 27), and TEAEs leading to treatment discontinuation (Figure 28). Refer to Section **Error! Reference source not found.** for further details regarding exposure-response analyses for both efficacy and safety.

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The E-R relationships for efficacy and safety are generally consistent with the dose-response findings, suggesting that higher loncastuximab tesirine exposures are associated with higher response rate and greater toxicity. Notably, loncastuximab tesirine exposure early in treatment was associated with the probability of objective response.

Overall, the clinical pharmacology review team assessed that the proposed dosing regimen showed an acceptable risk-benefit balance.

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

Data:
Simulations of the final population PK model demonstrated that most factors evaluated did not contribute substantially to exposure variability. Potentially noteworthy exceptions associated with lower exposures than respective reference groups were baseline albumin, hepatic function, and nonDLBCL disease subtype. Given the fragile nature of patients with relapsed or refractory DLBCL, and increased hazard for death for patients with mild/moderate hepatic impairment, dose adjustment was not considered appropriate.

The Applicant's Position:
No change in dosing regimen is required based on intrinsic patient factors for patients with relapsed or refractory DLBCL.

The FDA's Assessment:
The FDA agrees that no dose modifications are needed in the proposed DLBCL indication based on age (20-94 years), sex and ECOG status (0 to 2).

Body weight (42.1 to 160.5 kg) was shown to be a significant covariate of loncastuximab tesirine clearance and central volume of distribution based on the population PK analysis, which supports the body weight-normalized dosing. Based on the population PK analysis, loncastuximab tesirine Cycle 1 Cmax and Cavg in patients with a lower body weight (42.1 to 65 kg, n=82) were 14% and 18% lower, while loncastuximab tesirine Cycle 1 Cmax and Cavg in patients with higher body weight (85 to 160.5 kg, n=110) were 7% and 26% higher than those with a normal body weight (65 to 85 kg, n=136), respectively. Based on multivariate exposure-response analyses (See section 19.4.2), BW was not identified as a statistically significant predictor of ORR or of increased safety signals. However, consistent with the dosing used in Study 201, the dose in patients with BMI ≥35 kg/m^2 will be calculated based on adjusted body weight.

Based on the population PK analysis, patients with low albumin levels (<35 g/L) had a 52% lower loncastuximab tesirine Cycle 1 Cavg compared to patients with normal albumin levels (≥35 g/L). However, no dose increase in patients with low albumin is recommended based on baseline albumin (17 to 52 g/L), because patients with low albumin levels exhibited comparable rates of Grade ≥ 3 adverse events and SAEs as those with normal albumin levels at the proposed dosing regimen.

Baseline peripheral CD19+ B-cell count was not included in the population PK analyses as a covariate because CD19 expression data were only available in a subset of patients in Study 101 and no peripheral CD19 expression data were collected in Study 201.

Race and Ethnicity:

Of the 145 patients enrolled in the pivotal study ADCT-402-201, 90% (n=130) were White, 3% (n=5) were Black, 2% (n=3) were Asian, and 5% (n=7) were Other. Of those, 9% (n=13) of patients identified as Hispanic or Latino. The population PK analysis for Studies ADCT-402-101 and ADCT-402-201 included 294 (90%) White, 16 (5%) Black, 6 (2%) Asian and 10 (3%) grouped as Other races.
Based on observed PK parameter estimates in Study ADCT-402-201, higher geomean loncastuximab tesirine AUClast were observed in Black patients compared to White patients in Cycle 1 (21068 vs 15775 day.ng/mL) and in Cycle 2 (35136 vs 23642 day.ng/mL). PK data was only available in 3 Asian patients, as such, a comparison was not done. We note that this assessment is limited by the small number of patients in each race group and additional data will be needed.
Safety data from Study 201 (Table 6), indicated that a higher proportion of Black patients had Grade ≥3 adverse events and TEAEs leading to dose delays (primarily neutropenia) compared with White patients, with limited data available in Asian and other racial sub-groups.

Table 6: Summary of Adverse Events by Race in Study 201

	White	Black	Asian	Other*
N	**130 (%)**	**5 (%)**	**3 (%)**	**7 (%)**
Patients with any grade 3 or higher TEAE	92 (70.8)	4 (80)	2 (66.7)	7 (100)
Patients with any TEAE related to ADCT-402	105 (80.8)	4 (80)	1 (33.3)	7 (100)
Patients with any serious TEAE	52 (40)	1 (20)	1 (33.3)	3 (42.9)
Patients with any TEAE leading to ADCT-402 dose reduction	10 (7.7)	0 (0)	0 (0)	1 (14.3)
Patients with any TEAE leading to ADCT-402 dose delay	66 (50.8)	4 (80)	0 (0)	4 (57.1)
Patients with any TEAE leading to ADCT-402 withdrawal	32 (24.6)	1 (20)	0 (0)	1 (14.3)

* Includes American Indian or Alaskan Native (n=1), Native Hawaiian or Pacific Islander (n=1) and other (n=5)

Given the limited information regarding the effects of race and ethnicity on the PK, PD, safety and efficacy of loncastuximab tesirine, the numerically higher exposures in Black patients, and the data to suggest higher rates of Grade 3 TEAEs and TEAEs leading to discontinuation among racial and ethnic minority patients, a PMR will be issued to collect additional data in U.S. racial and ethnic minority patients with large B-cell lymphoma. Population PK and exposure-response analyses will be updated once these data are available.

Renal Impairment:

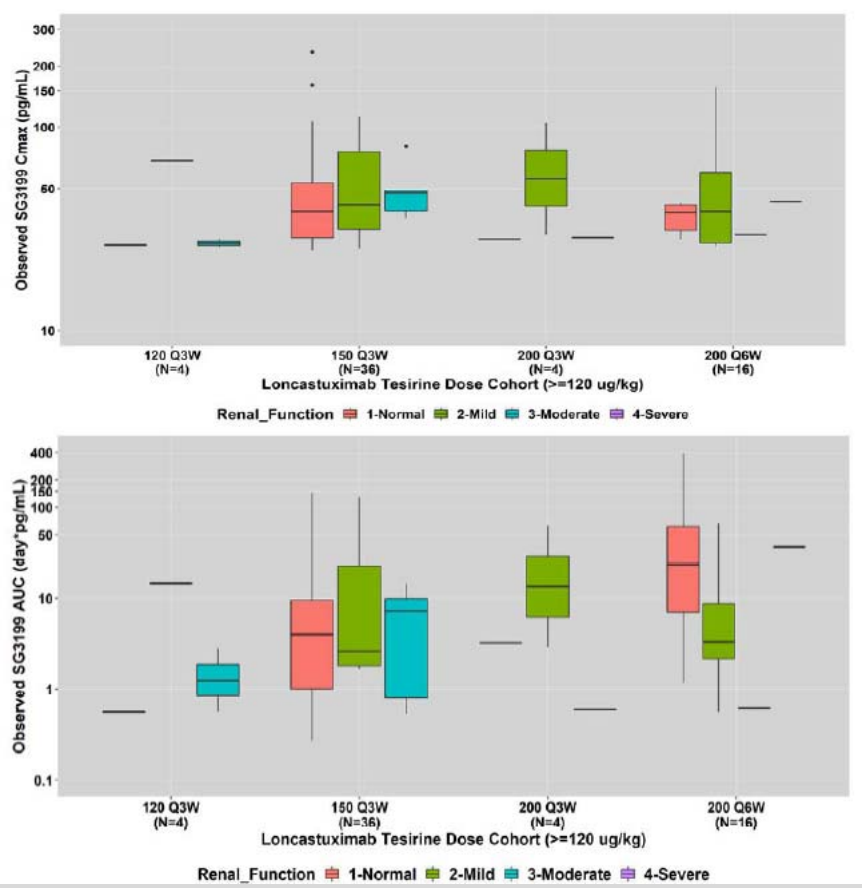
No dose adjustment is required for patients with mild or moderate renal impairment. There is insufficient clinical data in patients with severe renal impairment or end-stage renal disease to assess the impact on PK, although no significant effect would be expected.

The Applicant's population PK analysis included patients with mild (n=118) and moderate (n=50; one patient with severe renal impairment was analyzed with the moderate impairment group) renal impairment, in addition to patients with normal (n=159) renal function. Creatinine clearance was not identified as a statistically significant covariate of loncastuximab tesirine pharmacokinetics. Based on population PK analysis, loncastuximab tesirine Cmax and Cavg were not meaningfully different in the mild or moderate renal impairment subgroups compared to normal renal function.

For SG3199, the available measurable serum concentrations were compared across dose cohorts between normal renal function and renal impairment subgroups. There was no consistent increase in observed SG3199 exposure in the renal impairment subgroups compared

to patients with normal renal function (Figure 5). These observations are consistent with renal elimination not being a significant clearance pathway of loncastuximab tesirine due to its molecular weight or of unconjugated SG3199 based on non-clinical data.

Figure 5: Cmax and AUClast of Unconjugated SG3199 (Cycle 1) in Different Baseline Renal Function Subgroups by Dose Cohort in Studies ADCT-402-101 and ADCT-402-201



Source: 2.7.2 Summary of Clinical Pharmacology Studies

Safety information from Study 201 suggests no marked increase in adverse events in patients with renal impairment as summarized in Table 7

Table 7: Comparison of Adverse Events in Study 201 Patients with Normal Renal Function and Renal Impairment Who Received Loncastuximab Tesirine

	Normal	Mild RI	Mod RI

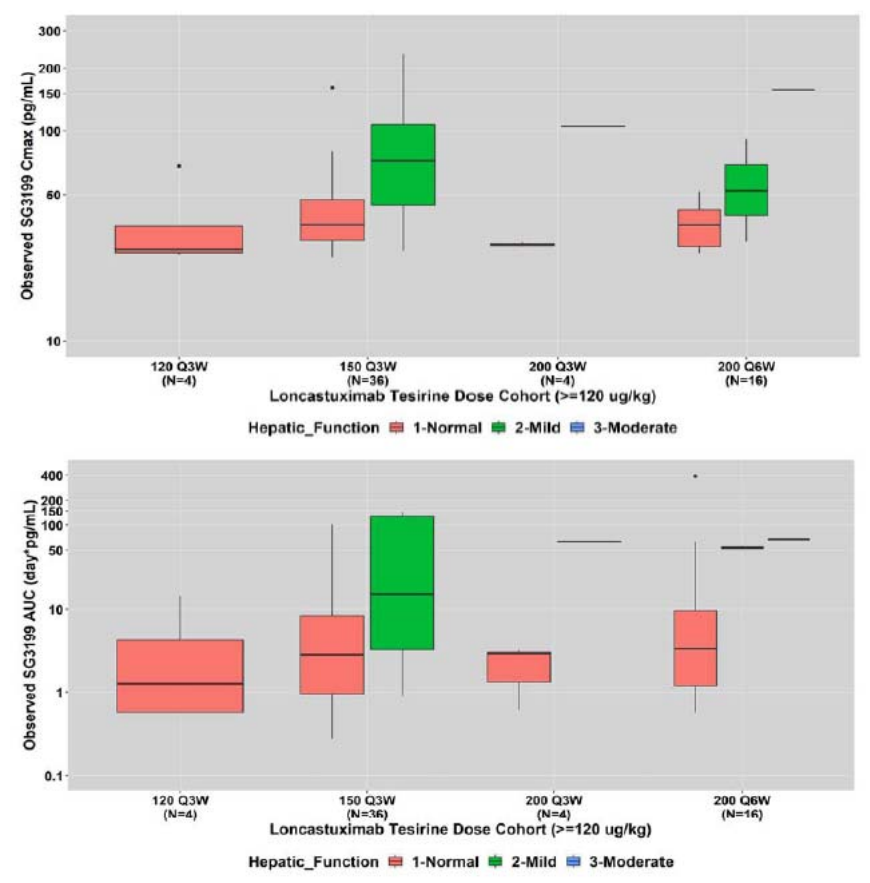
	(CLcr ≥ 90 mL/min)	(60 ≤ CLcr < 90 mL/min)	(30 ≤CLcr < 60 mL/min)
N	69 (%)	52 (%)	24 (%)
Patients with ≥Gr 3 TEAEs	54 (78.3)	35 (67.3)	16 (66.7)
Patients with treatment related TEAEs	53 (76.8)	43(82.7)	21 (87.5)
Patients with SAEs	28 (40.6)	19 (36.5)	10 (41.7)
Patients with TEAEs leading to dose reduction	5 (7.2)	2 (3.8)	4 (16.7)
Patients with TEAEs leading to dose delay	37 (53.6)	26 (50)	11 (45.8)
Patients with TEAEs leading to treatment withdrawal	13 (18.8)	14 (26.9)	7 (29.2)
Mean (SD) RDI (%)	93.7 (10.4)	95.9 (6.5)	91.7 (15.6)
Median (min, max) number of cycles	3 (1, 14)	3 (1, 15)	5 (1, 14)
Mean (SD) duration of treatment	70.1 (69.5)	76.9 (80.7)	113 (106)

RI = renal impairment by CLcr calculated per Cockcroft Gault equation
Source: Reviewer's analysis

Hepatic Impairment:

Loncastuximab tesirine clinical trials included patients with normal or mild hepatic function, according the NCI ODWG classification. The Applicant's population PK analysis includes patients with normal hepatic function (n =277) or mild hepatic impairment (n=49; one patient with moderate hepatic impairment was analyzed with the mild impairment group). Based on population PK analysis, loncastuximab tesirine Cavg in the mild hepatic impairment subgroup was 42% lower than that in patients with normal hepatic function. The lower exposure could be due to underlying factors such low albumin levels (32% of patients with mild/moderate hepatic impairment vs 12% of patients with normal hepatic function had albumin ≤ 34g/L in the population PK analysis). The observed median Cmax and AUClast of unconjugated SG3199 (150 µg/kg, Cycle 1) appeared to be higher (~2-fold and ~5-fold) in mild hepatic impairment than normal hepatic function subgroups (Figure 6).

Figure 6: Cmax and AUClast of SG3199 (Cycle 1) in Different Baseline Hepatic Function Subgroups by Dose Cohort in Studies ADCT-402-101 and ADCT-402-201



Source: 2.7.2 Summary of Clinical Pharmacology Studies

Analysis of safety information in Study 201 suggested that the frequency of adverse events is slightly higher in patients with mild hepatic impairment (Table 8). However, there does not appear to be a difference in the tolerability of loncastuximab tesirine in patients with mild impairment that is substantial enough to preclude dosing these patients with the proposed dosing regimen on loncastuximab tesirine. The FDA also evaluated the potential effect of the lower loncastuximab tesirine Cavg on response. While a trend towards lower ORR was observed, the FDA concluded this was likely due to underlying imbalances including bulky disease, baseline tumor sum of area and high risk disease phenotype. As such, no loncastuximab tesirine starting dose modification is recommended in mild hepatic impairment, but patients should be monitored for increased toxicity.

Table 8: Comparison of Adverse Events in Study 201 Patients with Normal Hepatic Function and Hepatic Impairment Who Received Loncastuximab Tesirine

	Normal	Mild HI
N	**122 (%)**	**22 (%)**
Patients with ≥Gr 3 TEAEs	88 (72.1)	16 (72.7)
Patients with treatment related TEAEs	101 (82.8)	15 (68.2)
Patients with SAEs	44 (36.1)	13 (59.1)
Patients with treatment related SAEs	17 (13.9)	5 (22.7)
Patients with TEAEs leading to dose reduction	9 (7.4)	1 (4.5)
Patients with TEAEs leading to dose delay	64 (52.5)	9 (40.9)
Patients with TEAEs leading to dose withdrawal	28 (23)	6 (27.3)
Mean (SD) RDI (%)	94.1 (9.7)	97.0 (7.1)
Median (min, max) number of cycles	4 (1,15)	1 (1, 12)
Mean (SD) duration of treatment (Day)	85.5 (79.1)	34.5 (59.7)
Select common AEs; Grade ≥3		
Thrombocytopenia	21 (17.2)	5 (22.7)
Neutropenia	34 (27.9)	3 (13.6)
Anemia	9 (7.4)	6 (27.3)
GGT increase	19 (15.6)	5 (22.7)
ALT increase	3 (2.5)	1 (4.5)
AST increase	0 (0)	1 (4.5)
ALP Increase	0 (0)	1 (4.5)
Blood bilirubin increase	0 (0)	2 (9.1)
Pleural effusion	2 (1.6)	1 (4.5)
Peripheral edema	1 (0.8)	1 (4.5)

HI = Hepatic impairment per NCI ODWG criteria
Source: Reviewer's analysis

The effect of moderate and severe hepatic impairment on the safety and PK of loncastuximab tesirine is unknown; a PMR will be issued to determine an appropriate starting dose in this population.

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

Data:
SG3199 is not a potent inhibitor of CYP enzymes and therefore is not expected to impact the disposition of coadministered agents which are substrates for these pathways. SG3199 however is a substrate of P-gp. Testing of coadministered P-gp inhibitors which included amiodarone, carvedilol, and clarithromycin in the population PK analysis indicated these did not have a significant impact on conjugated antibody or total antibody disposition.

The Applicant's Position:
As an IV administered agent, loncastuximab tesirine is not anticipated to be associated with a food-drug interaction. No clinically relevant drug-drug interactions are anticipated.

The FDA's Assessment:
FDA agrees that no food-drug interactions or drug-drug interactions requiring loncastuximab tesirine dose modifications are anticipated.

No clinical drug-drug interaction studies with loncastuximab tesirine have been conducted. In vitro, SG3199 is a substrate of CYP3A and P-gp. The FDA's analysis indicates that no loncastuximab tesirine dose modifications are required when used concomitantly with CYP3A or P-gp inhibitors, as summarized below. Concomitant use of CYP3A inducers leading to any potential decrease of unconjugated SG3199 concentration is not expected to meaningfully alter the efficacy of loncastuximab tesirine given the mechanism of action. The DDI risk as perpetrator associated with the unconjugated payload is expected to be low as unconjugated (free) SG3199 concentration in serum is BLQ in ~95% of clinical samples. In Study 201, the geomean (%CV) of unconjugated SG3199 Cmax was 0.049 ng/mL (78.8), which amounts to~84 pM and is orders of magnitude below the observed IC_{50}s for transporter inhibition.

Concomitant CYP3A inhibitors:
Study 101 and 201 protocols did not prohibit the use of CYP3A inhibitors. The acceptability of concomitant CYP3A inhibitor use with loncastuximab tesirine is based on available data in Studies 101 and 201. Loncastuximab tesirine-treated patients in Studies 101 and 201 received concomitant CYP3A inhibitors, as summarized in Table 9 below:

Table 9: Summary of Concomitant Strong and Moderate CYP3A Inhibitor Use with Loncastuximab Tesirine in Studies 101 and 201

	Study 101[1]	**Study 201[2]**
Number of patients who received concomitant strong CYP3A inhibitor	8	**6**
Duration of concomitant strong CYP3A inhibitor use (Range in Days)	4-28	**2-106**
Number of patients who received concomitant moderate CYP3A inhibitor	40	**22**
Duration of concomitant moderate CYP3A inhibitor use (Range in Days)	1-long term/ongoing	**1-long term/ongoing**

[1]Across all dose levels tested. Concomitant strong CYP3A inhibitors included Ketoconazole, Voriconazole, Posaconazole, Clarithromycin, Chloramphenicol; dosing not documented
[2] Concomitant strong CYP3A inhibitors included Voriconazole, Posaconazole, Clarithromycin at clinical dosages administered by routes leading to systemic exposure i.e oral or intravenous
Source: Applicant's response to FDA IR and reviewer's analysis

While PK data were of limited utility due to the limited number of patients receiving CYP3A inhibitors who had measurable unconjugated SG3199 concentrations, an exploratory analysis of safety data in patients from 201 who received concomitant strong or moderate CYP3A inhibitors was conducted, as summarized in Table 10 below.

Table 10: Comparison of Adverse Events in Study 201 Patients With or Without Receipt of Strong or Moderate CYP3A Inhibitors

	Strong CYP3A inhibitors	Moderate CYP3A inhibitors	None
N	**6 (%)**	**22 (%)**	**40 (%)**
Patients with ≥Gr 3 TEAEs	4 (66.7)	20 (90.9)	30 (75.0)
Patients with treatment related TEAEs	6 (100)	19 (86.4)	35 (87.5)
Patients with SAEs	3 (50.0)	15 (68.2)	14 (35.0)
Patients with TEAEs leading to dose reduction	2 (33.3)	1 (4.5)	2 (5)
Patients with TEAEs leading to dose delay	3 (50)	11 (50)	19 (47.5)
Patients with TEAEs leading to dose withdrawal	1 (16.7)	5 (22.7)	9 (22.5)
Select common AEs; Grade ≥3			
Thrombocytopenia	2 (33.3)	5 (22.7)	4 (10.0)
Neutropenia	2 (33.3)	9 (40.9)	7 (17.5)
Anemia	1 (16.7)	4 (18.2)	3 (7.5)
GGT increase	1 (16.7)	4 (18.2)	6 (15.0)
Lymphopenia	1 (16.7)	3 (13.6)	2 (5.0)
Hypokalaemia	1 (16.7)	1 (4.5)	1 (2.5)
ALT increase	0 (0)	0 (0)	3 (7.5)
AST increase	0 (0)	0 (0)	1 (2.5)
Pleural effusion	0 (0)	0 (0)	2 (5.0)
Peripheral edema	0 (0)	0 (0)	1 (2.5)

Source: Applicant's response to FDA IR

While the tables above suggest an increase in TEAEs leading to dose reduction in patients receiving strong CYP3A inhibitors as well as SAEs and Grade ≥ 3 hematological AEs (thrombocytopenia, neutropenia) in patients receiving concomitant strong and moderate CYP3A inhibitors, the FDA's analysis indicated that many of the relevant adverse events did not have onset during concomitant medication use (i.e. occurred prior to initiation or > 14 days after stopping concomitant medication). The limitations of this analysis include the small number of patients who received strong CYP3A inhibitors and the fact that not all the concomitant medications are equally potent at inhibiting CYP3A activity. However, concomitant CYP3A inhibitors have been used long term in patients in the studies to date and available data indicate no major increase in safety concerns with concomitant use of CYP3A inhibitors. As such, available data indicate that no loncastuximab tesirine dose modifications are needed with

concomitant CYP3A inhibitors and no labeling recommendation to avoid concomitant CYP3A inhibitors is warranted. These findings will be verified with additional PK and safety data from the ongoing phase 3 study.

Concomitant P-gp inhibitors:

PK and safety analyses similar to those described for CYP3A inhibitors were conducted based on available data in loncastuximab tesirine-treated patients in clinical studies, who received concomitant P-gp inhibitors (carvedilol, amiodarone and clarithromycin). Based on an analysis of PK data from Study 101 and 201 combined, concomitant use of P-gp inhibitors does not significantly alter the exposure of unconjugated SG3199 in cycle 1 or cycle 2 at the 150 µg/kg loncastuximab tesirine dose (in patients who received concomitant P-gp inhibitors during cycle 1 or cycle 2). The FDA's safety analysis of data from Study 201 in patients who received concomitant P-gp inhibitors is summarized in Table 11 below.

Table 11: Comparison of Adverse Events in Study 201 Patients With or Without Receipt of P-gp Inhibitors

	P-gp inhibitor	None
N	**11 (%)**	**134 (%)**
Patients with ≥Gr 3 TEAEs	6 (54.5)	99 (73.9)
Patients with treatment related TEAEs	9 (81.8)	108 (80.6)
Patients with SAEs	6 (54.5)	51 (38.1)
Patients with TEAEs leading to dose reductions	2 (18.2)	9 (6.7)
Patients with TEAEs leading to dose delays	6 (54.5)	68 (50.7)
Patients with TEAEs leading to dose withdrawal	4 (36.4)	30 (22.4)

Source: Reviewer's analysis

While the tables above suggest an increase in SAEs and TEAEs leading to dose reduction in patients receiving P-gp inhibitors, the FDA's analysis indicated that many of the relevant adverse events did not have onset during concomitant medication use (i.e. occurred prior to initiation or > 14 days after stopping concomitant medication). Available data indicate no loncastuximab tesirine starting dose modifications are needed with concomitant P-gp inhibitors.

Krithika Arun Shetty, PhD
Liang Li, PhD
Amanda Lewin, PhD
Primary Reviewers

Ruby Leong, PharmD
Lian Ma, PhD
Gopa Biswas, PhD
Team Leaders

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:
Table 12 summarizes the five clinical studies evaluated for efficacy and/or safety for the BLA.

Efficacy: Two studies contributed evidence of the effectiveness of loncastuximab tesirine monotherapy in patients with DLBCL: one pivotal efficacy study (ADCT-402-201) in patients with DLBCL, and one supportive first-in-human study (ADCT-402-101) in patients with B-NHL, including patients with DLBCL. Both studies were single-arm, open-label, and used loncastuximab tesirine as monotherapy.

Safety: The above two studies described above were also the focus of the safety analyses. In addition, there were three other studies with loncastuximab tesirine in other indications and/or in combination with other therapies: ADCT-402-102, ADCT-402-103, and ADCT-402-104.

Table 12: Applicant-Description of Clinical Studies

Trial Identity Start-End Dates	NCT Number[a]	Trial Design and Regimen	Study Endpoints	Treatment Duration Follow-up	Study Population N (F/M) Median Age (Range) in Yrs	Study Centers[b]/ Countries
Pivotal Efficacy and Safety Study						
ADCT-402-201 01 Aug 2018 to Ongoing Data cutoff date: 06 Apr 2020	NCT03589469	A Phase 2, open-label, single-arm study of loncastuximab tesirine monotherapy Loncastuximab tesirine: 150 µg/kg IV Q3W for two 3-week cycles, then 75 µg/kg for subsequent cycles	Primary: • ORR Secondary: • DOR, CRR, RFS, PFS, OS • Safety • PK • Immunogenicity • EQ-5D-5L, FACT-Lym	Until PD/toxicity/other reason for discontinuation for up to one year Follow-up: up to three years	Relapsed or refractory DLBCL 145 (60/85) 66.0 (23 to 94)	28/US and Europe 16/US 6/UK 5/Italy 1/Switz-erland
Supportive Efficacy and Safety Study						
ADCT-402-101 09 Mar 2016 to 21 Feb 2019	NCT02669017	A Phase 1, open-label, dose-escalation (Part 1) and expansion (Part 2) study of the safety and tolerability of loncastuximab tesirine monotherapy	Safety: • AEs, SAEs, treatment discontinuations due to AEs, DLTs, 12-lead ECGs, physical examinations, vital signs, ECOG performance status, and clinical laboratory tests • Assessment of DLTs and determination of MTD • Determination of RP2D Other: • ORR, DOR, OS, and PFS • PK • Immunogenicity	Until PD/toxicity/other reason for discontinuation Follow-up: up to 12 months after the last dose	Relapsed or refractory B-NHL (incl DLBCL) 183 (69/114) 63.0 (20 to 87) With DLBCL: 139 (59/80) 63.0 (20 to 86)	11/US and Europe 8/US 2/UK 1/Italy

Trial Identity Start-End Dates	NCT Number[a]	Trial Design and Regimen	Study Endpoints	Treatment Duration Follow-up	Study Population N (F/M) Median Age (Range) in Yrs	Study Centers[b]/ Countries
Additional Safety Studies						
ADCT-402-102 04 Apr 2016 to 03 Jul 2018	NCT02669264	A Phase 1, open-label, dose-escalation (Part 1) and expansion (Part 2) study of the safety and tolerability of loncastuximab tesirine monotherapy Loncastuximab tesirine Part 1: 15 to 150 µg/kg IV on Day 1 of each cycle (Q3W), or 50 µg/kg weekly Part 2: NA	Safety: • AEs, SAEs, treatment discontinuations due to AEs, DLTs, 12-lead ECGs, physical examinations, vital signs, ECOG performance status, and clinical laboratory tests • Assessment of DLTs and determination of MTD • Determination of RP2D Other: • ORR, DOR, OS, and PFS • PK • Immunogenicity	Until PD/toxicity/ other reason for discontinuation Follow-up: up to 12 months after the last dose	Relapsed or refractory B-ALL Part 1: 35 (16/19) 55.0 (20 to 80) Part 2: NA	11/US
ADCT-402-103 07 Feb 2019 to Ongoing Data cutoff date: 06 Apr 2020	NCT03684694	A Phase 1/2, open-label, single-arm combination study to assess the safety and efficacy of loncastuximab tesirine in combination with ibrutinib in patients with relapsed or refractory DLBCL (non-GCB, GCB) and MCL Loncastuximab tesirine: Phase 1: two 3 week cycles with two 4 week cycles after Week 14. Standard 3+3 escalation design was used Phase 2: The MTD or RP2D as determined in Phase 1. Ibrutinib: 560 mg/day orally for up to one year	Safety: • AEs, SAEs, DLTs, dose interruptions and reductions, 12-lead ECGs, physical examinations, vital signs, ECOG performance status, and clinical laboratory tests Other: • ORR, BOR, DOR, CRR, RFS, PFS, and OS • PK • Immunogenicity	Up to one year or until disease progression, unacceptable toxicity, or other discontinuation criteria Follow-up: up to two years after end of treatment	Relapsed or refractory DLBCL or MCL 25 (6/19) 69.0 (39 to 87)	9/US and Europe 4/US 3/Italy 1/Bel-gium 1/France

Trial Identity Start-End Dates	NCT Number[a]	Trial Design and Regimen	Study Endpoints	Treatment Duration Follow-up	Study Population N (F/M) Median Age (Range) in Yrs	Study Centers[b]/ Countries
ADCT-402-104 04 Feb 2019 to Ongoing Closed to enrollment: 21 Nov 2019 Data cutoff date: 06 Apr 2020	NCT03685344	A Phase 1, open-label, dose-escalation (Part 1) and expansion (Part 2) study of the safety and tolerability of loncastuximab tesirine and durvalumab Loncastuximab tesirine: Two 3-week cycles with up to two 4-week cycles beginning after Week 15. Dose levels of 90, 120, and 150 µg/kg IV are evaluated. Durvalumab: 1500 mg every 4 weeks up to one year	<u>Safety</u>: • AEs, SAEs, DLTs, dose interruptions and reductions, 12-lead ECGs, physical examinations, vital signs, ECOG performance status, and clinical laboratory tests <u>Other:</u> • ORR, BOR, DOR, CRR, RFS, PFS, and OS • PK • Immunogenicity	Up to one year or until disease progression, unacceptable toxicity, or other discontinuation criteria, whichever occurs first Follow-up: up to two years after end of treatment	Relapsed or refractory DLBCL, MCL, or FL 13 (6/7) 72.0 (42 to 82)	8/US and Europe 5/US 3/Spain

AE=adverse event; B-ALL=B-cell acute lymphoblastic leukemia; B-NHL=B-cell non-Hodgkin lymphoma; BOR=best overall response; CRR=complete response rate; DLBCL=diffuse large B-cell lymphoma; DLT=dose-limiting toxicity; DOR=duration of response; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EQ-5D-5L=European Quality of Life (EuroQol)-5 Dimensions-5 Levels; F=female; FACT-Lym=Functional Assessment of Cancer Therapy-Lymphoma; FL=follicular lymphoma; GCB=germinal center B-cell; IV=intravenous; M=male; MCL=mantle cell lymphoma; MTD=maximum tolerated dose; NA=not applicable; ORR=overall response rate; OS=overall survival; PBD=pyrrolobenzodiazepine; PD=progressive disease; PFS=progression-free survival; PK=pharmacokinetic; Q3W=every three weeks; RFS=relapse-free survival; RP2D=recommended Phase 2 dose; SAE=serious adverse event; UK=United Kingdom; US=United States; yrs=years

[a] www.clinicaltrials.gov (accessed 01 Nov 2020)

[b] Number of study centers listed reflects those which enrolled patients.

Source: ADCT-402-201 CSR, ADCT-402-101 CSR, ADCT-402-102 CSR, ADCT-402-103 Protocol Amendment 2, ADCT-402-104 Protocol Amendment 1, ISS Table 3.1.2

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

The clinical review of efficacy was primarily based on an analysis of the ADCT-402-201 trial, an open-label, multicenter, single-arm trial that included 145 patients with relapsed or refractory large B-cell lymphoma.

The review of safety is primarily based on the data from the 145 patients from ADCT-402-201 and 215 patients from trials ADCT-402-201 and ADCT-402-101 who received an initial dose of 150 µg/kg.

All major efficacy and safety analyses were reproduced or audited. Statistical analyses by the reviewers were performed using SAS/JMP 13.0 (SAS Institute, Inc., Cary, NC) and MedDRA-Based Adverse Event Diagnostics (MAED) 1.8 (Enterprise Performance and Lifecycle System Design).

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

Study ADCT-402-201 is the pivotal efficacy study for this application, and study ADCT-402-101 is supportive. Study ADCT-402-201 is summarized in detail in Sections 8.1.1 and 8.1.2 and study ADCT-402-101 is summarized briefly in Section 8.1.3. Data from both studies are summarized in Section 8.1.4.

8.1.1. Study ADCT-402-201

Trial Design

The Applicant's Description:
Study ADCT-402-201 is an ongoing, Phase 2, multicenter, open-label, single-arm, pivotal study of the efficacy and safety of loncastuximab tesirine as monotherapy in patients with relapsed or refractory DLBCL. The study was conducted at sites in the US and Europe (see Table 12).

The study was designed to provide evidence of efficacy of loncastuximab tesirine in a broad and representative population of relapsed or refractory DLCBL patients including those generally considered to have high risk characteristics. In addition, the inclusion criteria for the study did not place a restriction on transplant ineligibility. It was recognized that the comparatively broad inclusion criteria could result in a more heterogeneous population, but it was considered that the demonstration of activity in such a broad population, including those with high risk characteristics (disease that was refractory to first line therapy, high grade B-cell lymphoma, transformed disease, disease refractory to most recent therapy, and disease refractory to all prior lines of therapy) would be of value relative to a more restrictive but more homogeneous population. The size of the study (n=145 patients) also facilitated reasonable comparisons between the various subgroups included in the study.

The study enrolled 145 patients who were heavily pretreated, having experienced relapsed or refractory disease following two or more multi-agent systemic treatment options. Patients received loncastuximab tesirine as a 30-minute IV infusion on Day 1 of each cycle Q3W at a dose of 150 µg/kg for two cycles and then 75 µg/kg Q3W for subsequent cycles (see Section 6.2.2.1 for dosing rationale).

The study included a screening period (of up to 28 days), a treatment period (cycles of 3 weeks) for up to one year or until progressive disease, unacceptable toxicity, or other discontinuation criteria, whichever occurred first, and a follow-up period. The protocol prespecified criteria for dose delays and modifications based on the development of toxicities.

Disease assessments were performed at baseline and six and 12 weeks after Cycle 1, Day 1, then every nine weeks during the treatment period, and at end of treatment (EOT). For patients who discontinued treatment for reasons other than disease progression or initiation of other anticancer therapy (except stem cell transplant [SCT]), efficacy assessments were to continue every 12 weeks until one year from EOT, then every six months until disease progression or initiation of other anticancer therapy (except SCT) for up to three years from EOT. Health-related quality of life (HRQoL) assessments were performed on Day 1 of each cycle and at EOT.

Safety assessments were collected as per the study schedule of assessments throughout study participation and up to 30 days after the last dose of loncastuximab tesirine or start of new anticancer therapy, whichever occurred first. Thereafter, only serious adverse events (SAEs) considered related to study drug were reported with two exceptions: patients who underwent SCT were to be followed for 180 days posttransplant, and patients who underwent CAR-T therapy were to be followed for 90 days after receiving CAR-T therapy. Safety information collected during the 180 days after SCT and 90 days after CAR-T included prespecified Grade 3 or higher AEs, SAEs, and death, regardless of relationship to loncastuximab tesirine.

The FDA's Assessment:
The FDA agrees with the Applicant's description of the study design. Study ADCT-402-201 is a Phase 2 single-arm trial evaluating loncastuximab tesirine as monotherapy in patients with relapsed or refractory large B-cell lymphoma after at least 2 prior systemic therapies. The disease assessments were performed by clinical investigators and independent review committee (IRC). The pre-specified primary efficacy endpoint is overall response rate (ORR) by IRC per Lugano 2014 response criteria.

Study Endpoints

The Applicant's Description:
The primary efficacy endpoint was ORR defined as the proportion of patients who achieved either CR or partial response (PR) as best overall response (BOR) assessed by an independent central review according to the 2014 Lugano Classification Criteria (Cheson et al 2014). Additional efficacy endpoints included duration of response (DOR), time to tumor response, CRR, relapse-free survival (RFS), PFS, and OS.

The FDA's Assessment:
The FDA agrees with the Applicant's description of the study endpoints. The endpoints that FDA used to evaluate efficacy are ORR by IRC and DOR. Time-to event endpoints such as RFS, PFS and OS are not interpretable in single-arm trials.

Statistical Analysis Plan (SAP) and Amendments

The Applicant's Description:
The final SAP, version 2.0, was amended prior to the database cutoff for the Clinical Study Report (CSR).

An interim analysis on the first 52 patients was performed for futility. The final analysis was based on 145 patients using a single stage approach; ORR and exact 95% CI were reported, because of the practical consideration that accrual could not be limited to exactly 140 patients and because patients included in the interim analysis as nonresponding may have been included in the final analysis as responding if they experienced a late response.

Primary and key secondary endpoints analyses included all patients who received loncastuximab tesirine. All efficacy and safety endpoints were analyzed and reported.

The percentage of ORR with its 95% exact CI was presented. In this analysis, patients with missing BOR information were counted as failures.

DOR was defined for patients with CR or PR only as the interval between the date of initial documentation of a response and the date of the first documented evidence of progressive disease based on independent radiographic assessment or death, whichever occurred first. Patients who were progression-free and alive at the time of the clinical data cutoff, had unknown status, or had subsequent anticancer therapy/procedure were censored at the last valid tumor assessment on or before the clinical data cutoff or the start of subsequent anticancer therapy/procedure. DOR was estimated and displayed for the all-treated population using Kaplan-Meier methods. A Kaplan-Meier plot was presented.

Other efficacy endpoints, sensitivity analyses, subgroup analyses, and safety analyses (including summaries of AEs, laboratory results, vital signs, ECG, etc) were analyzed per protocol and SAP.

Follow-up analyses will be performed when all the patients have completed the study per protocol.

The FDA's Assessment:
The FDA does not agree with the Applicant's statement that "The final analysis was based on 145 patients using a single stage approach." According to the SAP, Simon's 2-stage design was employed with a futility interim analysis on the first 52 patients enrolled.

Additionally, according to the SAP, the primary hypothesis was that the null hypothesis (H0) of ORR ≤ 20% against the alternative hypothesis (H1) of ORR >20% (40% was used for sample size calculation). To demonstrate the efficacy of loncastuximab tesirine, the study was planned to

enroll at least 140 subjects to achieve >99% power to reject H0 at a 2-sided significance level of 0.05.

The analysis populations are defined in SAP as follows:
All-Treated Population: All patients who receive at least 1 dose of loncastuximab tesirine. This population will be used in the primary analyses of efficacy and safety.
Per-Protocol Population: All patients in the all-treated population who met the inclusion/exclusion criteria, did not take a prohibited concomitant treatment, nor had other protocol deviation which have major impact on efficacy results.
Stem Cell Transplant (SCT) Population: All patients who have responded to loncastuximab tesirine and undergo stem cell transplant (either autologous or allogeneic) after permanent discontinuation of loncastuximab tesirine treatment without any intervening anticancer therapy.
Patient Reported Outcome (PRO) Population: All patients in the all-treated patients with baseline score (at least one instrument) and at least 1 postbaseline score (in at least one instrument).

Protocol Amendments

The Applicant's Description:

The original protocol was finalized on 09 Mar 2018 and was amended before implementation in response to FDA recommendations; therefore, protocol amendment 1 dated 05 Apr 2018 is not summarized here. There were three other protocol amendments, one country-specific protocol amendment, and one protocol addendum, all summarized below. All protocol amendments were approved according to local requirements prior to implementation.

Protocol Amendment 1.1 UK was dated 28 Jun 2018. At the request of the United Kingdom (UK) Medicines and Healthcare Products Regulatory Agency, text was added to allow patients who were clinically benefiting to continue treatment beyond one year.

Protocol Addendum 1.1 SZ was dated 20 Jul 2018. At the request of the Switzerland Central Ethics Committee and Ministry of Health, text was added to allow patients who were clinically benefiting to continue treatment beyond one year.

Protocol Amendment 2 was dated 24 Sep 2018. The purposes of the amendment were the following:

- Patients with bulky disease (defined as at least one lymph node ≥10 cm in longest diameter) were excluded based on an interim analysis of Phase 1 data showing that

these patients had an ORR of 11%. Based on an interim analysis this was the ORR at the time of this analysis.

- The inclusion criterion regarding hepatic function was revised to no longer allow patients with alanine aminotransferase (ALT), aspartate aminotransferase (AST), and GGT ≤5 × upper limit of normal (ULN) if there was liver involvement, to be consistent with the requirement to hold the dose of loncastuximab tesirine for patients with Grade ≥2 LFT abnormalities as specified.

- Overdose reporting was added.

- Text was added to allow patients who were clinically benefiting to continue treatment beyond one year with Sponsor review and approval.

- Text was added to require dose discontinuation for dose delays >5 weeks due to toxicity at least possibly related to study drug.

- The requirement for IV contrast for positron-emission tomography-computed tomography was removed and the type and timing of efficacy assessments were clarified.

Protocol Amendment 3 was approved internally by ADCT and dated 07 Jun 2019. This amendment was not submitted to any study sites, regulatory agencies, or ethics committees. All changes from amendment 2 were included in amendment 4 (below).

Protocol Amendment 4 was dated 09 Jul 2019. The purposes of the amendment were the following:

- The text was updated to include information regarding monitoring for extravasation during or after loncastuximab tesirine infusion because of updated safety information.

- The instructions for dose delays and modifications for nonhematologic and hematologic toxicities were clarified and updated.

- Efficacy assessments were updated to allow for capture of response information during the follow-up period for patients who received CAR-T therapy after loncastuximab tesirine treatment.

- Adverse Event (AE)/SAE reporting requirements for patients who received CAR-T therapy after loncastuximab tesirine discontinuation were added.

The FDA's Assessment:
The FDA agrees with the Applicant's summary of the protocol amendments in Study ADCT-402-201.

8.1.2. Study Results ADCT-402-201

Compliance with Good Clinical Practices

Data:
The study was conducted in compliance with ICH Good Clinical Practice (GCP) and with the approvals of the relevant Ethics Committees or Institutional Review Boards. Informed consent was obtained for all patients, and the studies were performed in accordance with the version of the Declaration of Helsinki that applied at the time the study was conducted. Where required, regulatory approval was obtained from the relevant health authority.

The Applicant's Position:
The study was conducted in compliance with GCP standards.

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

Financial Disclosure

Data:
The Applicant disclosed all financial interests/arrangements with clinical Investigators as per 21 Code of Federal Regulations (CFR) Part 54. None of the Investigators or Subinvestigators involved in the clinical trial had financial interests to disclose or arrangements that required disclosure.

The Applicant's Position:
There are no concerns about the integrity of study data based on financial disclosures.

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

Patient Disposition

Data:
A total of 145 patients were enrolled and received at least one dose of loncastuximab tesirine. Of the 145 patients treated, 137 patients (94.5%) had withdrawal of treatment. The most common primary reasons for treatment withdrawal were progressive disease (81 patients; 55.9%) and unacceptable toxicity (30 patients; 20.7%).

There were 87 patients (60.0%) who discontinued from the study. The most common reason for study discontinuation was death (77 patients; 53.1%).

There were 50 patients in follow-up, and eight patients ongoing with loncastuximab tesirine treatment.

The Applicant's Position:
The majority of patients had treatment withdrawn due to progressive disease (55.9%) and the majority of patients discontinued the study due to death (53.1%).

The FDA's Assessment:
The FDA agrees with the Applicant's summary of patient disposition.

Protocol Violations/Deviations

Data:
Overall, there were 11 patients with an important CSR-reportable protocol deviation.

Eight patients had inclusion or exclusion criteria deviations:

- Three patients had elevated GGT levels (deviation of inclusion criterion #8c)
- One patient did not have results available for AST at screening so results were not confirmed before dosing (deviation of inclusion criterion #8c)
- Three patients tested positive for hepatitis virus and were receiving antiviral therapy (deviation of protocol amendment #2 exclusion criterion #11)

  One patient was enrolled with bulky disease (deviation of protocol amendment #2 exclusion criterion #4)

One patient received a prohibited concomitant therapy (radiation therapy for lytic lesion on C5 vertebrae).

Two patients had study drug deviations:

- One patient with a body mass index (BMI) >35 was administered loncastuximab tesirine based on actual weight instead of adjusted body weight (ABW) for the first infusion that was 19.6% higher than per protocol planned dose according to ABW.

- One patient was administered study drug that was 18% lower than the planned dose according to ABW for all three cycles.

The Applicant's Position:
The overall interpretation of efficacy and safety results were not impacted by these protocol deviations.

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

Table of Demographic Characteristics

Data:
Table 13 summarizes demographic and baseline characteristics in the All-Treated Population.

Of the 145 patients enrolled in this study, there were more male patients (85 patients; 58.6%) than female patients (60 patients; 41.4%), and most patients were white (130 patients; 89.7%). The median BMI was 25.97 kg/m^2 (range 17.2 to 50.5 kg/m^2).

There were 58 patients (40.0%) with an ECOG score of 0, 78 patients (53.8%) with an ECOG score of 1, and 9 patients (6.2%) with an ECOG score of 2. The median age was 66 years (range: 23 to 94 years). There were 65 patients (44.8%) <65 years of age, 59 patients (40.7%) ≥65 to <75 years of age, and 21 patients (14.5%) ≥75 years of age. Similar results were seen in the Per-Protocol Population.

Table 13: Applicant-Demographic and Baseline Characteristics (All-Treated Population)

	All-Treated Population (N=145)
Sex [n(%)]	
Female	60 (41.4)
Male	85 (58.6)
Race [n(%)]	
White	130 (89.7)
Black or African American	5 (3.4)
Asian	3 (2.1)
American Indian or Alaskan Native	1 (0.7)
Native Hawaiian or Pacific Islander	1 (0.7)
Other	5 (3.4)
Ethnicity [n(%)]	
Hispanic or Latino	13 (9.0)
Not Hispanic or Latino	132 (91.0)
Age (years)	
n	145
Mean	62.7
std	13.63
Median	66.0
Min, Max	23, 94
Age Group [n(%)]	
< 65 years	65 (44.8)
≥ 65 to < 75 years	59 (40.7)
≥ 75 years	21 (14.5)
Body Mass Index (kg/m^2)	
n	144
Mean	26.93
std	5.728
Median	25.97
Min, Max	17.2, 50.5
ECOG Score [n(%)]	
0	58 (40.0)
1	78 (53.8)
2	9 (6.2)
Country [n(%)]	
USA	59 (40.7)
UK	31 (21.4)
Italy	53 (36.6)
Switzerland	2 (1.4)

ECOG= Eastern Cooperative Oncology Group; std=standard deviation, max=maximum, min=minimum
Source: CSR ADCT-402-201, Table 14.1.3.1.1 (dataset: adsl)

The Applicant's Position:
Demographic characteristics were in general representative of the intended patient population with relapsed or refractory DLBCL. A low percentage of patients of races other than white were enrolled in this study.

The FDA's Assessment:
The FDA agrees with the Applicant's summary of demographic characteristics. As noted in the Applicant's position, there was limited racial and ethnic representation with race reported in 97% of patients; of these patients, 90% were White, 3% were Black, and 2% were Asian. For ethnicity, 9% identified as Hispanic or Latino.

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

Data:
Cancer History
The majority of patients had DLBCL not otherwise specified (NOS) according to the 2016 WHO classification (127 patients; 87.6%). There were 11 patients (7.6%) with high grade B-cell lymphoma (with MYC and BCL2 and/or BCL6 rearrangements), and 7 patients (4.8%) with primary mediastinal DLBCL. Cell of origin was reported as germinal center B-cell in 48 patients (33.1%), and activated B-cell in 23 patients (15.9%). Transformation from follicular lymphoma (FL) was noted in 25 patients (17.2%), and 15 patients (10.3%) had double hit or triple hit disease (reported by the Investigator). One hundred and twelve patients (77.2%) had advanced (Stage III/IV) disease.

Prior Systemic Anticancer Therapy, Radiotherapy, Surgery, and Stem Cell Transplant
All 145 patients received prior systemic anticancer therapy. The median number of prior systemic therapy lines was 3.0 (range: 2 to 7), with 63 patients (43.4%) having had 2 prior lines of therapy, 35 patients (24.1%) having had 3 prior lines of therapy, and 47 patients (32.4%) having had ≥3 prior lines of systemic therapy. Fifty-three patients (36.6%) had prior radiotherapy, 27 patients (18.6%) had prior surgery, and 24 patients (16.6%) had prior SCT.

In an ad hoc analysis, intensive salvage therapy (aggressive salvage chemoimmunotherapy ifosfamide, carboplatin, etoposide (ICE); gemcitabine, dexamethasone, cisplatin (GDP); cisplatin, cytarabine, dexamethasone (DHAP); dexamethasone, cytarabine, oxaliplatin (DHAX); all generally in combination with rituximab], SCT, and/or CAR-T therapy) was received by 103 patients (71.0%).

Twenty-nine patients (20.0%) had primary refractory disease (defined as no response to the first line of systemic therapy), and 84 patients (57.9%) were refractory to their most recent line of prior systemic therapy.

Ninety-nine patients (68.3%) relapsed after their first line of prior systemic therapy, and 43 patients (29.7%) relapsed after their most recent line of prior systemic therapy.

The Applicant's Position:
The patient population used in the pivotal ADCT-402-201 study was designed to provide evidence of efficacy of loncastuximab tesirine in a broad and representative population of relapsed or refractory DLCBL patients, including those with high risk characteristics, who were heavily pretreated. This study was more inclusive and therefore more representative of the relapsed/refractory population with respect to the types of patients eligible to enroll (eg, allowed inclusion of patients who were candidates for ASCT, patients with primary refractory disease, double/triple hit disease, transformed disease, or previous receipt of CAR-T therapy).

The inclusion criteria for the study did not place a restriction on transplant ineligibility. It was recognized that the comparatively broad inclusion criteria could result in a more heterogeneous population, but it was considered that the demonstration of activity in such a broad high risk population (disease that never responded to first line therapy, high grade B-cell lymphoma, disease refractory to most recent therapy, and refractory to all prior lines of therapy) would be of value relative to a more restrictive but more homogeneous population.

The FDA's Assessment:
The FDA agrees with the Applicant's summary of baseline disease characteristics and prior therapies.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:
Compliance
Loncastuximab tesirine was administered by study staff at the investigational site and administration information was recorded in the case report form (CRF).

Concomitant Medications
Of the 145 patients in the All-Treated Population, 145 patients (100%) received concomitant medications. The most common (≥20%) concomitant medications taken by patients were aciclovir (acyclovir) (55.2%); paracetamol (acetaminophen) (52.4%); allopurinol (49.0%); sulfamethoxazole/trimethoprim (42.8%); chlorphenamine (33.8%); ranitidine (30.3%); omeprazole (29.0%); levofloxacin and ondansetron (26.2% each); dexamethasone, filgrastim and, furosemide (21.4% each); and sodium chloride and spironolactone (20.7% each).

Rescue Medication Use
Not applicable.

The Applicant's Position:
Treatment compliance for loncastuximab tesirine was ensured as it was infused under the direct supervision of study personnel. No statistical analysis for measurement of treatment compliance was planned for this study.

Concomitant medications were used by all patients in the study. Due to the patient population (primarily elderly with advanced disease), high concomitant medication use is expected. No important protocol deviations pertained to concomitant medication use (see Protocol Violations/Deviations above).

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

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:
Primary Endpoint
ORR was the primary measure of efficacy/clinical activity in this study. ORR was defined as the proportion of patients who achieved either CR or PR as BOR using the 2014 Lugano Classification criteria before the start of subsequent anticancer therapy or procedure. In ADCT-402-201, this endpoint was assessed by an independent central reviewer.

In the All-Treated Population, the ORR was 48.3% (70/145 patients; 95% CI: 39.9% to 56.7%). BORs included 35 patients (24.1%) with CR and 35 patients (24.1%) with PR. There were 22 patients (15.2%) with a BOR of stable disease.

In the Per Protocol Population, the ORR was 53.7% (65/121 patients; 95% CI: 44.4% to 62.8%). BORs included 30 patients (24.8%) with CR and 35 patients (28.9%) with PR. There were 19 patients (15.7%) with a BOR of stable disease.

Table 14: Applicant-Overall Response Rate by Independent Reviewer (All-Treated Population)

	All-Treated Population (N=145)
Best Overall Response	
Complete response	35 (24.1)
Partial response	35 (24.1)
Stable disease	22 (15.2)
Not evaluable	23 (15.9)
Progressive disease	30 (20.7)
ORR (CR + PR)	70 (48.3)
95% CI for ORR	(39.9, 56.7)
95% CI for CR	(17.4, 31.9)

CI=confidence interval, CR=complete response, ORR=overall response rate, PR=partial response
Note: Best overall response by independent reviewer. Not evaluable included patients without any scan to the independent reviewer (even clinical progressive disease) or patients whose scan was determined to be not evaluable by the independent reviewer.
Source: CSR ADCT-402-201, Table 14.2.1.1.1 (datasets: adrs, adsl)

Sensitivity Analysis on Primary Endpoint
Sensitivity analysis on the primary endpoint used assessments of response by the Investigator.

In the All-Treated Population, the ORR using the Investigator assessment was 49.7% (72/145 patients; 95% CI: 41.3% to 58.1%). BORs included 36 patients (24.8%) with CR and 36 patients (24.8%) with PR. There were 20 patients (13.8%) with a BOR of stable disease.

In the Per Protocol Population, the ORR using the Investigator assessment was 52.9% (64/121 patients; 95% CI: 43.6% to 62.0%). Best overall responses included 29 patients (24.0%) with CR and 35 patients (28.9%) with PR. There were 19 patients (15.7%) with a BOR of stable disease.

The BOR by independent reviewer versus Investigator assessment in the All-Treated Population was analyzed. The independent reviewer classified 35 patients with CR and 35 patients with PR, and the Investigator classified 36 patients with CR and 36 patients with PR.

Subset Analyses of Overall Response Rate

ORR in patients with high risk features was as follows:

- Patients with double hit/triple hit disease (as reported by the Investigator) had an ORR of 33.3%
- Patients with advanced disease (Stage III/IV) had an ORR of 45.5%
- Patients with transformed disease had an ORR of 44.8%
- Patients with primary refractory disease (defined as no response to initial therapy) had an ORR of 37.9%
- Patients refractory to most recent line of therapy had an ORR of 36.9%
- Patients refractory to all prior therapies had an ORR of 36.0%
- Ad hoc analysis: Patients who had received prior intensive salvage treatment (aggressive salvage chemoimmunotherapy, SCT and/or CAR-T) had an ORR of 47.6%

Loncastuximab tesirine was also effective in elderly patients (ORR 45.8% in the ≥65 to <75 years age group, and ORR 52.4% in the ≥75 years of age group), and in patients who received previous CD19-directed CAR-T therapy (ORR of 46.2%).

The Applicant's Position:
Loncastuximab tesirine was effective in a broad and representative population of relapsed or refractory DLCBL patients, including those with high risk characteristics, who were heavily pretreated. Limitations to the data include that some subset populations were relatively small in number and the analyses were exploratory in nature.

The FDA's Assessment:
The primary efficacy results were able to be reproduced by the statistical reviewer. The ORR by IRC estimate is 48.3% with the lower bound of its 95% confidence interval of 39.9% which is greater than the pre-specified null hypothesis rate of 20%. Therefore, the study met its primary objective.

Sensitivity analyses were based on the investigator's assessments. The sensitivity analysis results indicated that the results were consistent with those by IRC.

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

ORR are considered exploratory. The numerical results of the sensitivity analyses on primary endpoint and subgroup analyses on ORR were able to be reproduced by the statistical reviewer.

Data Quality and Integrity

Data:
The study was conducted in accordance with ICH GCP guidelines. The Investigators were required to have been trained in GCP and the protocol requirements. Clinical monitoring was performed by the clinical research organization (CRO) in accordance with their standard operating procedures. Clinical laboratory tests were performed by a central laboratory and by accredited laboratories. Data were managed by the CRO under their standard operating procedures, including data checks for consistency and accuracy. The handling of data, including data quality control, complied with all applicable regulatory guidelines. Three external inspections were performed at three study sites.

The Applicant's Position:
No meaningful concerns are anticipated in the quality and integrity of the submitted datasets; these were sufficiently complete to allow for a thorough review of efficacy. No meaningful data integrity concerns were reported following completion of site audits.

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

Efficacy Results – Secondary and other relevant endpoints

Data:
Secondary endpoints of CRR, time to response, and OS are summarized here. Additional secondary endpoints of DOR, RFS, and PFS are summarized in other sections below.

Complete Response Rate
In the All-Treated Population there were 35 patients with CR by independent reviewer. The CRR was 24.1% (95% CI: 17.4, 31.9).

Time to Response
Overall, there were 70 patients who achieved CR or PR as BOR; 35 patients with a BOR of CR and 35 patients with a BOR of PR.

The median time to first response (CR or PR) was 41.0 days (range: 35 to 247 days) and the mean time was 51.5 days. In patients with CR as BOR, the median time to first response (CR or PR) was 42.0 days (range: 36 to 247 days) and the mean time was 54.8 days. In patients with PR as BOR, the median time to first response was 40.0 days (range: 35 to 142 days) and the mean time was 48.1 days. The median time to first CR was 43.0 days (range: 36 to 426 days) and the mean time was 74.0 days.

Overall Survival
OS was defined as the interval between the date of the first dose and the date of death from any cause. Of the 145 patients in the All-Treated Population, the median OS was 9.92 months (95% CI: 6.74, 11.47).

The Applicant's Position:
Secondary endpoints of CRR and OS showed loncastuximab tesirine was effective. The secondary endpoint of time to response showed that responses were rapid. Median time to first response was 41.0 days, indicating that the majority of responders demonstrated response after 2 doses (timepoint of first postbaseline disease assessment).

The FDA's Assessment:
The FDA does not agree with Applicant's statement about overall survival because time to event endpoints are not interpretable in single-arm trials and are considered exploratory.

Dose/Dose Response

Data:
Dose Level and Regimen
In clinical practice, in patients with relapsed or refractory DLBCL, loncastuximab tesirine monotherapy will be administered as an IV infusion over 30 minutes on Day 1 Q3W at a dose of 150 µg/kg for two cycles and then 75 µg/kg for subsequent cycles; the dosing regimen used in study ADCT-402-201.

This dosing regimen was based on the results of the Phase 1 study, ADCT-402-101.

The initial dose of 150 µg/kg Q3W was based on the fact that the response rate in patients treated in the Phase 1 study appeared to increase with increasing exposure, but toxicity was substantially increased at 200 µg/kg compared to lower dose levels. Thus, 150 µg/kg was chosen as the initial dose with manageable toxicity.

The dose reduction after two cycles was based on the fact that a substantial portion of patients treated on the Phase 1 study required dose reduction after two or more cycles, usually as a

result of prolonged dose delays because of AEs. Decreasing the dose after two cycles was intended to reduce the incidence of dose delay and the need for further dose reduction.

Dose and Exposure-Response Activity
Significant exposure-response relationships were identified following loncastuximab tesirine treatment for ORR and OS.

Based on univariate logistic regression of ORR, loncastuximab tesirine PBD-conjugated antibody C_{avg} during Cycle 1 was significantly associated with clinical response (exposure [$p<0.001$]). From multivariate analysis, the odds of overall response increased by 20% for each 0.1 µg/mL increase in Cycle 1 C_{avg}.

From univariate analysis for OS, increased loncastuximab tesirine C_{avg} exposure during Cycle 1 was significantly associated with decreased risk of death ($p<0.001$). From multivariate analysis, the hazard of death decreased by 4.76% for each 0.1 µg/mL increase in Cycle 1 C_{avg}.

Kaplan-Meier survival analysis showed no significant relationship apparent between exposure and DOR.

See also PK/exposure-response analyses in Section 6.3.1.

The Applicant's Position:
The results of the Phase 2 study, ADCT-402-201, demonstrate that the selected dosing regimen resulted in a consistent degree of exposure between Cycle 1 following the 150 µg/kg dose and steady state following subsequent 75 µg/kg doses.

The FDA's Assessment:
The FDA agrees with the Applicant's position. For further information, see Section 6: Clinical Pharmacology.

Durability of Response

Data:
Duration of Response
DOR was defined for patients with CR or PR as the interval between the date of initial documentation of a response and the date of the first documented evidence of progressive disease based on independent radiographic assessment or death, whichever occurred first. If progressive disease or death was not observed, the DOR was censored at the last valid disease assessment.

Of the 70 patients who achieved CR or PR by independent reviewer, the median DOR was 10.25 months (95% CI: 6.87 to not estimable).

The probability of maintaining response was 68.1% at 6 months, 63.8% at 9 months, and 38.3% at 12 months.

Subset Analyses Duration of Response
Durable responses were noted in patients with high risk features including:

- Patients with double hit/triple hit disease (as reported by the Investigator) had a median DOR of 13.37 months
- Patients with advanced disease (Stage III/IV) had a median DOR of 9.63 months
- Patients with transformed disease had a median DOR of not reached
- Patients with primary refractory disease (defined as no response to initial therapy) had a median DOR of 9.63 months
- Patients refractory to most recent line of therapy had a median DOR of 9.63 months
- Patients refractory to all prior therapies had a median DOR of 9.63 months
- Ad hoc Analysis: Patients who had received prior intensive salvage treatment (aggressive salvage chemoimmunotherapy, SCT, and/or CAR-T) had a median DOR of 9.63 months

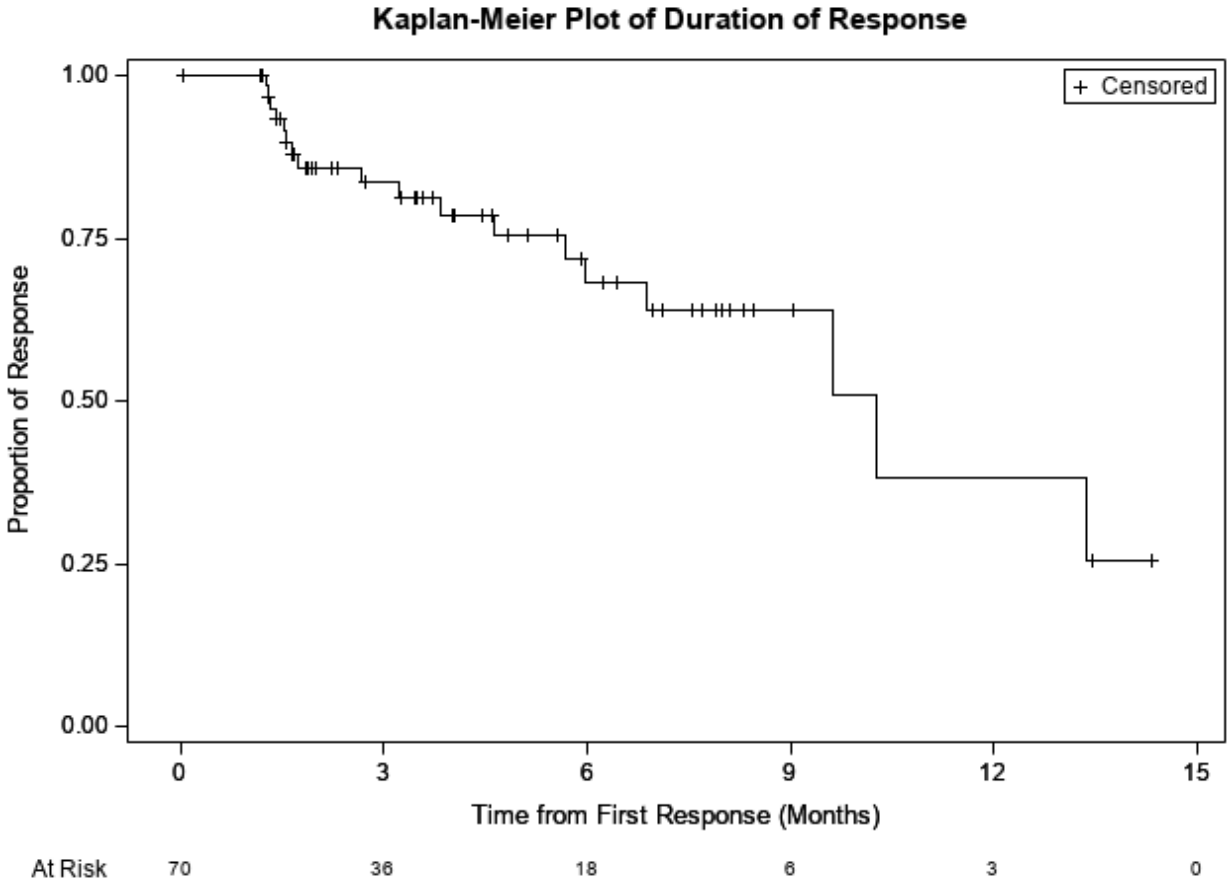
Loncastuximab tesirine also produced durable responses in elderly patients (median DOR of 10.25 months in the ≥65 to <75 years age group, and a median DOR of 13.37 months in the ≥75 years of age group).

The Applicant's Position:
Loncastuximab tesirine produced durable responses in heavily pretreated patients with DLBCL, including those with high risk features. Limitations to the data include that some subset populations were relatively small in number and the analyses were exploratory in nature.

The FDA's Assessment:
The FDA has concerns with the Applicant's statement about the duration of response (DOR). The median DOR and probability of maintaining response at 6, 9 and 12 months reported by the Applicant was based on Kaplan-Meier (KM) method. The KM plot is provided in the figure below. However, the FDA identified a large number of censored events (28 censored events,

40%) reported during the study which may substantially affect the interpretation of durability of response. The summary of censoring pattern is presented in the table below. The most common reason for censoring is the new anticancer treatment started, excluding SCT (17 patients, 24%).

Figure 7: Duration of Response per Kaplan-Meier in ADCT-402-201 - FDA Review



Source: FDA statistical reviewer generated using the adtte.xpt dataset

Table 15: Summary of Censoring Pattern for Responders in ADCT-402-201

Event/Censoring	N = 70 n (%)
Death	8 (11%)
Disease Progression	10 (14%)
Ongoing	24 (34%)
New Anticancer Treatment Started, Excluding SCT	17 (24%)

Transplant	7 (10%)
Discontinued Study	4 (6%)

Source: FDA statistical reviewer generated using the adtte.xpt dataset

Further, the FDA conducted sensitivity analyses on the proportion of patients maintaining response (responders who were either censored for DOR at greater than or equal to a certain month, or who had a DOR failure after a certain month), and the results are provided in the table below. Of the 70 responders, 36 (51%) responders had a DOR ≥3 months, 18 (26%) responders had a DOR ≥6 months, 6 (9%) responders had a DOR ≥9 months, and 3 (4%) responders had a DOR ≥12 months.

Table 16: Summary of Maintenance of Response in ADCT-402-201

Landmark	**N = 70 (%)**
3 Months	51%
6 Months	26%
9 Months	9%
12 Months	4%

Source: FDA statistical reviewer generated using the adtte.xpt dataset

The FDA also found that 15 out of a total 17 censored events due to initiation of new anticancer treatment, excluding SCT, were reported within 3 months after achieving the response. The investigators identified these subjects with clinical progressive disease and initiated subsequent therapy. However, these patients were determined later by IRC as non-progressive disease and were censored accordingly. The summary of censoring pattern within 3 months of response duration is presented in the table below. Twenty-five (36%) responders were censored within 3 months of response duration with the most common reason of starting a new anticancer treatment (excluding SCT) (15 responders; 21%).

Table 17: Censoring Patter within 3 Months of Response Duration

Censoring	**N = 70 N (%)**
New Anticancer Treatment Started, Excluding SCT	15 (21%)
Transplant	4 (6%)
Ongoing	4 (6%)
Discontinued Study	2 (3%)

Source: FDA statistical reviewer generated using the adtte.xpt dataset

Through an information request, the Applicant reported that a large number of censored events due to new anticancer treatment (excluding SCT) was caused by the difference between investigator and IRC in assessing the patient's response. In many censored cases, the investigator considered the patient with clinical progressive disease so the patient received new anticancer treatment. However, the IRC interpreted the radiographic data with a discordant assessment result. There were 72 patients with a complete response or partial response by investigator assessment with median DOR of 5.62 months (95% CI: 3.84 to 10.25).

Based on the above considerations for DOR, the median DOR per Kaplan-Meier can be considered for labeling as the Kaplan-Meier method takes into account the censoring pattern of the data. However, given the amount of early, informative censoring, primarily for new anticancer treatment due to clinical progression per investigator, the following statement was added to the label to supplement the DOR data. "Of 70 patients with objective response, 25 (36%) were censored prior to 3 months. Twenty-six percent of responders had a duration of response ≥6 months".

Due to the small sample size in some subgroups, the analysis results on subgroup DOR are considered exploratory in nature.

Persistence of Effect

Relapse-free Survival
RFS was defined among CR patients as the time from the date of first CR until the date of the first disease relapse based on independent radiographic assessment, or death, whichever occurred first. Of the 35 patients who achieved CR, the median RFS was 13.37 months (95% CI: 10.25 to not estimable).

With clinical progression imputed as an event, median RFS was 13.37 months (95% CI: 10.25 to not estimable). Similarly, with SCT not censored, median RFS was 13.37 months (95% CI: 10.25 to not estimable).

Progression-free Survival
PFS was defined as the interval between the date of first dose of loncastuximab tesirine and the date of first progressive disease based on independent radiographic assessment or death, whichever occurred first. There were 145 patients at risk in this analysis. The median PFS was 4.93 months (95% CI: 2.89, 8.31).

With clinical progression imputed as an event, median PFS was 4.40 months (95% CI: 2.76, 8.08), and with SCT not censored, median PFS was 4.93 months (95% CI: 2.92, 8.31).

The Applicant's Position:
The secondary endpoints of RFS and PFS provided supportive evidence of loncastuximab tesirine persistence of effect.

The FDA's Assessment:
The FDA does not agree with the Applicant's statement about the results of RFS and PFS analysis. In a single-arm trial, time-to-event endpoints have limited interpretability so the results for RFS and PFS are considered exploratory. The numerical results of the RFS and PFS analysis can be reproduced by the statistical reviewer.

Efficacy Results – Secondary or exploratory clinical outcome assessment (COA) (Patient Reported Outcome [PRO]) endpoints

Data:
The PRO/HRQoL were assessed using the European Quality of Life (EuroQol)-5 Dimensions-5 Levels (EQ-5D-5L) and Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) questionnaires in the PRO Population (n=130).

EQ-5D-5L
The mean (std) EQ-5D-5L visual analog scale (VAS) score (on a 1 to 100 scale, with higher scores indicating better health) was 71.4 (19.1) at baseline. During the course of treatment, 41.4% of patients showed improvement at one or more visits by at least 7 points, 39.6% showed deterioration at one or more visits by at least 7 points, and 65.8% remained stable (change <7 points) across visits. When averaging the change from baseline scores for each patient across visits during the course of treatment, more patients showed improvement by at least 7 points (27.9%) than deterioration by at least 7 points (20.7%), and approximately half of the patients (51.4%) remained stable.

The mean EQ-5D-5L VAS change from baseline score showed a trend of improvement on overall health over time. The mean change score reached minimally important difference (change of at least 7 points) in 36.4% of patients at Cycle 8, Day 1, although the sample size was reduced dramatically compared to baseline. At each visit during treatment, a higher percentage of patients experienced clinically meaningful improvement than experienced deterioration.

FACT-Lym
Higher FACT-Lym scores indicate higher functioning/quality of life (scales range 0 to 28 for physical, social/family, and functional well-beings, 0 to 24 for emotional well-being, 0 to 60 for Lymphoma Subscale [LymS], 0 to 116 for FACT-Lym Trial Outcome Index [TOI], 0 to 108 for Functional Assessment of Cancer Therapy-General [FACT-G total], and 0 to 168 for FACT-Lym

Total).

The mean (std) baseline FACT-Lym scores were 21.9 (5.23) for physical well-being; 21.9 (5.70) for social/family well-being; 16.9 (4.62) for emotional well-being; 14.8 (6.32) for functional well-being; 43.4 (10.34) for LymS; 79.8 (18.39) for TOI; 75.2 (15.65) for FACT-G total; and 118.4 (23.84) for FACT-Lym Total.

During the course of the treatment, for the LymS score, 42.5% of the patients showed improvement for one or more visits by at least 3 points, 43.4% showed deterioration for one or more visits by at least 3 points, and 60.2% remained stable (change less than 3 points) in all visits. When averaging the change from baseline scores for each patient across visits during the course of the treatment, 26.5% of patients showed improvement by at least 3 points, and 27.4% showed deterioration by at least 3 points, and approximately half showed no change.

Mean changes in all FACT-Lym subscale and composite scores were generally stable over time. The best mean change from baseline scores were 0.98 for physical well-being, 1.12 for social/family well-being, 1.86 for emotional well-being, 1.89 for functional well-being, 3.75 for LymS, 4.90 for FACT-Lym TOI, 4.37 for FACT-G total, and 6.52 for FACT-Lym Total. FACT-Lym subscales that showed improvement from baseline over time were physical well-being and emotional well-being. The subscale of functional well-being was relatively consistent from baseline over time, and the subscale of social/family well-being deteriorated from baseline over time.

The Applicant's Position:
In the EQ-5D-5L VAS score, the number of patients who showed improvement by at least 7 points increased as the number of cycle increased. Over time, improvement from baseline was seen in the individual categories of usual activities, pain/discomfort, and anxiety. Similarly, the FACT-Lym subscores showed an improvement over baseline in the individual categories of physical well-being and emotional well-being. Both of these PRO assessments demonstrate that the quality of life is improved in patients who are responsive to treatment.

The FDA's Assessment:
The FDA does not agree with Applicant's statement about PRO assessments. There was no pre-specified formal hypothesis in the analysis plan. Additionally, the PRO data has limited interpretability in the open label and single-arm trial setting. The treatment effect may be subject to systematic overestimation due to patients' knowledge of treatment assignment. In addition, the number of assessments completed substantially decreased after the first 2 cycles, for both instruments. Therefore, these PRO assessments are only considered exploratory and should be interpreted with caution.

Additional Analyses Conducted on the Individual Trial

Data:
Not applicable.

The Applicant's Position:
Not applicable.

8.1.3. Study ADCT-402-101 and Study Results

Study ADCT-402-101 was a supportive trial for efficacy and was also used for safety analyses. Methodology and results are described briefly below. More detailed results for this study are presented in comparison to the pivotal study ADCT-402-201 in Section 8.1.4.

Objectives and Endpoints: The primary objectives of this study were to evaluate the safety and tolerability, and determine, as appropriate, the maximum tolerated dose (MTD) of loncastuximab tesirine in patients with relapsed or refractory B-NHL in Part 1; to determine the recommended dose(s) of loncastuximab tesirine for Part 2 (expansion); and to evaluate the safety and tolerability of loncastuximab tesirine in Part 2 at the dose level(s) determined in Part 1. Secondary objectives were to evaluate the clinical activity of loncastuximab tesirine as measured by ORR, DOR, OS, PFS, to characterize the PK profile of loncastuximab tesirine and free warhead SG3199, and to evaluate ADAs to loncastuximab tesirine.

The efficacy endpoints were evaluated using the Efficacy Analysis Set, defined as all patients who received at least one dose of loncastuximab tesirine with a valid baseline and at least one valid postbaseline disease assessment or patients who had documented progression of disease or death at any time after the first dose of study drug and before the start of any subsequent anticancer therapy or procedure.

The primary measure of clinical activity was ORR according to the Lugano criteria (Cheson et al 2014) as assessed by the Investigator. Other efficacy measures were DOR, OS, time to tumor response, and PFS.

Subgroup analyses were provided for sex, age, country, bulky disease (yes/no), double hit/triple hit disease (yes/no), response to first line of prior systemic therapy, response to most recent line of prior systemic therapy, number of prior systemic therapies, transformed or de novo disease, and disease stage. Not all subgroups were analyzed for each efficacy endpoint.

Safety was assessed based on AEs, SAEs, treatment discontinuations due to AEs, dose-limiting toxicities, 12-lead ECGs, physical examination, vital signs, ECOG performance status, clinical laboratory tests, and pregnancy testing (women of childbearing potential).

Design: Study ADCT-402-101 was a Phase 1, open-label, dose-escalation (Part 1) and expansion (Part 2) study to evaluate the safety and tolerability of loncastuximab tesirine as monotherapy in patients with relapsed or refractory B-NHL (including DLBCL).

The patients enrolled in this study had failed or were intolerant to established therapy or had no available treatment options.

For each patient, the study included a screening period (up to 28 days), a treatment period (repeated treatment cycles until withdrawal), and a follow-up period to assess disease progression and survival for up to 12 months after the last dose of loncastuximab tesirine.

In Part 1, patients were assigned to treatment according to a 3+3 dose escalation design and oversight of a Dose Escalation Steering Committee. Dosing was planned to escalate from an initial dose of 15 µg/kg Q3W to a maximum of up to 300 µg/kg Q3W. Following completion of Dose Level 7 (200 µg/kg Q3W), the protocol was amended (Amendment 5) to allow for alternative dosing with 120 or 150 µg/kg Q3W for two cycles (two infusions) followed by 60 µg/kg every six weeks, 200 µg/kg every six weeks for two cycles (two infusions) followed by 60 µg/kg every six weeks, and 200 µg/kg every six weeks for one cycle (one infusion) followed by 60 µg/kg every six weeks.

In Part 2 (expansion), all patients were assigned to the dose levels of loncastuximab tesirine identified in Part 1. The following doses and schedules were selected for Part 2 (expansion):

- 120 µg/kg Q3W
- 150 µg/kg Q3W. Some patients in this group had their dose reduced to 75 µg/kg Q3W after three cycles at 150 µg/kg

Disease assessments were performed at baseline and six and 12 weeks after Cycle 1, Day 1, then every nine weeks during the treatment period and at EOT. For patients who discontinued treatment for reasons other than disease progression, efficacy assessments were to continue every 12 weeks until disease progression or initiation of other anticancer therapy for up to one year from EOT.

Demographics and Baseline Characteristics: Study ADCT-402-101 enrolled 183 patients with B-NHL. The majority of patients enrolled in this study had subtype DLBCL (76.0%). Other B-NHL subtypes enrolled were mantle cell lymphoma (MCL) (8.2%), FL (7.7%), marginal zone B-cell lymphoma (3.3%), chronic lymphocytic leukemia (3.3%), Waldenstrom macroglobulinemia (0.5%), Burkitt lymphoma (0.5%), and other.

Of the 139 patients enrolled with DLBCL, 59 patients (42.4%) were female, and 80 patients (57.6%) were male. Most patients (90.6%) were white. The median age was 63.0 years with a range of 20 to 86 years. There were 33 patients (23.7%) with an ECOG score of zero, 86 patients (61.9%) with a score of one, 18 patients (12.9%) with a score of two, and two patients (1.4%) with a score of three.

Fifty-five patients (39.6%) had ≥4 prior lines of systemic therapy, with a median number of three lines (range: one to 10). Twenty-seven patients (19.4%) had prior SCT, and 52 patients (37.4%) had prior radiotherapy.

A substantial proportion of the 139 patients in the DLBCL subset had high risk features including 37 patients (26.6%) with transformed DLBCL, 23 patients (16.5%) with double hit or triple hit disease, and 89 patients (64.0%) with Ann Arbor Stage IV disease.

Disposition: There were 139 patients enrolled with a primary diagnosis of DLBCL who received at least one dose of loncastuximab tesirine. The most common reasons for treatment withdrawal were progressive disease (71 patients; 51.1%), AEs (25 patients; 18.0%), physician decision (20 patients; 14.4%), and other (14 patients; 10.1%). Most patients who discontinued treatment remained in the study for long-term follow-up and the primary reasons for discontinuing the study were death (92 patients; 66.2%) and completed the study (31 patients; 22.3%).

Exposure: Dose levels explored in the study ranged from 15 to 200 µg/kg. In the DLBCL Efficacy Analysis Set, the median treatment duration (all dose levels combined) was 64 days (range: 22 to 277 days), and the median average weight-adjusted dose per cycle was 131.13 µg/kg (range: 14.6 to 203.3 µg/kg). The median number of treatment cycles administered was 2.0 (range 1 to 13) and the mean number of treatment cycles administered was 3.1.

Efficacy/Clinical Activity: The clinical activity results are presented for all dose levels ≥120 µg/kg (ie, 120, 150, and 200 µg/kg), and for all dose levels combined. Results for all dose levels are presented in the ADCT-402-101 CSR.

Of the 139 patients with DLBCL, the total N for clinical activity analyses was 137 patients in the Efficacy Analysis Set (two patients with DLBCL were excluded from the Efficacy Analysis Set because of a lack of posttreatment efficacy assessments).

There was substantial evidence of clinical activity with loncastuximab tesirine. The ORR in patients with DLBCL was 42.3% and the median DOR was 4.47 months. The ORR was encouraging in several hard to treat patient populations: in patients ≥75 years the ORR was 55.6%, in patients with primary refractory disease the ORR was 23.3%, and in patients with

double hit or triple hit disease the ORR was 21.7%. There was evidence of durable response in these groups; the median DOR was 5.11 months in patients ≥75 years and not reached in patients with primary refractory disease.

Pharmacokinetics/Pharmacodynamics: PK and pharmacodynamics were assessed in all patients with adequate data for evaluation, including all B-NHL subtypes which varied by endpoint.

Safety: One hundred eighty-three patients with B-NHL enrolled in the study and received at least one dose of loncastuximab tesirine, including 139 patients with DLBCL, 15 patients with MCL, and 14 patients with FL.

The MTD was not reached during the study due to the low number of dose-limiting toxicities, but cumulative toxicity was apparent at the 200 µg/kg dose level, supporting the choice of 120 µg/kg and 150 µg/kg as initial dosing in the dose expansion portion of the study. There continued to be cumulative toxicity at these dose levels, with 19.1% patients (all dose levels) withdrawing from treatment because of TEAEs and 37.2% requiring a treatment delay because of TEAEs. The probability of a dose modification increased after two cycles. There was a trend toward better response with higher PK exposure. The median time to response was 43.0 days, approximately equivalent to two cycles of treatment. Based on the cumulative safety data, the PK exposure data, and the efficacy data, a treatment regimen of 150 µg/kg Q3W for the first two cycles, then 75 µg/kg Q3W for subsequent cycles was selected for the Phase 2 study.

Loncastuximab tesirine was well tolerated. Toxicities were reversible and manageable in most patients with dose delays or reductions and standard supportive care.

8.1.4. Integrated Review of Effectiveness

The FDA's Assessment:
The FDA's assessment of efficacy was based primarily on the ADCT-402-201 trial. The efficacy data from ADCT-402-101 is descriptive and considered supportive.

The pivotal ADCT-402-201 trial enrolled 8% of patients with high grade B-cell lymphoma, which on subgroup analysis, had an ORR of 33% (5/15), with all 5 responses being a complete response. To further support efficacy in patients with high grade B-cell lymphoma, through an information request, the Applicant provided data for 23 patients with high grade B-cell lymphoma from ADCT-402-101. For the 23 patients, the ORR per investigator was 22% (5/23), with 3 patients achieving a complete response. Of the 23 patients, there were 11 patients treated with an initial loncastuximab tesirine dose of 150 µg/kg. The ORR for these 11 patients was 27% (3/11), with 2 patients achieving a complete response.

The data for patients with high grade B-cell lymphoma from ADCT-402-201 and 101 are consistent and provide sufficient data to support a meaningful benefit in these high-risk patients and inclusion in labeling. Thus, the indication for loncastuximab tesirine can include the subtypes of large B-cell lymphoma enrolled in the ADCT-402-201 trial.

8.1.5. Assessment of Efficacy Across Trials

Study ADCT-402-201 is the pivotal efficacy study for this application, and study ADCT-402-101 is supportive. Because the two studies used to assess efficacy of loncastuximab tesirine had different dose regimens and imaging reviewers (independent central review in ADCT-402-201 and Investigator assessment in ADCT-402-101), the results were not integrated. Rather, relevant data are presented for each study to demonstrate efficacy across these two studies.

Primary Endpoint

Data:
ORR was the primary measure of efficacy/clinical activity in studies ADCT-402-201 and ADCT-402-101. ORR was defined as the proportion of patients who achieved either CR or PR as BOR using the 2014 Lugano Classification criteria before the start of subsequent anticancer therapy or procedure.

In ADCT-402-201, this endpoint was assessed by an independent central reviewer, and in ADCT-402-101, this endpoint was assessed by the Investigator.

In ADCT-402-201, the ORR was 48.3% and in ADCT-402-101 the ORR was 42.3% (Table 18).

Table 18: Applicant-Best Overall Response and Overall Response Rate

	ADCT-402-201 (All-Treated Population) (N=145)	ADCT-402-101 DLBCL (all dose levels) (Efficacy Analysis Set) (N=137)
Best Overall Response		
Complete response	35 (24.1)	32 (23.4)
Partial response	35 (24.1)	26 (19.0)
Stable disease	22 (15.2)	23 (16.8)
Not evaluable	23 (15.9)	2 (1.5)
Progressive disease	30 (20.7)	54 (39.4)
ORR (CR + PR)	70 (48.3)	58 (42.3)
95% CI for ORR	(39.9, 56.7)	(33.9, 51.1)

CR=complete response; DLBCL=diffuse large B-cell lymphoma; ORR=overall response rate; PR=partial response
Note: Best overall response is the best visit response, based on the 2014 Lugano Classification criteria.
For ADCT-402-201, not evaluable included patients without any scan to the independent reviewer (even clinical progressive disease) or patients whose scan was determined as not evaluable by the independent reviewer.
For ADCT-402-101, patients were considered not evaluable if they had only one valid disease assessment which was stable disease and the assessment was within 35 days after the first dose.
Source: ADCT-402-201 CSR Table 14.2.1.1.1 (datasets: adrs, adsl) and ADCT-402-101 CSR Table 14.2.1.1.2 (datasets: adrs, adsl)

The Applicant's Position:
Both studies showed that loncastuximab tesirine was effective in treating a broad and representative population of patients with relapsed or refractory DLBCL, including those with high risk characteristics, who were heavily pretreated. The pivotal study ADCT-402-201 used the optimal dosing regimen proposed in the BLA application, which likely accounts for the greater efficacy observed in this study compared to study ADCT-402-101.

The FDA's Assessment:
The FDA's assessment of efficacy was based primarily on the ADCT-402-201 trial. The efficacy data from ADCT-402-101 is descriptive and considered supportive.

Secondary and Other Endpoints

Data:

Duration of Response

In ADCT-402-201, there were 70 patients included in this analysis and the median DOR was 10.25 months (95% CI: 6.87, not estimable). In ADCT-402-101 there were 58 patients included in this analysis, and the median DOR was 4.47 months (95% CI: 3.94 to 9.46).

The difference in results between the two studies is possibly related to the varying dose levels in study ADCT-402-101, but perhaps more importantly, to the fact that the dosage regimen in study ADCT-402-201 included a planned decreased in dose after the second cycle based on the observation in study ADCT-402-101 that following Cycle 2 and subsequent cycles, many patients had AEs that required prolonged dose holds as well as reductions and discontinuations. The dosage regimen in study ADCT-402-201 thus allowed for more prolonged exposure in patients.

Time to Response

The median time to tumor response was 41.0 days (range: 35 to 247 days) in ADCT-402-201 and 43.0 days (range: 31 to 323 days) in ADCT-402-101.

Median time to tumor response in both ADCT-402-201 and ADCT-402-101 indicated that the majority of responders demonstrated response after two doses of loncastuximab tesirine, which was the timepoint of the first response assessment.

Complete Response Rate

The CRR was comparable between the ADCT-402-201 and ADCT-402-101 studies at 24.1% and 23.4%, respectively. These consistent CRR results demonstrate the robustness of loncastuximab tesirine antitumor activity across a wide range of relapsed or refractory DLBCL population, including patients with high risk disease.

Progression-free Survival

In study ADCT-402-201, the median PFS was 4.93 months (95% CI: 2.89 to 8.31 months) and in study ADCT-402-101, the median PFS was 2.83 months (95% CI: 1.91 to 3.75 months).

Relapse-free Survival

In study ADCT-402-201, the median RFS was 13.37 months (95% CI: 10.25, not estimable). RFS was not an endpoint in study ADCT-402-101.

Overall Survival

The median OS in study ADCT-402-201 was 9.92 months (95% CI: 6.74 to 11.47 months) and the median OS in study ADCT-402-101 was 7.46 months (95% CI: 5.95 to 9.79 months).

The Applicant's Position:
Secondary endpoints showed that loncastuximab tesirine was effective in treating a broad and representative population of patients with relapsed or refractory DLBCL, including those with high risk characteristics, who were heavily pretreated in both studies. Effectiveness was observed not only with CRR, but also with efficacy endpoints measured over time (DOR, time to response, PFS, relapse-free survival, and OS).

The pivotal study ADCT-402-201 used the optimal dosing regimen proposed in the BLA application, which likely accounts for the greater efficacy observed in this study compared to study ADCT-402-101. Median time to first response was rapid in both studies (41.0 days for ADCT-402-201 and 43.0 days for ADCT-402-101) indicating that the majority of responders demonstrated response after 2 doses (timepoint of the first response assessment).

The FDA's Assessment:
The FDA's assessment of efficacy was based primarily on the ADCT-402-201 trial. The efficacy data from ADCT-402-101 is descriptive and considered supportive. Further, in a single-arm trial, time-to-event endpoints have limited interpretability so the results for PFS, RFS and OS are considered exploratory.

Subpopulations

Data:
Intrinsic Characteristics

Overall Response Rate
The ORRs were not notably affected by the intrinsic characteristics of sex, age group, transformed or de novo disease, and disease stage. Within these groups which included patients with high risk disease, the separate categories performed equally well. In addition, prior intensive salvage therapy, SCT, or CAR-T therapy did not notably affect ORR.
The ORRs appeared to be affected somewhat by the known negative prognostic factors/intrinsic characteristics of bulky disease, tumor maximal longest diameter, double hit/triple hit disease, and patients who were refractory to first line, most recent line, or any line of prior systemic therapies. Meaningful responses were seen in patients with these characteristics, but the response rate was better in patients without these traits.

Duration of Response
DOR was not affected by intrinsic characteristics. In the ADCT-402-201 study, there were numeric differences in DOR among various subgroups, most of which were minor. The larger numeric differences in patients with primary mediastinal disease and bulky disease are to be viewed with caution due to the small number of patients in these categories.

Complete Response Rate
In ADCT-402-201 there were 35 patients with CR and in ADCT-402-101 there were 32 patients with CR. Interpretation of CRR by subgroups would not be meaningful due to the small sample sizes for the categories in each subgroup.

Progression-free Survival
Interpretation of intrinsic characteristics on PFS is challenging because of the differences in dose levels and treatment regimens between the two studies.

Extrinsic Characteristics

Overall Response Rate
When ORR was evaluated by extrinsic characteristics, there did not appear to be any notable differences by country, formulation type, or response assessment by independent central reviewer versus Investigator.

The Applicant's Position:
Of all intrinsic and extrinsic characteristics evaluated, only ORRs appeared to be affected somewhat by the known negative prognostic factors/intrinsic characteristics of bulky disease, tumor maximal longest diameter, double hit/triple hit disease, and patients who were refractory to first line, most recent line, or any line of prior systemic therapies. Meaningful responses were seen in patients with these characteristics, but the response rate was better in patients without these traits.

The FDA's Assessment:
The FDA's assessment of efficacy was based primarily on the ADCT-402-201 trial. The efficacy data from ADCT-402-101 is descriptive and considered supportive.

8.1.6. Integrated Assessment of Effectiveness

Data:
Because the two studies used to assess efficacy of loncastuximab tesirine had different dose regimens and imaging reviewers (independent central review in ADCT-402-201 and Investigator assessment in ADCT-402-101), the results were not merged into integrated analyses. Rather, relevant data were presented for each study in the BLA to demonstrate efficacy across these two studies (see Section 8.1.4).

The Applicant's Position:
Although an integrated assessment of effectiveness was not performed because of the

differences in trial characteristics, the results from both trials support the effectiveness of loncastuximab tesirine in patients with relapsed/refractory DLBCL.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment that the data from the two trials cannot be pooled together due to the differences in the criteria of the two trials.

The efficacy of loncastuximab tesirine was based on ADCT-402-201, an open-label, single-arm trial in 145 adult patients with relapsed or refractory large B-cell lymphoma after at least 2 prior systemic regimens. The trial excluded patients with bulky disease and active central nervous system lymphoma. Patients received loncastuximab tesirine 150 µg/kg every 3 weeks for 2 cycles, then 75 µg/kg every 3 weeks for subsequent cycles and received treatment until progressive disease, or unacceptable toxicity. The primary endpoint was overall response rate (ORR) as assessed by an Independent Review Committee (IRC) using Lugano 2014 criteria.

Of the 145 patients enrolled, the median age was 66 years (range 23 to 94), 59% male, and 94% had an ECOG performance status of 0 to 1. Race was reported in 97% of patients; of these patients, 90% were White, 3% were Black, and 2% were Asian. The diagnosis was DLBCL not otherwise specified (NOS) in 88% (including 20% with DLBCL arising from low grade lymphoma) and high-grade B-cell lymphoma in 8%. The median number of prior therapies was 3 (range 2 to 7), 63% with refractory disease, 17% with prior stem cell transplant, and 9% with prior chimeric antigen receptor (CAR) T-cell therapy.

Among the 145 patients, the median follow-up time was 7.3 months (range 0.3 to 20.2). The ORR per IRC was 48.3% (95% CI 39.9, 56.7), with 24.1% achieving a complete response. The median duration of response (DOR) per Kaplan-Meier was 10.3 months (95% CI 6.9, not evaluable). Notably, of the 70 patients with an objective response, 36% were censored for DOR prior to 3 months.

Based on the characteristics of the DLBCL patient population enrolled in ADCT-402-201, the data support the determination that loncastuximab tesirine has clinically meaningful activity in patients with relapsed or refractory large B-cell lymphoma who have received at least two prior systemic therapies. Some limitations of the efficacy data include the limited racial and ethnic representation with race reported in 97% of patients; of these patients, 90% were White, 3% were Black, and 2% were Asian. For ethnicity, 9% identified as Hispanic or Latino. Further characterization of loncastuximab tesirine in broader racial and ethnic population is warranted and informed a post marketing requirement. Further, the pivotal ADCT-402-201 trial enrolled only 8% of patients with high grade B-cell lymphoma, which on subgroup analysis, had an ORR of 33% (5/15), with all 5 responses being a complete response. To further support efficacy in patients with high grade B-cell lymphoma, through an information request, the Applicant

provided data for 23 patients with high grade B-cell lymphoma from ADCT-402-101. For the 23 patients, the ORR per investigator was 22% (5/23), with 3 patients achieving a complete response. Of the 23 patients, there were 11 patients treated with an initial loncastuximab tesirine dose of 150 µg/kg. The ORR for these 11 patients was 27% (3/11), with 2 patients achieving a complete response. Thus, the data for patients with high grade B-cell lymphoma from ADCT-402-201 and 101 are consistent and provide sufficient data to support a meaningful benefit in these high-risk patients and inclusion in labeling. The indication for loncastuximab tesirine can include the subtypes of large B-cell lymphoma enrolled in the ADCT-402-201 trial.

8.2. **Review of Safety**

Data:
Assessment of the safety of loncastuximab tesirine was based on data from 401 patients in five studies, analyzed at three integrated levels, as summarized in Table 19. The primary safety evaluation was based on the Level 1 pooled analyses as these data support the intended indication being sought in the BLA.

Table 19: Applicant-Overview of Studies and Patients Included in Integrated Analyses

Study and Treatment	Population and Numbers of Patients, N	Numbers of Patients		
		Level 1	Level 2	Level 3
		Loncastuximab Tesirine Monotherapy DLBCL Population N	Loncastuximab Tesirine Monotherapy Population N	Loncastuximab Tesirine All-Treated Population N
ADCT-402-201 loncastuximab tesirine alone	DLBCL, 145	145	145	145
ADCT-402-101 loncastuximab tesirine alone	All B-NHL, 183	139	183	183
ADCT-402-102 loncastuximab tesirine alone	All B-ALL, 35	NA	35	35
ADCT-402-103 loncastuximab tesirine + ibrutinib	All B-NHL, 25[a]	NA	NA	25[a]
ADCT-402-104 loncastuximab tesirine + durvalumab	All B-NHL, 13	NA	NA	13
All studies combined	401	284	363	401

B-ALL=B-cell acute lymphoblastic leukemia; B-NHL=B-cell non-Hodgkin lymphoma; DLBCL= diffuse large B-cell lymphoma; NA=not applicable
[a] Still recruiting
Source: Statistical Analysis Plan; ISS Table 3.2.1 (datasets: adsl, adexsum)

The Applicant's Position:
The total safety data available allow for a comprehensive assessment of the safety profile of loncastuximab tesirine and an evaluation of the overall benefit-risk, in a broad and representative population of relapsed or refractory DLBCL patients, including those with high risk characteristics, who were heavily pretreated, without regard to transplant eligibility. This safety population is considered adequate for the detection and characterization of common AEs and to provide guidance on toxicity management.

The FDA's Assessment:
The FDA agrees with the Applicant's position that the available safety data allowed for an adequate assessment of safety.

Safety Review Approach

Data:
Safety data from five clinical studies involving 401 patients with loncastuximab tesirine were evaluated. The same data cutoff of 06 Apr 2020 used in efficacy analyses was also used in safety analyses.

The analysis set used for all integrated safety analyses was comprised of all patients who received at least one dose of loncastuximab tesirine. Patients were analyzed as treated. Due to the large range of the lower doses and very few patients enrolled in some dose levels, the dose levels were grouped by initial dose of loncastuximab tesirine as shown in Table 20.

The primary safety evaluation was based on the Level 1 pooled analyses as these data support the intended indication being sought in the BLA. The Level 1 pool consisted of a total of 284 patients with relapsed or refractory DLBCL who received loncastuximab tesirine monotherapy, of which 145 patients were from pivotal study ADCT-402-201 and 139 patients were from study ADCT-402-101.

Data from the Level 2 pooled analyses were supportive based on a relevant larger safety database that included a total of 363 patients with relapsed or refractory disease who received loncastuximab tesirine monotherapy in three studies as follows: 145 DLBCL patients from pivotal study ADCT-402-201, 183 B-NHL patients from study ADCT-402-101, and 35 B-ALL patients from study ADCT-402-102. Safety data for the 328 B-NHL patients included in the Level 2 pool were generally similar to the data from the Level 1 pool. Given this similarity, the remainder of this discussion will focus on the data from the Level 1 pool of 284 patients with DLBCL treated with loncastuximab tesirine monotherapy.

Level 3 pooled analyses added an additional 38 relapsed or refractory B-NHL patients from ADCT-402-103 and ADCT-402-104 studies who received loncastuximab tesirine in combination with either ibrutinib or durvalumab, respectively.

Table 20: Applicant-Mapping Rule of Individual Study Dose and Dose Group in Reporting Results

	SCS Dose Group[a]					
Study	**≤90 µg/kg**	**120 µg/kg**	**150 µg/kg**	**200 µg/kg**	**With ibrutinib**	**With durvalumab**
ADCT-402-201	--	--	150 µg/kg	--	--	--
ADCT-402-101	15, 30, 60, and 90 µg/kg	120 µg/kg	150 µg/kg	200 µg/kg	--	--
ADCT-402-102	15, 30, 60, and 90 µg/kg	120 µg/kg	150 µg/kg Q3W, 50 µg/kg QW[b]	--	--	--
ADCT-402-103	--	--	--	--	60 and 90 µg/kg +ibrutinib	--
ADCT-402-104	--	--	--	--	--	90, 120, and 150 µg/kg +durvalumab

SCS=Summary of Clinical Safety, QW=every week, Q3W=every three weeks
[a] Based on initial dose of loncastuximab tesirine
[b] 50 µg/kg QW x3 for a total cycle dose of 150 µg/kg
Source: Statistical Analysis Plan

The Applicant's Position:
The safety analysis strategy was designed to rationally assess the safety of loncastuximab tesirine in DLBCL patients and facilitate comparisons with a larger patient pool that included other B-NHL subtypes and those receiving loncastuximab tesirine in combination with other therapies. The strategy was agreed with FDA as part of the preBLA meeting (17 Apr 2020).

The FDA's Assessment:
The FDA's safety evaluation focused primarily on 2 populations, the 145 patients from the pivotal trial ADCT-402-201 and 215 patients from ADCT-402-201 and ADCT-402-101 that received an initial dose of 150 µg/kg. The safety pools, Level 1 and Level 2 as discussed above, were also evaluated to confirm the Applicant's data, but the safety populations of 145 patients and 215 patients noted above will be presented in this review.

8.2.1. Review of the Safety Database

Overall Exposure

Data:

Table 21**Error! Reference source not found.** summarizes loncastuximab tesirine exposure in the 284 DLBCL patients who received loncastuximab tesirine monotherapy, based on initial dose level.

In the Phase 1, first-in-human study ADCT-402-101, patients received initial doses of loncastuximab tesirine ranging from 15 to 200 μg/kg. Based on the observation of increased toxicity at the 200 μg/kg dose level and on the fact that a substantial proportion of patients required dose reduction after two cycles, the recommended dose of loncastuximab tesirine used in the pivotal Phase 2 ADCT-402-201 study in patients with relapsed or refractory DLBCL was 150 μg/kg Q3W for two cycles followed by 75 μg/kg Q3W for subsequent cycles.

Of the 284 DLBCL patients who received loncastuximab tesirine monotherapy, 10 patients received initial doses of ≤90 μg/kg, 32 patients 120 μg/kg, 215 patients 150 μg/kg, and 27 patients 200 μg/kg. The median treatment duration in all doses combined was 43.0 days (range: 1 to 351 days). The median number of treatment cycles administered was 3.0 cycles (range: 1 to 15 cycles). The median total dose administered was 28,430 μg (range: 2,000 to 112,500 μg), and the median total weight-adjusted dose administered was 371.40 μg/kg (range: 29.2 to 1646.2 μg/kg). The median average weight-adjusted dose per cycle was 125.00 μg/kg (range: 14.6 to 203.3 μg/kg).

Table 21: Applicant Study Drug Administration and Extent of Exposure Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

			150 µg/kg				
	<=90 µg/kg (N=10)	120 µg/kg (N=32)	s101 (N=70)	s201 (N=145)	subtotal (N=215)	200 µg/kg (N=27)	All Doses (N=284)
Total number of cycles dose administered							
n	10	32	70	145	215	27	284
Mean	3.8	3.3	3.3	4.3	4.0	2.1	3.7
std	3.79	1.86	2.31	3.43	3.14	1.12	2.96
Median	2.0	3.0	3.0	3.0	3.0	2.0	3.0
Min, Max	1, 13	1, 9	1, 12	1, 15	1, 15	1, 5	1, 15
Duration of treatment (days)							
n	10	32	70	145	215	27	284
Mean	63.0	57.5	62.0	79.6	73.9	45.1	68.9
std	83.84	52.49	62.54	81.39	76.07	53.00	72.44
Median	22.0	42.0	44.0	45.0	45.0	22.0	43.0
Min, Max	1, 253	1, 238	1, 256	1, 351	1, 351	1, 177	1, 351
Total dose administered (µg*1000)							
n	10	32	70	145	215	27	284
Mean	15.66	30.88	32.68	33.78	33.42	30.70	32.25
std	17.510	18.488	18.552	19.874	19.417	15.985	19.157
Median	5.93	23.40	28.43	30.00	30.00	28.00	28.43
Min, Max	2.0, 45.5	5.8, 71.8	7.5, 88.5	7.5, 112.5	7.5, 112.5	9.7, 71.1	2.0, 112.5
Total weight adjusted dose (µg/kg)							
n	10	32	70	145	215	27	284
Mean	185.10	386.82	427.07	443.84	438.38	345.19	414.79
std	202.295	216.959	258.746	257.511	257.429	151.352	248.016
Median	89.27	293.95	361.37	375.68	375.51	317.42	371.40
Min, Max	29.2, 617.2	118.5, 1125.3	129.0, 1646.2	122.4, 1264.5	122.4, 1646.2	196.0, 600.0	29.2, 1646.2
Average dose per cycle (µg*1000)							
n	10	32	70	145	215	27	284
Mean	3.75	9.31	10.72	9.25	9.73	15.59	10.03
std	2.845	2.531	3.336	2.780	3.044	5.640	3.919
Median	3.25	9.00	10.50	9.08	9.40	15.75	9.50
Min, Max	1.0, 10.4	5.1, 16.4	5.1, 22.2	3.1, 17.4	3.1, 22.2	7.0, 32.1	1.0, 32.1
Average weight adjusted dose per cycle (µg/kg)							
n	10	32	70	145	215	27	284
Mean	46.56	117.73	136.06	120.15	125.33	175.42	126.47
std	27.076	7.690	19.791	26.226	25.396	34.229	33.000
Median	42.76	119.87	147.25	113.50	125.97	197.61	125.00
Min, Max	14.6, 94.9	95.7, 125.2	84.8, 156.5	51.7, 160.6	51.7, 160.6	105.8, 203.3	14.6, 203.3

DLBCL=diffuse large B-cell lymphoma; s101=study ADCT-402-101; s201=study ADCT-402-201
Source: ISS Table 1.2.1 (datasets: adsl, adexsum)

The Applicant's Position:
The exposure to study drug was considered adequate to allow for a comprehensive assessment of safety in patients who were representative of the intended target population.

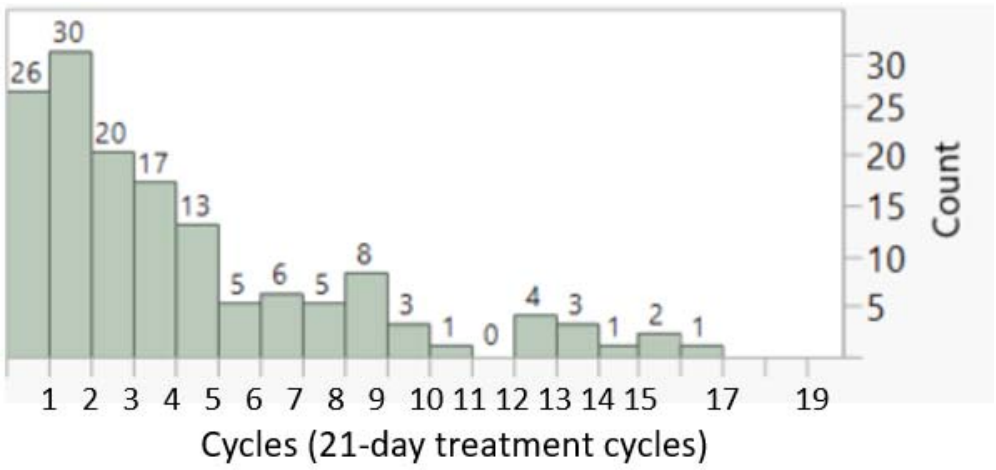
The FDA's Assessment:
Exposure in the FDA's safety populations are summarized in the tables below. In the 145 patients from ADCT-402-201, the median exposure was 3 cycles (range 1 to 15) or 45 days (range 1 to 351) with 34% receiving 5 or more cycles. The relative dose intensity was greater than 90% in the majority of patients (~94%). The exposure was sufficient to evaluate the short-term risks with loncastuximab tesirine, however the data is limited in those patients who received at least 5 or more cycles. This is important given the prespecified dose reduction from 150 µg/kg to 75 µg/kg following the initial 2 cycles and the ability of the data to inform longer-term safety.

Table 22: Loncastuximab Exposure in Safety Populations – FDA Review

Exposure	**ADCT-402-201** **N=145**	**150 µg/kg Dose Pool** **N = 215**
Median cycles administered	3	3
Range	(1, 15)	(1, 15)
3 or more cycles	60%	58%
5 or more cycles	34%	30%
Median exposure (days)	45	45
Range	(1, 351)	(1, 351)
Relative dose intensity		
< 60%	<1%	*
≥ 60% to < 80%	3%	*
≥ 80% to < 90%	2%	*
≥ 90% to < 110%	93%	*
≥ 110%	<1%	*

Source: FDA review of ADEX dataset
*Relative dose intensity data not provided for the entire 150 µg/kg Dose Pool

Figure 8: Distribution of Exposure in ADCT-402-201 – FDA Review



Source: FDA review of ADEX dataset

Relevant characteristics of the safety population

Data:
Table 23 summarizes selected demographic and baseline characteristics in DLBCL patients who received loncastuximab tesirine monotherapy.

In the 284 DLBCL patients in all doses combined, there were fewer females (41.9%) than males (58.1%). Most patients were white (90.1%), followed by all others (5.6%), and black (4.2%). A small percentage of patients were Hispanic or Latino (6.7%). Patients were about evenly divided by region with 51.1% from the US and 48.9% from Europe. The median age was 65.0 years (range: 20 to 94 years). Age groups were about evenly divided with 48.6% of patients aged <65 years and 51.4% aged ≥65 years. The majority of patients had a baseline ECOG performance status of Grade 1 (57.7%), followed by Grade 0 (32.0%), Grade 2 (9.5%), and Grade 3 (0.7%).

Table 23: Applicant-Demographic and Baseline Characteristics-Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

			150 µg/kg				
	<=90 µg/kg (N=10)	120 µg/kg (N=32)	s101 (N=70)	s201 (N=145)	subtotal (N=215)	200 µg/kg (N=27)	All Doses (N=284)
Sex [n(%)]							
Female	7 (70.0)	9 (28.1)	34 (48.6)	60 (41.4)	94 (43.7)	9 (33.3)	119 (41.9)
Male	3 (30.0)	23 (71.9)	36 (51.4)	85 (58.6)	121 (56.3)	18 (66.7)	165 (58.1)
Race [n(%)]							
White	9 (90.0)	24 (75.0)	67 (95.7)	130 (89.7)	197 (91.6)	26 (96.3)	256 (90.1)
Black or African American	1 (10.0)	4 (12.5)	2 (2.9)	5 (3.4)	7 (3.3)	0	12 (4.2)
Asian	0	3 (9.4)	0	3 (2.1)	3 (1.4)	0	6 (2.1)
American Indian or Alaskan Native	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)
Native Hawaiian or Pacific Islander	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)
Other	0	1 (3.1)	0	5 (3.4)	5 (2.3)	1 (3.7)	7 (2.5)
Missing	0	0	1 (1.4)	0	1 (0.5)	0	1 (0.4)
Race Group [n(%)]							
White	9 (90.0)	24 (75.0)	67 (95.7)	130 (89.7)	197 (91.6)	26 (96.3)	256 (90.1)
Black	1 (10.0)	4 (12.5)	2 (2.9)	5 (3.4)	7 (3.3)	0	12 (4.2)
All Others	0	4 (12.5)	1 (1.4)	10 (6.9)	11 (5.1)	1 (3.7)	16 (5.6)
Region [n(%)]							
USA	10 (100)	25 (78.1)	31 (44.3)	59 (40.7)	90 (41.9)	20 (74.1)	145 (51.1)
Europe	0	7 (21.9)	39 (55.7)	86 (59.3)	125 (58.1)	7 (25.9)	139 (48.9)
Ethnicity [n(%)]							
Hispanic or Latino	0	1 (3.1)	4 (5.7)	13 (9.0)	17 (7.9)	1 (3.7)	19 (6.7)
Not Hispanic or Latino	10 (100)	31 (96.9)	66 (94.3)	132 (91.0)	198 (92.1)	26 (96.3)	265 (93.3)
Age (years)							
n	10	32	70	145	215	27	284
Mean	65.6	67.5	57.6	62.7	61.1	62.4	62.1
std	18.05	13.36	15.50	13.63	14.43	13.32	14.43
Median	74.0	70.0	59.0	66.0	64.0	65.0	65.0
Min, Max	24, 83	33, 85	20, 86	23, 94	20, 94	29, 79	20, 94
Age Group [n(%)]							
< 65 years	4 (40.0)	11 (34.4)	45 (64.3)	65 (44.8)	110 (51.2)	13 (48.1)	138 (48.6)
≥ 65 years	6 (60.0)	21 (65.6)	25 (35.7)	80 (55.2)	105 (48.8)	14 (51.9)	146 (51.4)

			150 µg/kg				
	<=90 µg/kg (N=10)	120 µg/kg (N=32)	s101 (N=70)	s201 (N=145)	subtotal (N=215)	200 µg/kg (N=27)	All Doses (N=284)
Body Mass Index (kg/m^2)							
n	10	32	70	144	214	26	282
Mean	27.72	27.06	26.97	26.93	26.94	30.41	27.30
std	7.582	6.348	6.680	5.728	6.040	7.856	6.359
Median	27.32	27.06	25.58	25.97	25.97	28.16	26.35
Min, Max	19.8, 44.5	17.0, 41.5	16.5, 50.1	17.2, 50.5	16.5, 50.5	18.7, 46.4	16.5, 50.5
ECOG Performance Status [n(%)]							
Grade 0	2 (20.0)	9 (28.1)	17 (24.3)	58 (40.0)	75 (34.9)	5 (18.5)	91 (32.0)
Grade 1	5 (50.0)	22 (68.8)	40 (57.1)	78 (53.8)	118 (54.9)	19 (70.4)	164 (57.7)
Grade 2	3 (30.0)	1 (3.1)	11 (15.7)	9 (6.2)	20 (9.3)	3 (11.1)	27 (9.5)
Grade 3	0	0	2 (2.9)	0	2 (0.9)	0	2 (0.7)

DLBCL=diffuse large B-cell lymphoma; ECOG=Eastern Cooperative Oncology Group; s101=study ADCT-402-101; s201=study ADCT-402-201; USA=United States of America
Source: ISS Table 1.1.2 (dataset: adsl)

DLBCL Subtypes

In the 284 DLBCL patients in all doses combined, the disease subtypes were most commonly categorized as DLBCL NOS (91.9%), followed by high grade B-cell lymphoma (4.9%), and primary mediastinal B-cell lymphoma (3.2%).

Pretreatment Disease Characteristics

In the same population, the most common stage was Stage IV disease at enrollment (64.1%). Subtypes included Subtype E (extranodal involvement; 51.4%), Subtype X (bulky disease; 9.5%), and Subtype S (spleen involved; 4.2%). The median time since initial diagnosis was 18.87 (range: 1.4 to 355.0) months.

Prior Anticancer Therapies for DLBCL

In the same population, the median number of lines of prior systemic therapy was 3.0 (range: 1 to 10). Prior numbers of lines of systemic therapy had been received by patients as follows: $\leq$2 or >3 (35.9% each) or 3 (28.2%). Approximately one-third of patients (37.0%) had received prior radiotherapy and 18.0% had received a prior SCT (most commonly autologous). Most patients had relapsed (66.5%) or were refractory (20.8%) to their first-line systemic therapy (refractory disease was defined as no response to therapy), and most patients had relapsed (32.4%) or were refractory (58.8%) to their most recent systemic therapy.

The Applicant's Position:

The characteristics of the patients included in Level 1 for the primary safety analysis were representative of the target population with loncastuximab tesirine monotherapy.

The FDA's Assessment:

The FDA agrees with the Applicant's position. For the demographics and disease characteristics of the ADCT-402-201 trial population (N = 145), refer to Section 8.1.2.

Adequacy of the safety database

Data:
An integrated safety database was created to support the integrated safety analyses described in this application.

Integrated Clinical Data Interchange Standards Consortium (CDISC) Analysis Data Model (ADaM) datasets were created from individual SDTM datasets and followed the CDISC Analysis Data Model Implementation Guide version 1.1. A process of data reconciliation ensured that SAE data on the safety database were consistent with those on the clinical trials database. The data cutoff date for the safety analyses was 06 Apr 2020.

The primary safety evaluation was based on the Level 1 pooled analyses described in Section 0.

The Applicant's Position:
The safety database is sufficient to evaluate the safety of loncastuximab tesirine monotherapy in the target population.

The FDA's Assessment:
The safety database was acceptable for review.

8.2.2. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:
The clinical sites were monitored by clinical research associates following standard operating procedures. Data were queried per study-specific data management plans. Individual case safety reports were followed up as necessary to obtain complete information on the case. SAEs were reconciled between the clinical and safety databases. No meaningful data integrity concerns were reported from site audits.

The Applicant's Position:
No meaningful concerns have been detected in the quality and integrity of the submitted datasets, individual case narratives, and CSRs; these are sufficiently complete to allow for a thorough review of safety.

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

Categorization of Adverse Events

Data:
AEs were updated to Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 for pooled analyses. Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 was used for grading AEs. The primary focus of AE reporting was on TEAEs. An AE was considered to be a TEAE if it began or worsened on or after the first dose date of loncastuximab tesirine and until 30 days after the last dose date of loncastuximab tesirine, or start of a new anticancer therapy/procedure, whichever came earlier.

For studies ADCT-402-103 and ADCT-402-104, ibrutinib and durvalumab were not counted as new anticancer therapies, respectively. However, any AE that occurred or worsened >30 days after the last dose date of loncastuximab tesirine, but while the patient was still on ibrutinib or durvalumab alone, was not counted as a TEAE for this analysis.

An AE occurring before the date of the first dose or more than 30 days after the last dose of loncastuximab tesirine or after the start of a new anticancer therapy/procedure was not included in TEAE displays but was listed as a non-TEAE.

Multiple TEAE summaries were generated as described in detail in the SAP. Summaries included those pertaining to all TEAEs, treatment-emergent SAEs, TEAEs considered treatment-related, TEAEs by severity, and TEAEs that led to treatment withdrawal, dose delay, or dose reduction. TEAEs were also summarized by subgroups including age group, sex, race, and region.

In addition, summaries of grouped TEAEs were provided by Standardized MedDRA Query (SMQ) or ADCT-modified SMQ for the following groups: edema or effusion, fatigue, LFTs, pain, skin reactions and nail disorders, and Torsades de pointes/QT prolongation/seizure. Most of these groups were chosen based on the AE profiles of other PBD-based therapies reported in the literature and early clinical data. Torsades de pointes/QT prolongation/seizure was added in per request pursuant to a pre-BLA meeting with the FDA on 17 Apr 2020.

Time to event analyses were initially planned for the top five most frequent nonhematologic TEAEs Grade $\geq$3 as well as for grouped TEAEs Grade $\geq$3 if the number of patients with events was >20 in any dose group. Out of the top five most frequent nonhematologic TEAEs Grade ≥3, only GGT increased met the criteria for this analysis and only LFTs met the criteria for analysis for grouped TEAEs Grade $\geq$3.

The Applicant's Position:
The approach to categorization of AEs was consistent with regulatory guidance and appropriate for evaluation of the safety data.

The FDA's Assessment:
The FDA agrees with the Applicant's position. To inform the safety review, FDA used grouped preferred terms for more sensitive and informative safety analyses. The FDA preferred terms are listed in Section 19.5.

Routine Clinical Tests

Data:
Hematological and biochemical laboratory assessments were carried out as specified in the study protocols.

Shifts of clinical laboratory parameters for hematology and biochemistry graded according to CTCAE version 4.0 were summarized. The worst case postbaseline including all data, scheduled or unscheduled, up to the start of subsequent anticancer therapy/procedure was used in the shift tables.

Time to event analyses (time to the first onset of Grade 3 and 4 events and time to resolution) for Grade 3 and 4 laboratory abnormalities were planned for hemoglobin decrease; neutrophil count decrease; platelet count decrease; increases in GGT, ALT, AST; and other relevant parameters. The analyses were performed only if there were a minimum of 20 patients with an event in at least one dose group. The criteria were met for the following laboratory parameters: time to first onset of hemoglobin, neutrophil count decrease, platelet count decrease, and increased GGT; time to onset of Grade 3 or higher TEAEs for most common nonhematological Grade 3 or higher TEAE (GGT increased) and for the LFT SMQ; and time to recovery of neutrophil count decrease and platelet count decrease.

The Applicant's Position:
The approach to laboratory assessments and analysis was consistent with regulatory guidance and appropriate for evaluation of the safety data.

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

8.2.3. Safety Results

8.2.4. Deaths

Data:

All Deaths

Table 24 summarizes the number and percent of patients who died during the studies and the reasons for death in DLBCL patients who received loncastuximab tesirine monotherapy.

In the 284 patients in all doses combined, 59.5% of patients died during the studies. Disease progression was the reason for death in 46.1% of patients and other reasons in 13.4%.

Table 24: Applicant-Number (%) of Patients Who Died During the Studies and Reasons for Death-Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

			150 µg/kg				
	<=90 µg/kg (N=10)	120 µg/kg (N=32)	s101 (N=70)	s201 (N=145)	subtotal (N=215)	200 µg/kg (N=27)	All doses (N=284)
Death during study	6 (60.0)	22 (68.8)	49 (70.0)	77 (53.1)	126 (58.6)	15 (55.6)	169 (59.5)
Disease progression	4 (40.0)	20 (62.5)	36 (51.4)	60 (41.4)	96 (44.7)	11 (40.7)	131 (46.1)
Other	2 (20.0)	2 (6.3)	13 (18.6)	17 (11.7)	30 (14.0)	4 (14.8)	38 (13.4)

DLBCL=diffuse large B-cell lymphoma; s101=study ADCT-402-101; s201=study ADCT-402-201
Source: ISS Table 1.3.27 (dataset: adsl)

Table 25 summarizes the number and percent of patients who died within 30 days after the last dose of study drug without taking new anticancer therapy and reasons for death in DLBCL patients who received loncastuximab tesirine monotherapy.

In the 284 patients in all doses combined, 6.3% of patients died within 30 days after the last dose of study drug without taking new anticancer therapy. Disease progression was the reason for death in 3.5% of patients and other reasons in 2.8%.

Table 25: Applicant-Number (%) of Patients Who Died Within 30 Days After the Last Dose of Study Drug-Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

			150 µg/kg				
	<=90 µg/kg (N=10)	120 µg/kg (N=32)	s101 (N=70)	s201 (N=145)	subtotal (N=215)	200 µg/kg (N=27)	All doses (N=284)
Death within 30 days of last dose without taking new anticancer therapy	0	2 (6.3)	6 (8.6)	10 (6.9)	16 (7.4)	0	18 (6.3)
Disease progression	0	1 (3.1)	4 (5.7)	5 (3.4)	9 (4.2)	0	10 (3.5)
Other	0	1 (3.1)	2 (2.9)	5 (3.4)	7 (3.3)	0	8 (2.8)

DLBCL=diffuse large B-cell lymphoma; s101=study ADCT-402-101; s201=study ADCT-402-201

Source: ISS Table 1.3.28 (dataset: adsl)

TEAEs with a Fatal Outcome

Table 26 summarizes TEAEs with a fatal outcome by SOC and preferred term in DLBCL patients who received loncastuximab tesirine monotherapy.

In the 284 patients in all doses combined, 7.7% of patients had TEAEs with a fatal outcome, but only lung infection (0.4%) was assessed as treatment-related.

The most common TEAEs with a fatal outcome pertained to the underlying DLBCL, 3.5% total, with specific events, as follows: disease progression in 1.8% of patients, DLBCL in 1.4% of patients, and lymphoma in 0.4% of patients. Gastrointestinal hemorrhage and sepsis both occurred in 0.7% of patients.

Table 26: Applicant-Fatal TEAEs by SOC and Preferred Term-Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

			150 µg/kg				
System Organ Class Preferred Term	**<=90 µg/kg (N=10)**	**120 µg/kg (N=32)**	**s101 (N=70)**	**s201 (N=145)**	**subtotal (N=215)**	**200 µg/kg (N=27)**	**All Doses (N=284)**
Patients with any Fatal TEAE	0	3 (9.4)	11 (15.7)	8 (5.5)	19 (8.8)	0	22 (7.7)
Gastrointestinal disorders	0	1 (3.1)	2 (2.9)	1 (0.7)	3 (1.4)	0	4 (1.4)
Gastrointestinal haemorrhage	0	1 (3.1)	1 (1.4)	0	1 (0.5)	0	2 (0.7)
Abdominal compartment syndrome	0	0	1 (1.4)	0	1 (0.5)	0	1 (0.4)
Small intestinal perforation	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)
General disorders and administration site conditions	0	1 (3.1)	3 (4.3)	1 (0.7)	4 (1.9)	0	5 (1.8)
Disease progression	0	1 (3.1)	3 (4.3)	1 (0.7)	4 (1.9)	0	5 (1.8)
Infections and infestations	0	0	2 (2.9)	3 (2.1)	5 (2.3)	0	5 (1.8)
Sepsis	0	0	1 (1.4)	1 (0.7)	2 (0.9)	0	2 (0.7)
Lung infection	0	0	1 (1.4)	0	1 (0.5)	0	1 (0.4)
Pneumonia	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)
Septic shock	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)
Injury, poisoning and procedural complications	0	0	1 (1.4)	0	1 (0.5)	0	1 (0.4)
Subdural haematoma	0	0	1 (1.4)	0	1 (0.5)	0	1 (0.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (3.1)	3 (4.3)	1 (0.7)	4 (1.9)	0	5 (1.8)
Diffuse large B-cell lymphoma	0	1 (3.1)	2 (2.9)	1 (0.7)	3 (1.4)	0	4 (1.4)
Lymphoma	0	0	1 (1.4)	0	1 (0.5)	0	1 (0.4)
Renal and urinary disorders	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)
Acute kidney injury	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)
Respiratory, thoracic and mediastinal disorders	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)
Haemoptysis	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)

DLBCL=diffuse large B-cell lymphoma; MedDRA=Medical Dictionary for Regulatory Activities; s101=study ADCT-402-101; s201=study ADCT-402-201; SOC=system organ class; TEAE=treatment-emergent adverse event
Adverse events were coded using MedDRA version 22.0. For each SOC and preferred term, patients were included only once.
Source: ISS Table 1.3.16.1 (datasets: adae, adsl)

The Applicant's Position:

Disease progression was the most common reason for all deaths. The most common TEAEs with a fatal outcome pertained to the underlying DLBCL.

The FDA's Assessment:
The table below provides a summary of deaths in the safety population. Of the 145 patients in the ADCT-402-201 trial, there were 4 fatal treatment-emergent adverse events, which included sepsis or septic shock, pneumonia, and small intestine perforation. Of the additional patients included in the 150 µg/kg dose pool (N = 215), there were 4 additional fatal treatment-emergent adverse events that included sepsis, pneumonia, abdominal compartment syndrome, and subdural hematoma (secondary to a fall). As noted, the most common fatal adverse events were due to infection.

Table 27: Summary of Deaths in Safety Population - FDA Review

Primary Cause of Death	**ADCT-402-201 N = 145 n (%)**	**150 µg/kg Dose Pool N = 215 n (%)**
Death within 30 days of last dose of loncastuximab	8 (5%)	19 (9%)
Disease progression	4 (3%)	11 (5%)
Adverse event		
Sepsis	2 (1%)	3 (1%)
Pneumonia	1 (<1%)	2 (<1%)
Small intestine perforation	1 (<1%)	1 (<1%)
Abdominal compartment syndrome	0	1 (<1%)
Subdural hematoma	0	1 (<1%)
Source: FDA review of narratives and ADSL and ADAE datasets		

Serious Adverse Events
Data:
In the 284 DLBCL patients in all doses combined, 37.7% of patients had at least one serious TEAE and 12.3% had at least one serious TEAE assessed as treatment-related. The majority of these patients had serious TEAEs Grade 3 or higher. The incidence of these and those that were assessed as treatment-related, respectively, was as follows: Grade 3 (19.4% and 8.5%), Grade 4 (4.2% and 2.1%), and Grade 5 (7.7% and 0.4%).

Most Common
Table 28 summarizes the most common (≥1% of patients in all doses combined) serious TEAEs by preferred term in DLBCL patients who received loncastuximab tesirine monotherapy.

In the 284 DLBCL patients in all doses combined, the incidence of the most common serious TEAEs and those that were assessed as treatment-related, respectively, was as follows: pyrexia (3.2% and 0.7%), febrile neutropenia (2.8% and 2.5%), abdominal pain and hypercalcemia (2.1% and 0.4% each), pleural effusion (1.8% and 1.4%), dyspnea (1.8% and 1.1%), disease progression

(1.8% and 0%), DLBCL (1.4% and 0%), lung infection and pericardial effusion (1.1% and 1.1% each), anemia and noncardiac chest pain (1.1% and 0.7% each), mental status changes (1.1% and 0.4%), and acute kidney injury and sepsis (1.1% and 0% each).

Table 28: Applicant-Most Common (≥1% of Patients in All Doses Combined) Serious TEAEs by Preferred Term-Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

			150 µg/kg				
Preferred Term	**<=90 µg/kg (N=10)**	**120 µg/kg (N=32)**	**s101 (N=70)**	**s201 (N=145)**	**subtotal (N=215)**	**200 µg/kg (N=27)**	**All Doses (N=284)**
Patients with any serious TEAE	2 (20.0)	12 (37.5)	30 (42.9)	57 (39.3)	87 (40.5)	6 (22.2)	107 (37.7)
Pyrexia	0	4 (12.5)	1 (1.4)	4 (2.8)	5 (2.3)	0	9 (3.2)
Febrile neutropenia	1 (10.0)	0	2 (2.9)	5 (3.4)	7 (3.3)	0	8 (2.8)
Abdominal pain	0	1 (3.1)	1 (1.4)	3 (2.1)	4 (1.9)	1 (3.7)	6 (2.1)
Hypercalcaemia	0	0	0	6 (4.1)	6 (2.8)	0	6 (2.1)
Disease progression	0	1 (3.1)	3 (4.3)	1 (0.7)	4 (1.9)	0	5 (1.8)
Dyspnoea	0	1 (3.1)	3 (4.3)	1 (0.7)	4 (1.9)	0	5 (1.8)
Pleural effusion	0	0	1 (1.4)	3 (2.1)	4 (1.9)	1 (3.7)	5 (1.8)
Diffuse large B-cell lymphoma	0	1 (3.1)	2 (2.9)	1 (0.7)	3 (1.4)	0	4 (1.4)
Acute kidney injury	0	0	1 (1.4)	2 (1.4)	3 (1.4)	0	3 (1.1)
Anaemia	0	1 (3.1)	0	2 (1.4)	2 (0.9)	0	3 (1.1)
Lung infection	0	1 (3.1)	1 (1.4)	1 (0.7)	2 (0.9)	0	3 (1.1)
Mental status changes	1 (10.0)	0	0	2 (1.4)	2 (0.9)	0	3 (1.1)
Non-cardiac chest pain	0	1 (3.1)	0	2 (1.4)	2 (0.9)	0	3 (1.1)
Pericardial effusion	0	1 (3.1)	0	2 (1.4)	2 (0.9)	0	3 (1.1)
Sepsis	0	0	2 (2.9)	1 (0.7)	3 (1.4)	0	3 (1.1)

DLBCL=diffuse large B-cell lymphoma; MedDRA=Medical Dictionary for Regulatory Activities; s101=study ADCT-402-101; s201=study ADCT-402-201; TEAE=treatment-emergent adverse event
Adverse events were coded using MedDRA version 22.0. For each preferred term, patients were included only once.
Source: ISS Table 1.3.15 (datasets: adae, adsl)

The Applicant's Position:
The incidence and type of SAEs is representative of the overall safety profile of loncastuximab tesirine. These data indicate that loncastuximab tesirine is tolerable.

The FDA's Assessment:
In general, the FDA agrees with the Applicant's summary of all-cause serious treatment-emergent adverse events. For safety, the FDA considers all-cause treatment-emergent adverse events in the evaluation versus those indicated as treatment-related by the Applicant. The table below provides a summary of the SAEs, using grouped preferred terms, in the 145 patients from ADCT-402-201 and the 215 patients in the 150 µg/kg pool.

Table 29: Summary of Serious Adverse Events in Safety Population - FDA Review

Serious Adverse Events (SAE)	ADCT-402-201 N = 145	150 µg/kg Dose Pool N = 215
Any SAE	39%	40%
Grade ≥3 SAE	34%	34%
SAE in ≥5% by System Organ Class		
Infection and infestations	8%	9%
General disorders	8%	7%
Gastrointestinal disorders	6%	7%
Metabolism and nutrition disorders	5%	5%
Respiratory disorders	5%	6%
SAE in ≥2% by Preferred Term or Grouped Preferred Term		
Hypercalcemia	4%	3%
Febrile neutropenia	3%	3%
Pneumonia	3%	3%
Pyrexia	3%	2%
Edema	2%	2%
Pleural effusion	2%	2%
Sepsis	2%	3%
Abdominal pain	2%	2%
Musculoskeletal pain	2%	1%
Source: FDA review of ADAE dataset		

Dropouts and/or Discontinuations Due to Adverse Effects

Data:
In the 284 DLBCL patients in all doses combined, 18.3% of patients had at least one TEAE that led to treatment withdrawal and 14.4% had at least one treatment-related event. The incidence of Grade 3 or higher events and those assessed as treatment-related, respectively, was as follows: Grade 3 (6.0% and 4.2%), Grade 4 (2.5% and 2.5%), and Grade 5 (1.8% and 0%).

Most Common
Table 30 summarizes the most common (≥1% of patients in all doses combined) TEAEs leading to treatment withdrawal by preferred term in DLBCL patients who received loncastuximab tesirine monotherapy.

In the 284 patients, the most common TEAEs leading to treatment withdrawal and those that were assessed as treatment-related, respectively, were as follows: GGT increased (6.7% and 6.3%); thrombocytopenia (2.1% and 1.8%); edema peripheral (2.1% and 2.1%); and pericardial

effusion, localized edema, and blood alkaline phosphatase increased (1.1% and 1.1% each); and pleural effusion (1.1% and 0.7%).

Table 30: Applicant-TEAEs Leading to Treatment Withdrawal (≥1% of Patients in All Doses Combined) by Preferred Term-Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

			150 µg/kg				
Preferred Term	<=90 µg/kg (N=10)	120 µg/kg (N=32)	s101 (N=70)	s201 (N=145)	subtotal (N=215)	200 µg/kg (N=27)	All Doses (N=284)
Patient with any treatment withdrawal TEAE	1 (10.0)	5 (15.6)	8 (11.4)	34 (23.4)	42 (19.5)	4 (14.8)	52 (18.3)
Gamma-glutamyltransferase increased	1 (10.0)	1 (3.1)	1 (1.4)	15 (10.3)	16 (7.4)	1 (3.7)	19 (6.7)
Thrombocytopenia	0	0	2 (2.9)	2 (1.4)	4 (1.9)	2 (7.4)	6 (2.1)
Oedema peripheral	0	0	2 (2.9)	4 (2.8)	6 (2.8)	0	6 (2.1)
Pericardial effusion	0	0	1 (1.4)	2 (1.4)	3 (1.4)	0	3 (1.1)
Localised oedema	0	0	0	3 (2.1)	3 (1.4)	0	3 (1.1)
Blood alkaline phosphatase increased	1 (10.0)	1 (3.1)	0	1 (0.7)	1 (0.5)	0	3 (1.1)
Pleural effusion	0	0	0	3 (2.1)	3 (1.4)	0	3 (1.1)

CTCAE=Common Terminology Criteria for Adverse Events; DLBCL=diffuse large B-cell lymphoma; MedDRA=Medical Dictionary for Regulatory Activities; s101=study ADCT-402-101; s201=study ADCT-402-201; TEAE=treatment-emergent adverse event
Adverse events were coded using MedDRA version 22.0 and graded using CTCAE v4.0. For each preferred term, patients were included only once at the maximum severity.
Source: ISS Table 1.3.14 (dataset: adae, adsl)

The Applicant's Position:
The incidence and type of the most common TEAEs that led to treatment withdrawal is representative of the overall safety profile of loncastuximab tesirine (incidence by TEAE ranged from 1.1% to 6.7%). These data indicate that loncastuximab tesirine is tolerable.

The FDA's Assessment:
In general, the FDA agrees with the Applicant position. For safety, the FDA considers all-cause treatment-emergent adverse events in the evaluation versus those indicated as treatment-related by the Applicant. The table below provides a summary of the 145 patients in ADCT-402-201 and the 215 patients in the 150 µg/kg pool.

Table 31: Summary of Adverse Events Leading to Treatment Discontinuation - FDA Review

Outcome/event	ADCT-402-201 N = 145	150 µg/kg Dose Pool N = 215
Any TEAE leading to discontinuation	23%	19%
GGT increased	10%	7%
Edema	3%	3%
Localized edema	2%	1%

Pleural effusion	2%	1%
Pericardial effusion	1%	1%
Thrombocytopenia	<1%	2%

Abbreviations: GGT, gamma-glutamyl transferase, TEAE, treatment-emergent adverse event
Source: FDA Review of ADAE dataset

Dose Interruption/Reduction Due to Adverse Effects

Data:

Dose Delay

In the 284 DLBCL patients in all doses combined, 43.0% of patients had at least one TEAE leading to dose delay and 35.6% had at least one treatment-related event. The incidence of Grade 3 or higher events and those assessed as treatment-related, respectively, was as follows: Grade 3 (19.0% and 13.4%) and Grade 4 (9.2% and 8.8%). In the ADCT-402-201 study using optimized dosing, delays were generally short, with approximately 80% of the delays being two weeks or less.

Most Common

Table 32 summarizes the most common (≥1% patients in all doses combined) TEAEs leading to dose delay by preferred term in DLBCL patients who received loncastuximab tesirine monotherapy.

In the 284 patients, the most common TEAEs leading to dose delay and those that were assessed as treatment-related, respectively, were as follows: GGT increased (15.1% and 13.0%); neutropenia (9.5% and 8.5%); thrombocytopenia (6.0% and 3.9%); edema peripheral (3.2% and 2.8%); blood alkaline phosphatase increased (2.8% and 2.1%); ALT increased (2.5% and 2.5%); leukopenia, fatigue, and pleural effusion (2.1% and 1.8% each); anemia (2.1% and 1.4%); AST increased, platelet count decreased, and rash (1.8% and 1.8% each); pyrexia (1.8% and 0.7%); photosensitivity reaction (1.4% and 1.4%); face edema (1.4% and 1.1%); abdominal pain and blood bilirubin increased (1.4% and 0.7% each); erythema (1.1% and 0.7%); and hypophosphatemia (1.1% and 0%).

Table 32: Applicant-Most Common (≥1% of Patients in All Doses Combined) TEAEs Leading to Dose Delay by Preferred Term-Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

			150 µg/kg				
Preferred Term	<=90 µg/kg (N=10)	120 µg/kg (N=32)	s101 (N=70)	s201 (N=145)	subtotal (N=215)	200 µg/kg (N=27)	All Doses (N=284)
Patient with any dose delayed TEAE	1 (10.0)	14 (43.8)	26 (37.1)	74 (51.0)	100 (46.5)	7 (25.9)	122 (43.0)
Gamma-glutamyltransferase increased	0	3 (9.4)	7 (10.0)	30 (20.7)	37 (17.2)	3 (11.1)	43 (15.1)
Neutropenia	1 (10.0)	0	6 (8.6)	18 (12.4)	24 (11.2)	2 (7.4)	27 (9.5)
Thrombocytopenia	0	0	4 (5.7)	13 (9.0)	17 (7.9)	0	17 (6.0)
Oedema peripheral	0	2 (6.3)	2 (2.9)	5 (3.4)	7 (3.3)	0	9 (3.2)
Blood alkaline phosphatase increased	0	0	2 (2.9)	6 (4.1)	8 (3.7)	0	8 (2.8)
Alanine aminotransferase increased	0	0	2 (2.9)	5 (3.4)	7 (3.3)	0	7 (2.5)
Anaemia	0	1 (3.1)	1 (1.4)	4 (2.8)	5 (2.3)	0	6 (2.1)
Leukopenia	0	0	0	6 (4.1)	6 (2.8)	0	6 (2.1)
Fatigue	1 (10.0)	2 (6.3)	3 (4.3)	0	3 (1.4)	0	6 (2.1)
Pleural effusion	0	1 (3.1)	2 (2.9)	2 (1.4)	4 (1.9)	1 (3.7)	6 (2.1)
Pyrexia	0	1 (3.1)	1 (1.4)	3 (2.1)	4 (1.9)	0	5 (1.8)
Aspartate aminotransferase increased	0	0	2 (2.9)	3 (2.1)	5 (2.3)	0	5 (1.8)
Platelet count decreased	0	0	3 (4.3)	0	3 (1.4)	2 (7.4)	5 (1.8)
Rash	0	1 (3.1)	1 (1.4)	2 (1.4)	3 (1.4)	1 (3.7)	5 (1.8)
Abdominal pain	0	0	1 (1.4)	3 (2.1)	4 (1.9)	0	4 (1.4)
Face oedema	0	2 (6.3)	0	2 (1.4)	2 (0.9)	0	4 (1.4)
Blood bilirubin increased	0	0	2 (2.9)	2 (1.4)	4 (1.9)	0	4 (1.4)
Photosensitivity reaction	0	0	0	4 (2.8)	4 (1.9)	0	4 (1.4)
Hypophosphataemia	0	0	0	3 (2.1)	3 (1.4)	0	3 (1.1)
Erythema	0	0	0	3 (2.1)	3 (1.4)	0	3 (1.1)

DLBCL=diffuse large B-cell lymphoma; MedDRA=Medical Dictionary for Regulatory Activities; s101=study ADCT-402-101; s201=study ADCT-402-201; TEAE=treatment-emergent adverse event
Adverse events were coded using MedDRA version 22.0. For each preferred term, patients were included only once at the maximum severity.
Source: ISS Table 1.3.12 (datasets: adae, adsl)

Dose Reduction

In the 284 DLBCL patients in all doses combined, 7.4% of patients had at least one TEAE leading to dose reduction and 6.7% had at least one treatment-related event. The incidence of Grade 3 or higher events and those assessed as treatment-related, respectively, was as follows: Grade 3 (1.8% and 1.8%) and Grade 4 (0.7% and 0.7%).

Most Common

In the 284 DLBCL patients who received loncastuximab tesirine monotherapy, the most common (≥1% patients in all doses combined) TEAEs leading to dose reduction and those that were assessed as treatment-related, respectively, included GGT increased (2.5% and 1.8%).

The Applicant's Position:
The majority of patients received treatment as intended. Dose delays were required more often than dose reductions to manage toxicities. The incidence and type of the most common TEAEs that led to dose delay or dose reduction is representative of the overall safety profile of loncastuximab tesirine (incidence by TEAE ranged from 1.1% to 15.1% for dose delay and was 2.5% for dose reduction). These data indicate that loncastuximab tesirine is tolerable.

The FDA's Assessment:
The FDA agrees with the Applicant's position and the summary table above providing the all-cause treatment-emergent adverse events leading to dose delay. For safety, the FDA considers all-cause treatment-emergent adverse events in the evaluation versus those indicated as treatment-related by the Applicant. The table below provides a summary of all-cause treatment-emergent adverse events, using grouped preferred terms, leading to dose delay or dose reduction in the 145 patients in ADCT-402-201 and the 215 patients in the 150 µg/kg pool.

Table 33: Summary of Adverse Events Leading to Dose Reduction or Dose Delay - FDA Review

Outcome/event	ADCT-402-201 N = 145	150 µg/kg Dose Pool N = 215
Any TEAE leading to dose reduction	8%	7%
GGT increased	4%	3%
Any TEAE leading to dose delay	51%	46%
GGT increased	21%	17%
Neutropenia	12%	11%
Thrombocytopenia	9%	9%
Edema	5%	5%
Rash	5%	5%
Abbreviations: GGT, gamma-glutamyl transferase, TEAE, treatment-emergent adverse event Source: FDA Review of ADAE dataset		

Significant Adverse Events
Data:
Selected TEAEs by grouped AE are described in detail in Section 8.2.5. Other significant AEs leading to dose modification and/or discontinuation are described in detail under Dropouts and/or Discontinuations Due to Adverse Effects in this section.

The Applicant's Position:
See The Applicant's Position for selected TEAEs by grouped AEs in Section 8.2.5 and for Dropouts and/or Discontinuations Due to Adverse Effects in this section.

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

Treatment-emergent Adverse Events and Adverse Reactions

Overview of TEAEs
Table 34 is an overall summary of TEAEs in DLBCL patients who received loncastuximab tesirine monotherapy.

In the 284 patients in all doses combined, at least one TEAE occurred in 98.9% of patients, at least one treatment-related TEAE in 82.4% of patients, and at least one Grade 3 or higher TEAE in 73.2% of patients. At least one serious TEAE occurred in 37.7% of patients and 7.7% of patients had an event with a fatal outcome. At least one TEAE led to loncastuximab tesirine dose delay or reduction in 43.7% of patients and treatment withdrawal in 18.3% of patients.

Table 34: Applicant-Overall Summary of TEAEs-Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

Treatment-emergent adverse event	<=90 µg/kg (N=10)	120 µg/kg (N=32)	150 µg/kg s101 (N=70)	150 µg/kg s201 (N=145)	150 µg/kg subtotal (N=215)	200 µg/kg (N=27)	All Doses (N=284)
Number of TEAEs	93	453	1061	1761	2822	458	3826
Patients with any TEAE	10 (100)	32 (100)	69 (98.6)	143 (98.6)	212 (98.6)	27 (100)	281 (98.9)
Patients with any Grade 3 or higher TEAE	4 (40.0)	23 (71.9)	53 (75.7)	105 (72.4)	158 (73.5)	23 (85.2)	208 (73.2)
Patients with any TEAE related to ADCT-402	7 (70.0)	29 (90.6)	58 (82.9)	117 (80.7)	175 (81.4)	23 (85.2)	234 (82.4)
Patients with any TEAE leading to ADCT-402 dose delay or reduction	1 (10.0)	14 (43.8)	27 (38.6)	75 (51.7)	102 (47.4)	7 (25.9)	124 (43.7)
Patients with any TEAE leading to ADCT-402 withdrawal	1 (10.0)	5 (15.6)	8 (11.4)	34 (23.4)	42 (19.5)	4 (14.8)	52 (18.3)
Patients with any serious TEAE	2 (20.0)	12 (37.5)	30 (42.9)	57 (39.3)	87 (40.5)	6 (22.2)	107 (37.7)
Patients with any TEAE with fatal outcome	0	3 (9.4)	11 (15.7)	8 (5.5)	19 (8.8)	0	22 (7.7)

ADCT-402=loncastuximab tesirine; CTCAE=Common Terminology Criteria for Adverse Events; DLBCL=diffuse large B-cell lymphoma; s101=study ADCT-402-101; s201=study ADCT-402-201; TEAE=treatment-emergent adverse event
Related TEAEs include TEAEs that were considered by the Investigator to be possibly or probably related to the study drug, or TEAEs with a missing relationship on the case report form. Adverse events were graded using CTCAE v4.0. For each category (except for Number of TEAEs), patients were included only once, even if they experienced multiple events in that category.
Source: ISS Table 1.3.1 (datasets: adsl, adae)

Most Common

Table 35 summarizes the most common (≥10% of patients in all doses combined) TEAEs by preferred term in DLBCL patients who received loncastuximab tesirine monotherapy.

In the 284 patients, at least one TEAE occurred in 98.9% of patients. The most common TEAEs included fatigue (34.9%), followed by GGT increased (34.2%), neutropenia (31.3%), anemia (28.2%), nausea and thrombocytopenia (27.1% each), edema peripheral (24.3%), cough (19.7%), rash (19.0%), blood alkaline phosphatase increased (18.3%), pyrexia (17.3%), constipation, decreased appetite, and dyspnea (16.5% each), AST increased and diarrhea (16.2% each), ALT increased and vomiting (15.5% each), hypokalemia and pleural effusion (14.4% each), abdominal pain (13.4%), pruritus (11.6%), and hypomagnesemia and hypophosphatemia (10.2% each).

Table 35: Applicant-Most Common (≥10% of Patients in All Doses Combined) TEAEs by Preferred Term-Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

			150 µg/kg				
Preferred Term	**<=90 µg/kg (N=10)**	**120 µg/kg (N=32)**	**s101 (N=70)**	**s201 (N=145)**	**subtotal (N=215)**	**200 µg/kg (N=27)**	**All Doses (N=284)**
Patients with any TEAE	10 (100.0)	32 (100.0)	69 (98.6)	143 (98.6)	212 (98.6)	27 (100.0)	281 (98.9)
Fatigue	4 (40.0)	19 (59.4)	25 (35.7)	40 (27.6)	65 (30.2)	11 (40.7)	99 (34.9)
Gamma-glutamyltransferase increased	2 (20.0)	10 (31.3)	16 (22.9)	59 (40.7)	75 (34.9)	10 (37.0)	97 (34.2)
Neutropenia	1 (10.0)	5 (15.6)	17 (24.3)	57 (39.3)	74 (34.4)	9 (33.3)	89 (31.3)
Anaemia	3 (30.0)	5 (15.6)	24 (34.3)	38 (26.2)	62 (28.8)	10 (37.0)	80 (28.2)
Nausea	2 (20.0)	7 (21.9)	23 (32.9)	34 (23.4)	57 (26.5)	11 (40.7)	77 (27.1)
Thrombocytopenia	1 (10.0)	8 (25.0)	13 (18.6)	48 (33.1)	61 (28.4)	7 (25.9)	77 (27.1)
Oedema peripheral	1 (10.0)	9 (28.1)	21 (30.0)	29 (20.0)	50 (23.3)	9 (33.3)	69 (24.3)
Cough	0	5 (15.6)	13 (18.6)	32 (22.1)	45 (20.9)	6 (22.2)	56 (19.7)
Rash	1 (10.0)	5 (15.6)	24 (34.3)	19 (13.1)	43 (20.0)	5 (18.5)	54 (19.0)
Blood alkaline phosphatase increased	1 (10.0)	4 (12.5)	12 (17.1)	29 (20.0)	41 (19.1)	6 (22.2)	52 (18.3)
Pyrexia	1 (10.0)	6 (18.8)	8 (11.4)	28 (19.3)	36 (16.7)	6 (22.2)	49 (17.3)
Constipation	0	10 (31.3)	18 (25.7)	17 (11.7)	35 (16.3)	2 (7.4)	47 (16.5)
Decreased appetite	2 (20.0)	5 (15.6)	9 (12.9)	22 (15.2)	31 (14.4)	9 (33.3)	47 (16.5)
Dyspnoea	0	7 (21.9)	17 (24.3)	17 (11.7)	34 (15.8)	6 (22.2)	47 (16.5)
Aspartate aminotransferase increased	0	3 (9.4)	11 (15.7)	23 (15.9)	34 (15.8)	9 (33.3)	46 (16.2)
Diarrhoea	2 (20.0)	2 (6.3)	13 (18.6)	25 (17.2)	38 (17.7)	4 (14.8)	46 (16.2)
Alanine aminotransferase increased	0	4 (12.5)	12 (17.1)	23 (15.9)	35 (16.3)	5 (18.5)	44 (15.5)
Vomiting	1 (10.0)	5 (15.6)	14 (20.0)	19 (13.1)	33 (15.3)	5 (18.5)	44 (15.5)
Hypokalaemia	1 (10.0)	2 (6.3)	14 (20.0)	22 (15.2)	36 (16.7)	2 (7.4)	41 (14.4)
Pleural effusion	1 (10.0)	6 (18.8)	13 (18.6)	15 (10.3)	28 (13.0)	6 (22.2)	41 (14.4)
Abdominal pain	1 (10.0)	7 (21.9)	8 (11.4)	16 (11.0)	24 (11.2)	6 (22.2)	38 (13.4)
Pruritus	1 (10.0)	4 (12.5)	6 (8.6)	18 (12.4)	24 (11.2)	4 (14.8)	33 (11.6)
Hypomagnesaemia	0	1 (3.1)	8 (11.4)	20 (13.8)	28 (13.0)	0	29 (10.2)
Hypophosphataemia	1 (10.0)	2 (6.3)	1 (1.4)	23 (15.9)	24 (11.2)	2 (7.4)	29 (10.2)

DLBCL=diffuse large B-cell lymphoma; MedDRA=Medical Dictionary for Regulatory Activities; s101=study ADCT-402-101; s201=study ADCT-402-201; TEAE=treatment-emergent adverse event
The 10% cutoff was based on All Doses. Adverse events were coded using MedDRA version 22.0. For each preferred term, patients were included only once.
Source: ISS Table 1.3.3 (datasets: adae, adsl)

Treatment-related TEAEs

Table 36 is an overall summary of treatment-related TEAEs by preferred term in DLBCL patients who received loncastuximab tesirine monotherapy.

In the 284 patients in all doses combined, at least one treatment-related TEAE occurred in 82.4% of patients and at least one Grade 3 or higher treatment-related TEAE in 51.8% of patients. At least one treatment-related serious TEAE occurred in 12.3% of patients and 0.4% of patients had a treatment-related event with a fatal outcome. At least one treatment-related TEAE led to loncastuximab tesirine dose delay or reduction in 36.3% of patients and treatment withdrawal in 14.4% of patients.

Table 36: Applicant-Overall Summary of Treatment-related TEAEs-Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

			150 µg/kg				
Related treatment-emergent adverse event	**<=90 µg/kg (N=10)**	**120 µg/kg (N=32)**	**s101 (N=70)**	**s201 (N=145)**	**subtotal (N=215)**	**200 µg/kg (N=27)**	**All Doses (N=284)**
Number of related TEAEs	48	273	491	846	1337	229	1887
Patients with any related TEAE	7 (70.0)	29 (90.6)	58 (82.9)	117 (80.7)	175 (81.4)	23 (85.2)	234 (82.4)
Patients with any Grade 3 or higher related TEAE	2 (20.0)	19 (59.4)	35 (50.0)	74 (51.0)	109 (50.7)	17 (63.0)	147 (51.8)
Patients with any related TEAE leading to ADCT-402 dose delay or reduction	1 (10.0)	12 (37.5)	21 (30.0)	63 (43.4)	84 (39.1)	6 (22.2)	103 (36.3)
Patients with any related TEAE leading to ADCT-402 withdrawal	1 (10.0)	5 (15.6)	7 (10.0)	24 (16.6)	31 (14.4)	4 (14.8)	41 (14.4)
Patients with any related serious TEAE	1 (10.0)	3 (9.4)	8 (11.4)	22 (15.2)	30 (14.0)	1 (3.7)	35 (12.3)
Patients with any related TEAE with fatal outcome	0	0	1 (1.4)	0	1 (0.5)	0	1 (0.4)

ADCT-402=Loncastuximab tesirine; CTCAE=Common Terminology Criteria for Adverse Events; DLBCL=diffuse large B-cell lymphoma; s101=study ADCT-402-101; s201=study ADCT-402-201; TEAE=treatment-emergent adverse event
Related TEAEs include TEAEs that were considered by the Investigator to be possibly or probably related to the study drug, or TEAEs with a missing relationship on the case report form. Adverse events were graded using CTCAE v4.0. For each category (except for Number of TEAEs), patients were included only once, even if they experienced multiple events in that category.
Source: ISS Table 1.3.1.0 (datasets: adsl, adae)

Most Common

Table 37 summarizes the most common (≥10% of patients in all doses combined) treatment-related TEAEs by preferred term in the 284 DLBCL patients who received loncastuximab tesirine monotherapy.

The most common treatment-related TEAEs included GGT increased (28.5%), fatigue (25.7%), neutropenia (23.9%), rash (18.0%), edema peripheral (17.6%), thrombocytopenia (16.9%), nausea (16.5%), blood alkaline phosphatase increased (14.8%), anemia (14.4%), pleural effusion (12.7%), AST increased (12.3%), and ALT increased (10.9%).

Table 37: Applicant-Most Common (≥10% of Patients in All Doses Combined) Treatment-related TEAEs by Preferred Term-Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

			150 µg/kg				
Preferred Term	<=90 µg/kg (N=10)	120 µg/kg (N=32)	s101 (N=70)	s201 (N=145)	subtotal (N=215)	200 µg/kg (N=27)	All Doses (N=284)
Patients with any Related TEAE	7 (70.0)	29 (90.6)	58 (82.9)	117 (80.7)	175 (81.4)	23 (85.2)	234 (82.4)
Gamma-glutamyltransferase increased	2 (20.0)	10 (31.3)	10 (14.3)	50 (34.5)	60 (27.9)	9 (33.3)	81 (28.5)
Fatigue	3 (30.0)	15 (46.9)	17 (24.3)	28 (19.3)	45 (20.9)	10 (37.0)	73 (25.7)
Neutropenia	1 (10.0)	5 (15.6)	14 (20.0)	41 (28.3)	55 (25.6)	7 (25.9)	68 (23.9)
Rash	0	5 (15.6)	24 (34.3)	18 (12.4)	42 (19.5)	4 (14.8)	51 (18.0)
Oedema peripheral	1 (10.0)	9 (28.1)	16 (22.9)	20 (13.8)	36 (16.7)	4 (14.8)	50 (17.6)
Thrombocytopenia	1 (10.0)	7 (21.9)	9 (12.9)	26 (17.9)	35 (16.3)	5 (18.5)	48 (16.9)
Nausea	1 (10.0)	2 (6.3)	12 (17.1)	24 (16.6)	36 (16.7)	8 (29.6)	47 (16.5)
Blood alkaline phosphatase increased	1 (10.0)	4 (12.5)	5 (7.1)	27 (18.6)	32 (14.9)	5 (18.5)	42 (14.8)
Anaemia	2 (20.0)	4 (12.5)	10 (14.3)	19 (13.1)	29 (13.5)	6 (22.2)	41 (14.4)
Pleural effusion	1 (10.0)	6 (18.8)	11 (15.7)	12 (8.3)	23 (10.7)	6 (22.2)	36 (12.7)
Aspartate aminotransferase increased	0	3 (9.4)	6 (8.6)	19 (13.1)	25 (11.6)	7 (25.9)	35 (12.3)
Alanine aminotransferase increased	0	4 (12.5)	7 (10.0)	17 (11.7)	24 (11.2)	3 (11.1)	31 (10.9)

DLBCL=diffuse large B-cell lymphoma; MedDRA=Medical Dictionary for Regulatory Activities; s101=study ADCT-402-101; s201=study ADCT-402-201; TEAE=treatment-emergent adverse event
Related TEAEs include TEAEs that were considered by the Investigator to be possibly or probably related to the study drug, or TEAEs with a missing relationship on the case report form. Adverse events were coded using MedDRA version 22.0. For each preferred term, patients were included only once.
Source: ISS Table 1.3.17 (datasets: adae, adsl)

TEAEs by Severity

All Grades

Maximum CTCAE Grade

In the 284 DLBCL patients in all doses combined, the incidence for any TEAE by maximum CTCAE grade was highest for Grade 3 (37.7%), followed by Grade 4 (27.8%), Grade 2 (18.0%), and Grades 1 and 5 (7.7% each).

The incidence of any treatment-related TEAE by maximum CTCAE grade was also highest for Grade 3 (28.2%), followed by Grade 4 (23.2%), Grade 2 (19.7%), Grade 1 (10.9%), and Grade 5 (0.4%).

Grade 3 or Higher

Maximum CTCAE Grade 3 or Higher

In the 284 DLBCL patients in all doses combined, 73.2% of patients experienced Grade 3 or higher TEAEs and 51.8% of patients had such events assessed as treatment-related.

Most Common Grade 3 or Higher

Table 38 summarizes the most common (≥5% of patients in all doses combined) Grade 3 or higher TEAEs, by preferred term in this population.

In the 284 DLBCL patients in all doses combined, the most common Grade 3 or higher TEAEs (incidence of all and those assessed as treatment-related, respectively), were as follows: neutropenia (21.8% and 17.6%), GGT increased (17.3% and 14.1%), thrombocytopenia (15.5% and 9.5%), anemia (10.9% and 6.0%), and neutrophil count decreased (6.3% and 6.0%).

Table 38: Applicant-Most Common (≥5% of Patients in All Doses Combined) TEAEs Grade 3 and Higher by Preferred Term-Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

			150 µg/kg				
Preferred Term	**<=90 µg/kg (N=10)**	**120 µg/kg (N=32)**	**s101 (N=70)**	**s201 (N=145)**	**subtotal (N=215)**	**200 µg/kg (N=27)**	**All Doses (N=284)**
Patients with any TEAE of Grade ≥ 3	4 (40.0)	23 (71.9)	53 (75.7)	105 (72.4)	158 (73.5)	23 (85.2)	208 (73.2)
Neutropenia	1 (10.0)	4 (12.5)	14 (20.0)	37 (25.5)	51 (23.7)	6 (22.2)	62 (21.8)
Gamma-glutamyltransferase increased	1 (10.0)	6 (18.8)	12 (17.1)	24 (16.6)	36 (16.7)	6 (22.2)	49 (17.3)
Thrombocytopenia	1 (10.0)	5 (15.6)	8 (11.4)	26 (17.9)	34 (15.8)	4 (14.8)	44 (15.5)
Anaemia	2 (20.0)	2 (6.3)	10 (14.3)	15 (10.3)	25 (11.6)	2 (7.4)	31 (10.9)
Neutrophil count decreased	1 (10.0)	4 (12.5)	7 (10.0)	0	7 (3.3)	6 (22.2)	18 (6.3)

CTCAE=Common Terminology Criteria for Adverse Events; DLBCL=diffuse large B-cell lymphoma; MedDRA=Medical Dictionary for Regulatory Activities; s101=study ADCT-402-101; s201=study ADCT-402-201; TEAE=treatment-emergent adverse event
The 5% cutoff was based on All Doses. Adverse events were coded using MedDRA version 22.0, and graded using CTCAE v4.0. For each preferred term, patients were included only once.
Source: ISS Table 1.3.5 (datasets: adae, adsl)

The Applicant's Position:

The majority of patients experienced Grade 3 or higher TEAEs. The most common of these events were neutropenia, GGT increased, thrombocytopenia, anemia, and neutrophil count decreased.

The FDA's Assessment:

The FDA agrees with the Applicant's position and the summary tables above providing the all-cause treatment-emergent adverse events. For safety, the FDA considers all-cause treatment-emergent adverse events in the evaluation versus those indicated as treatment-related by the Applicant. The table below provides a summary of all-cause treatment-emergent adverse events, excluding abnormal laboratory events (see laboratory section below), using grouped preferred terms in the 145 patients in ADCT-402-201 and the 215 patients in the 150 µg/kg pool.

Table 39: Summary of Common (≥13%) Treatment Emergent Adverse Events - FDA Review

Preferred Term	ADCT-402-201 N = 145		150 µg/kg Dose Pool N = 215	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any TEAE	99%	72%	99%	73%
Fatigue	38%	1%	37%	2%
Rash	30%	2%	36%	2%
Edema	28%	3%	32%	3%
Cough	23%	<1%	24%	<1%
Musculoskeletal pain	23%	1%	23%	<1%
Nausea	23%	0	26%	<1%
Pyrexia	19%	1%	17%	1%
Diarrhea	17%	2%	18%	2%
Decreased appetite	15%	0	14%	0
Abdominal pain	14%	3%	16%	2%
Dyspnea	13%	1%	18%	2%
Vomiting	13%	0	15%	0
Pleural effusion	10%	2%	13%	3%
Abbreviations: TEAE, treatment-emergent adverse event Source: FDA review of ADAE dataset				

Laboratory Findings

Data:

Hematology

Maximum CTCAE Grade

Table 40 is a summary of the maximum postbaseline hematology CTCAE grade for parameters of interest in DLBCL patients who received loncastuximab tesirine monotherapy.

In the 284 patients in all doses combined, the majority of patients had maximum postbaseline decreases in neutrophils, platelets, leukocytes, or hemoglobin that were Grade 2 or lower. The incidence of maximum postbaseline Grade 3 or 4 values for these parameters was as follows:

- Decreases in neutrophils: Grade 4 (20.4%) and Grade 3 (13.4%)
- Decreases in platelets: Grade 4 (8.8%) and Grade 3 (13.0%)
- Decreases in leukocytes: Grade 4 (7.4%) and Grade 3 (20.8%)
- Decreases in hemoglobin: Grade 3 (11.3%)

Table 40: Applicant-Maximum Postbaseline CTCAE Grade for Hematology-Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

Parameter Toxicity Grade	<=90 µg/kg (N=10)	120 µg/kg (N=32)	150 µg/kg s101 (N=70)	150 µg/kg s201 (N=145)	150 µg/kg subtotal (N=215)	200 µg/kg (N=27)	All doses (N=284)
Hemoglobin (g/L) - DEC	10 (100.0)	31 (96.9)	69 (98.6)	145 (100.0)	214 (99.5)	26 (96.3)	281 (98.9)
Grade 0	0	1 (3.1)	2 (2.9)	9 (6.2)	11 (5.1)	0	12 (4.2)
Grade 1	5 (50.0)	18 (56.3)	25 (35.7)	76 (52.4)	101 (47.0)	11 (40.7)	135 (47.5)
Grade 2	4 (40.0)	9 (28.1)	31 (44.3)	45 (31.0)	76 (35.3)	13 (48.1)	102 (35.9)
Grade 3	1 (10.0)	3 (9.4)	11 (15.7)	15 (10.3)	26 (12.1)	2 (7.4)	32 (11.3)
Grade 4	0	0	0	0	0	0	0
Leukocytes (10^9/L) - DEC	10 (100.0)	31 (96.9)	69 (98.6)	145 (100.0)	214 (99.5)	26 (96.3)	281 (98.9)
Grade 0	4 (40.0)	7 (21.9)	22 (31.4)	45 (31.0)	67 (31.2)	1 (3.7)	79 (27.8)
Grade 1	2 (20.0)	7 (21.9)	7 (10.0)	29 (20.0)	36 (16.7)	9 (33.3)	54 (19.0)
Grade 2	2 (20.0)	11 (34.4)	16 (22.9)	34 (23.4)	50 (23.3)	5 (18.5)	68 (23.9)
Grade 3	2 (20.0)	6 (18.8)	17 (24.3)	27 (18.6)	44 (20.5)	7 (25.9)	59 (20.8)
Grade 4	0	0	7 (10.0)	10 (6.9)	17 (7.9)	4 (14.8)	21 (7.4)
Lymphocytes (10^9/L) - DEC	10 (100.0)	31 (96.9)	69 (98.6)	144 (99.3)	213 (99.1)	26 (96.3)	280 (98.6)
Grade 0	0	3 (9.4)	3 (4.3)	10 (6.9)	13 (6.0)	1 (3.7)	17 (6.0)
Grade 1	5 (50.0)	4 (12.5)	3 (4.3)	17 (11.7)	20 (9.3)	3 (11.1)	32 (11.3)
Grade 2	2 (20.0)	7 (21.9)	10 (14.3)	37 (25.5)	47 (21.9)	4 (14.8)	60 (21.1)
Grade 3	2 (20.0)	14 (43.8)	36 (51.4)	49 (33.8)	85 (39.5)	11 (40.7)	112 (39.4)
Grade 4	1 (10.0)	3 (9.4)	17 (24.3)	31 (21.4)	48 (22.3)	7 (25.9)	59 (20.8)
Neutrophils (10^9/L) - DEC	10 (100.0)	31 (96.9)	68 (97.1)	144 (99.3)	212 (98.6)	26 (96.3)	279 (98.2)
Grade 0	5 (50.0)	15 (46.9)	29 (41.4)	67 (46.2)	96 (44.7)	7 (25.9)	123 (43.3)
Grade 1	0	1 (3.1)	7 (10.0)	10 (6.9)	17 (7.9)	3 (11.1)	21 (7.4)
Grade 2	3 (30.0)	5 (15.6)	6 (8.6)	24 (16.6)	30 (14.0)	1 (3.7)	39 (13.7)
Grade 3	1 (10.0)	5 (15.6)	6 (8.6)	18 (12.4)	24 (11.2)	8 (29.6)	38 (13.4)
Grade 4	1 (10.0)	5 (15.6)	20 (28.6)	25 (17.2)	45 (20.9)	7 (25.9)	58 (20.4)
Platelets (10^9/L) - DEC	10 (100.0)	31 (96.9)	69 (98.6)	144 (99.3)	213 (99.1)	26 (96.3)	280 (98.6)
Grade 0	5 (50.0)	12 (37.5)	22 (31.4)	48 (33.1)	70 (32.6)	6 (22.2)	93 (32.7)
Grade 1	3 (30.0)	8 (25.0)	20 (28.6)	56 (38.6)	76 (35.3)	6 (22.2)	93 (32.7)
Grade 2	1 (10.0)	4 (12.5)	9 (12.9)	15 (10.3)	24 (11.2)	3 (11.1)	32 (11.3)
Grade 3	1 (10.0)	2 (6.3)	8 (11.4)	19 (13.1)	27 (12.6)	7 (25.9)	37 (13.0)
Grade 4	0	5 (15.6)	10 (14.3)	6 (4.1)	16 (7.4)	4 (14.8)	25 (8.8)

CTCAE= Common Terminology Criteria for Adverse Events; DEC=decrease; DLBCL=diffuse large B-cell lymphoma; s101=study ADCT-402-101; s201=study ADCT-402-201
Baseline was defined as the last nonmissing value before the initial administration of loncastuximab tesirine. CTCAE v4.0 was used for grading. For each parameter, patients were included only once at the maximum severity.
Source: ISS Table 1.4.3 (datasets: adsl, adlb)

TEAEs Pertaining to Hematology

In the 284 patients in all doses combined, the incidence of notable TEAEs pertaining to hematology and those assessed as treatment-related, respectively, was as follows: neutropenia (31.3% and 23.9%), anemia (28.2% and 14.4%), thrombocytopenia (27.1% and 16.9%), platelet

count decreased (8.8% and 8.1%), leukopenia (7.7% and 7.0%), neutrophil count decreased (6.7% and 6.3%), white blood cell count decreased (5.6% and 4.9%), and febrile neutropenia (2.8% and 2.5%).

TEAEs that pertained to hematology that led to treatment withdrawal included thrombocytopenia (2.1%), platelet count decreased (0.7%), and neutropenia (0.4%).

Biochemistry

LFTs

Maximum CTCAE Grade

Table 41 is a summary of the maximum postbaseline CTCAE grade for LFTs in DLBCL patients who received loncastuximab tesirine monotherapy.

In the 284 patients in all doses combined, the majority of patients had maximum postbaseline LFTs Grade 2 or lower. The incidence of maximum postbaseline Grade 3 or 4 LFT values was as follows:

- Increases in GGT: Grade 4 (1.8%) and Grade 3 (23.2%)
- Increases in ALT: Grade 4 (0.4%) and Grade 3 (4.2%)
- Increases in bilirubin: Grade 4 (0.4%) and Grade 3 (2.1%)
- Increases in alkaline phosphatase: Grade 3 (3.9%)
- Increases in AST: Grade 3 (2.8%)
- Decreases in albumin: Grade 3 (0.7%)

Table 41: Applicant-Maximum Postbaseline CTCAE Grade for LFTs-Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

Parameter Toxicity Grade	<=90 µg/kg (N=10)	120 µg/kg (N=32)	150 µg/kg s101 (N=70)	150 µg/kg s201 (N=145)	150 µg/kg subtotal (N=215)	200 µg/kg (N=27)	All doses (N=284)
Alanine Aminotransferase (U/L) - INC	10 (100.0)	31 (96.9)	69 (98.6)	145 (100.0)	214 (99.5)	26 (96.3)	281 (98.9)
Grade 0	8 (80.0)	21 (65.6)	35 (50.0)	89 (61.4)	124 (57.7)	16 (59.3)	169 (59.5)
Grade 1	2 (20.0)	5 (15.6)	23 (32.9)	41 (28.3)	64 (29.8)	7 (25.9)	78 (27.5)
Grade 2	0	2 (6.3)	7 (10.0)	10 (6.9)	17 (7.9)	2 (7.4)	21 (7.4)
Grade 3	0	3 (9.4)	4 (5.7)	4 (2.8)	8 (3.7)	1 (3.7)	12 (4.2)
Grade 4	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)
Albumin (g/L) - DEC	10 (100.0)	31 (96.9)	68 (97.1)	144 (99.3)	212 (98.6)	26 (96.3)	279 (98.2)
Grade 0	6 (60.0)	12 (37.5)	28 (40.0)	79 (54.5)	107 (49.8)	8 (29.6)	133 (46.8)
Grade 1	3 (30.0)	16 (50.0)	22 (31.4)	41 (28.3)	63 (29.3)	13 (48.1)	95 (33.5)
Grade 2	1 (10.0)	3 (9.4)	18 (25.7)	22 (15.2)	40 (18.6)	5 (18.5)	49 (17.3)
Grade 3	0	0	0	2 (1.4)	2 (0.9)	0	2 (0.7)
Grade 4	0	0	0	0	0	0	0
Alkaline Phosphatase (U/L) - INC	10 (100.0)	31 (96.9)	68 (97.1)	145 (100.0)	213 (99.1)	26 (96.3)	280 (98.6)
Grade 0	8 (80.0)	17 (53.1)	27 (38.6)	67 (46.2)	94 (43.7)	15 (55.6)	134 (47.2)
Grade 1	1 (10.0)	9 (28.1)	32 (45.7)	61 (42.1)	93 (43.3)	4 (14.8)	107 (37.7)
Grade 2	0	1 (3.1)	6 (8.6)	14 (9.7)	20 (9.3)	7 (25.9)	28 (9.9)
Grade 3	1 (10.0)	4 (12.5)	3 (4.3)	3 (2.1)	6 (2.8)	0	11 (3.9)
Grade 4	0	0	0	0	0	0	0
Aspartate Aminotransferase (U/L) - INC	10 (100.0)	31 (96.9)	69 (98.6)	145 (100.0)	214 (99.5)	26 (96.3)	281 (98.9)
Grade 0	5 (50.0)	16 (50.0)	21 (30.0)	70 (48.3)	91 (42.3)	8 (29.6)	120 (42.3)
Grade 1	5 (50.0)	11 (34.4)	37 (52.9)	64 (44.1)	101 (47.0)	15 (55.6)	132 (46.5)
Grade 2	0	2 (6.3)	8 (11.4)	10 (6.9)	18 (8.4)	1 (3.7)	21 (7.4)
Grade 3	0	2 (6.3)	3 (4.3)	1 (0.7)	4 (1.9)	2 (7.4)	8 (2.8)
Grade 4	0	0	0	0	0	0	0
Bilirubin (umol/L) - INC	10 (100.0)	31 (96.9)	68 (97.1)	145 (100.0)	213 (99.1)	26 (96.3)	280 (98.6)
Grade 0	10 (100.0)	29 (90.6)	59 (84.3)	132 (91.0)	191 (88.8)	22 (81.5)	252 (88.7)
Grade 1	0	2 (6.3)	4 (5.7)	6 (4.1)	10 (4.7)	1 (3.7)	13 (4.6)
Grade 2	0	0	1 (1.4)	5 (3.4)	6 (2.8)	2 (7.4)	8 (2.8)
Grade 3	0	0	3 (4.3)	2 (1.4)	5 (2.3)	1 (3.7)	6 (2.1)
Grade 4	0	0	1 (1.4)	0	1 (0.5)	0	1 (0.4)
Gamma Glutamyl Transferase (U/L) - INC	10 (100.0)	31 (96.9)	69 (98.6)	143 (98.6)	212 (98.6)	26 (96.3)	279 (98.2)
Grade 0	4 (40.0)	12 (37.5)	18 (25.7)	38 (26.2)	56 (26.0)	4 (14.8)	76 (26.8)
Grade 1	4 (40.0)	8 (25.0)	16 (22.9)	49 (33.8)	65 (30.2)	11 (40.7)	88 (31.0)
Grade 2	1 (10.0)	2 (6.3)	14 (20.0)	24 (16.6)	38 (17.7)	3 (11.1)	44 (15.5)
Grade 3	1 (10.0)	8 (25.0)	19 (27.1)	30 (20.7)	49 (22.8)	8 (29.6)	66 (23.2)
Grade 4	0	1 (3.1)	2 (2.9)	2 (1.4)	4 (1.9)	0	5 (1.8)

CTCAE=Common Terminology Criteria for Adverse Events; DEC=decrease; DLBCL=diffuse large B-cell lymphoma; INC=increase; LFT=liver function test; s101=study ADCT-402-101; s201=study ADCT-402-201

Baseline was defined as the last nonmissing value before the initial administration of loncastuximab tesirine. CTCAE v4.0 was used for grading. For each parameter, patients were included only once at the maximum severity.

Source: ISS Table 1.4.4 (adsl, adlb)

TEAEs Pertaining to LFTs

In the 284 patients in all doses combined, the incidence of TEAEs pertaining to LFTs and those assessed as treatment-related, respectively, was as follows (ISS Tables 1.3.6 and 1.3.19): GGT increased (34.2% and 28.5%), blood alkaline phosphatase increased (18.3% and 14.8%), AST increased (16.2% and 12.3%), ALT increased (15.5% and 10.9%), hypoalbuminemia (4.2% and 1.4%), blood bilirubin increased (2.5% and 1.4%), and hepatic enzyme increased (0.4% and 0.4%).

TEAEs that pertained to LFTs that led to treatment withdrawal included GGT increased (6.7%) and blood alkaline phosphatase increased (1.1%).

Renal Function Tests

Maximum CTCAE Grade

In the 284 DLBCL patients in all doses combined, the majority of patients had maximum postbaseline renal function tests Grade 2 or lower. The incidence of maximum postbaseline Grade 3 or 4 renal function test values was as follows:

- Increases in creatinine, Grade 3 (1.4%)
- Decreases in creatinine clearance, Grade 3 (0.7%); note: creatinine clearance was reported in only 23.9% of patients

TEAEs Pertaining to Renal Function Tests

In the 284 DLBCL patients in all doses combined, the incidence of TEAEs pertaining to renal function tests and those assessed as treatment-related, respectively, was as follows: blood creatinine increased (4.6% and 1.4%) and blood urea increased (1.4% and 0.7%). No TEAEs pertaining to renal function tests led to treatment withdrawal.

Electrolytes and Glucose

Maximum CTCAE Grade

In the 284 DLBCL patients in all doses combined, the majority of patients had maximum postbaseline glucose and electrolytes Grade 2 or lower. The incidence of maximum postbaseline Grade 3 or 4 glucose and electrolyte values was as follows:

- Increases in calcium: Grades 4 and 3 (1.1% each)
- Decreases in calcium: Grade 4 (1.1%) and Grade 3 (0.4%)
- Increases in glucose: Grade 4 (0.7%) and Grade 3 (10.2%)

- Decreases in potassium: Grade 4 (0.7%) and Grade 3 (5.3%)
- Decreases in phosphate: Grade 4 (0.4%) and Grade 3 (7.7%)
- Increases in potassium: Grade 4 (0.4%) and Grade 3 (0.7%)
- Decreases in sodium: Grade 3 (6.7%)
- Increases in magnesium: Grade 3 (1.1%)
- Decreases in magnesium: Grade 3 (0.4%)

No maximum postbaseline Grade 3 or 4 values were reported for decreases in glucose or increases in sodium.

TEAEs Pertaining to Glucose and Electrolytes

In the 284 DLBCL patients in all doses combined, the incidence of TEAEs pertaining to glucose and electrolytes and those assessed as treatment-related, respectively, was as follows: hypokalemia (14.4% and 1.1%), hypophosphatemia (10.2% and 2.5%), hypomagnesemia (10.2% and 1.1%), hyperglycemia (8.5% and 1.4%), hyponatremia (6.7% and 2.5%), hypocalcemia (6.7% and 0.4%), hypercalcemia (3.9% and 0.4%), hyperkalemia (2.5% and 0.4%), blood glucose increased (1.4% and 0%), hypoglycemia (1.1% and 0.4%), hypermagnesemia (0.7% and 0.4%), blood phosphorous decreased (0.7% and 0%), blood potassium decreased and adjusted calcium decreased (0.4% and 0.4% each), and blood magnesium decreased (0.4% and 0%).

TEAEs that pertained to glucose and electrolytes in all doses combined that led to treatment withdrawal included hyponatremia (0.4%).

Other Biochemistry Parameters (Amylase, Lipase, and Lipids)

Maximum CTCAE Grade

In the 284 DLBCL patients in all doses combined, the majority of patients had maximum postbaseline amylase, lipase, and lipid values Grade 2 or lower. The incidence of maximum postbaseline Grade 3 or 4 values for these parameters was as follows:

- Increases in lipase: Grade 4 (1.4%) and Grade 3 (3.5%)
- Increases in amylase: Grade 3 (1.4%)
- Increases in triglycerides: Grade 3 (1.4%); note: triglycerides were reported in only 47.5% of patients

- Increases in cholesterol: Grade 3 (0.7%); note: cholesterol was reported in only 47.5% of patients

TEAEs Pertaining to Other Biochemistry Parameters (Amylase, Lipase, and Lipids)
In the 284 patients in all doses combined, the incidence of TEAEs pertaining to amylase, lipase, and lipids, and those assessed as treatment-related, respectively, was as follows: amylase increased (3.2% and 0.4%); lipase increased (2.5% and 1.1%); hypertriglyceridemia (2.1% and 0.4%); blood cholesterol increased (1.4% and 0.7%); low density lipoprotein increased (0.4% and 0.4%); and dyslipidemia (0.4% and 0.4%).

No TEAEs pertaining to amylase, lipase, or lipids led to treatment withdrawal.

The Applicant's Position:
In the 284 DLBCL patients in the Level 1 pool, the majority of patients had maximum postbaseline Grade 2 or lower abnormalities for hematology; LFTs; renal function tests; electrolytes and glucose; and amylase, lipase, or lipid laboratory values. However, notable maximum postbaseline Grade 3 or 4 values were observed for decreases in leukocytes and neutrophils, platelets, and hemoglobin. Notable maximum postbaseline Grade 3 or 4 values were observed for increases in GGT and glucose, and for decreases in potassium, phosphate, and sodium.

The FDA's Assessment
In general, the FDA agrees with the Applicant's position. The tables below provide a summary of the FDA's lab-shift analysis for hematologic and chemistry laboratory abnormalities. For hematologic abnormalities, in the 215 patients in the 150 µg/kg pool, the rates of Grade 3 and Grade 4 neutropenia were 22% and 21%, respectively. Despite this, the incidence of febrile neutropenia remained low at 3%. For thrombocytopenia, Grade 4 occurred in 5% to 7%, however, this was not associated with an increase in bleeding events. For chemistry laboratory abnormalities, GGT increased was a common event with 57% to 58% of patients experiencing any grade event. Grade 3 GGT increased occurred in 21% and 23%, respectively and Grade 4 GGT increased in 1% and 2% respectively. As shown in the tables below, the incidence of GGT increased, especially Grade 3 or 4, did not correlate with Grade 3 or 4 AST or ALT or total bilirubin elevation indicative of hepatotoxicity. Further, no patients met criteria for Hy's laws.

Table 42: Treatment Emergent Laboratory Abnormalities - FDA Laboratory Shift Analysis

Lab Abnormality	**ADCT-402-201** **N = 145**	**150 µg/kg Dose Pool** **N = 215**

	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Hematology				
Neutropenia	52%	30%	53%	32%
Thrombocytopenia	58%	18%	59%	20%
Anemia	52%	11%	52%	13%
Chemistry				
GGT increased	57%	21%	58%	23%
ALT increased	34%	3%	36%	4%
AST increased	41%	<1%	46%	2%
Total Bilirubin	9%	1%	10%	3%
Albumin decreased	38%	<1%	40%	<1%
Creatinine increased	79%	3%	79%	2%
Glucose increased	48%	8%	45%	9%

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, Gamma-glutamyl transferase
Source: FDA review of ADLB dataset

Table 43: Treatment Emergent Grade 3 or 4 Laboratory Abnormalities - FDA Laboratory Shift Analysis

Lab Abnormality	ADCT-402-201 N = 145		150 µg/kg Dose Pool N = 215	
	Grade 3	Grade 4	Grade 3	Grade 4
Hematology				
Neutropenia	22%	17%	22%	21%
Thrombocytopenia	17%	5%	19%	7%
Anemia	11%	0	13%	0
Chemistry				
GGT increased	21%	1%	23%	2%
ALT increased	3%	<1%	4%	<1%
AST increased	<1%	0	2%	0
Total Bilirubin	1%	0	2%	<1%
Albumin decreased	<1%	0	<1%	0
Creatinine increased	3%	0	2%	0
Glucose increased	8%	<1%	8%	<1%

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, Gamma-glutamyl transferase
Source: FDA review of ADLB dataset

Based on the data, specifically Grade 3 and 4 cytopenias, myelosuppression is an important identified risk for patients treated with loncastuximab tesirine. Therefore, labeling will include a Warning and Precaution for myelosuppression and dose modifications to ensure safe use of the drug.

Vital Signs

Data:
In studies ADCT-402-201 and ADCT-402-101, there was no evidence of a clinically meaningful mean or median change in systolic or diastolic blood pressure, heart rate, respiration rate, or temperature during or after an infusion on treatment days, over time after treatment within a cycle, or over time across treatment cycles.

The Applicant's Position:
No evidence of clinically significant toxicity for vital signs was observed in individual studies ADCT-402-201 or ADCT-402-101.

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

Electrocardiograms (ECGs)

Data:
Study ADCT-402-201
For heart rate, PR interval, and QRS duration, there was no consistent or meaningful change from baseline values to posttreatment values during cycles.

Maximum change from baseline by QTcB is summarized by category (increase of >30 to ≤60 msec and of >60 msec). There were 31 patients (21.4%) who had QTcB increase from baseline of >30 and ≤60 msec, and 4 patients (2.8%) who had QTcB increase from baseline of >60 msec.

Maximum change from baseline by QT corrected by QTcF is summarized by category (increase of >30 to ≤60 msec and of >60 msec). There were 23 patients (15.9%) who had QTcF increase from baseline of >30 and ≤60 msec, and 1 patient (0.7%) who had QTcF increase from baseline of >60 msec.

There was no evidence of cumulative increase in mean QTcB or QTcF over time.
For QTcB, there were 10 patients (6.9%) who shifted >480 to 500 msec, and 7 patients (4.8%) who shifted >500 msec. For QTcF, there were 6 patients (4.1%) who shifted >480 to 500 msec, and 1 patient (0.8%) who shifted >500 msec.

Study ADCT-402-101
There was no evidence of a clinically meaningful change from baseline in QTc. The median baseline QTc (all doses combined) was 419 msec. During Cycle 1, the median changes from baseline to 30 minutes, 3 hours, and 24 hours posttreatment were 3.0, 5.0, and -3.0 msec, respectively. The median changes from baseline to 30 minutes, 3 hours, and 24 hours posttreatment were 7.0, 10.0, and 3.0 msec during Cycle 2. There was no evidence of a meaningful change from baseline (Cycle 1 pretreatment) to pretreatment on Day 1 of subsequent cycles.

Maximum change from baseline in QTc was summarized by category (increases of >30 to ≤60 and of >60 msec). A total of 50 of 183 (27.3% all doses combined) patients had QTc increases from baseline of 30 to ≤60 msec, and 11 patients (6.0%) had increases from baseline of >60 msec. Maximum QTc was summarized by category (≤450, >450 to ≤480, >480 to ≤500, and >500 msec). A total of 18 of 183 (9.8% all doses combined) patients had shifts to maximum QTc >480 to ≤500 msec postbaseline, and four patients (2.2%) had shifts to maximum QTc >500 msec postbaseline (one patient with baseline QTc >500 should not be considered as a shift from baseline).

The Applicant's Position:
No evidence of clinically significant toxicity regarding depolarization/repolarization of myocardium as measured by ECG was observed in individual studies ADCT-402-201 or ADCT-402-101.

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

QT

Data:
Section 6.3.1 summarizes analyses of PK/QTc.

The Applicant's Position:
In study ADCT-402-201, the magnitude of QTc prolongation change from baseline with loncastuximab tesirine peak exposure was not clinically relevant.

The FDA's Assessment:
The FDA agrees with the Applicant's position. Based on the FDA QT IRT's analysis, at the maximum recommended therapeutic dose of 150 µg/kg during Cycle 1 and Cycle 2, loncastuximab tesirine did not cause large mean increases (i.e., > 20 msec) in the QTc interval.

Immunogenicity

Data:
Section 6.3.1 summarizes analyses of immunogenicity.

The Applicant's Position:
Loncastuximab tesirine did not exert a clinically relevant ADA induction effect.

The FDA's Assessment:
See Section 6.3.1 for FDA's review of immunogenicity.

8.2.5. Analysis of Submission-Specific Safety Issues Data:

Selected TEAEs by Grouped AE

Based on the AE profiles of other PBD-based therapies reported in the literature and early clinical data, AE groups of edema or effusion, fatigue, LFTs, pain, skin reactions, and nail disorders were defined for potential additional analysis. Torsades de pointes/QT prolongation/seizure was added in per request pursuant to a preBLA meeting with the FDA on 17 Apr 2020. Based on evolving clinical data and the FDA request, edema and effusion, LFTs, skin reactions and nail disorders, and Torsades de pointes/QT prolongation seizures were chosen for further analysis.

In the 284 DLBCL patients in all doses combined, 87.7% of patients had at least one selected TEAE and 71.1% had at least one selected treatment-related TEAE in any of the six specified groups.

Most Common
Table 44 summarizes the most common (≥10% of patients in all doses combined) selected TEAEs by the four grouped AEs of particular interest in the 284 DLBCL patients who received loncastuximab tesirine monotherapy. The incidence for the group overall and the most common specific events (all and those assessed as treatment-related, respectively) was as follows:

- Edema or effusion group (38.4% and 29.6%): edema peripheral (24.3% and 17.6%) and pleural effusion (14.4% and 12.7%)

- LFT group (42.6% and 33.8%): GGT increased (34.2% and 28.5%), blood alkaline phosphatase increased (18.3% and 14.8%), AST increased (16.2% and 12.3%), and ALT increased (15.5% and 10.9%). Of note, there was only one patient (0.4%) with a hepatobiliary TEAE (Grade 2 cholestasis in a single patient on the Phase 1 ADCT-402-101 study).

- Skin reaction and nail disorder group (46.8% and 44.4%): rash (19.0% and 18.0%) and pruritus (11.6% and 8.1%)

Torsades de pointes/QT prolongation/seizure group: this group did not meet the cutoff of 10%, but 3.5% of patients experienced at least one event and 2.1% had at least one event assessed as treatment-related. The incidence of specific events and those assessed as treatment-related, respectively, included ECG QT prolonged (2.5% and 2.1%), syncope (0.7% and 0%), and cardiac arrest (0.4% and 0%).

Table 44: Applicant-Most Common (≥10% of Patients in All Doses Combined) Selected TEAEs by Grouped AEs of Particular Interest and Preferred Term-Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

			150 µg/kg				
AE Group Preferred Term	**<=90 µg/kg (N=10)**	**120 µg/kg (N=32)**	**s101 (N=70)**	**s201 (N=145)**	**subtotal (N=215)**	**200 µg/kg (N=27)**	**All Doses (N=284)**
Edema or Effusion	2 (20.0)	16 (50.0)	33 (47.1)	45 (31.0)	78 (36.3)	13 (48.1)	109 (38.4)
Oedema peripheral	1 (10.0)	9 (28.1)	21 (30.0)	29 (20.0)	50 (23.3)	9 (33.3)	69 (24.3)
Pleural effusion	1 (10.0)	6 (18.8)	13 (18.6)	15 (10.3)	28 (13.0)	6 (22.2)	41 (14.4)
Liver Function Test	2 (20.0)	10 (31.3)	22 (31.4)	74 (51.0)	96 (44.7)	13 (48.1)	121 (42.6)
Gamma-glutamyltransferase increased	2 (20.0)	10 (31.3)	16 (22.9)	59 (40.7)	75 (34.9)	10 (37.0)	97 (34.2)
Blood alkaline phosphatase increased	1 (10.0)	4 (12.5)	12 (17.1)	29 (20.0)	41 (19.1)	6 (22.2)	52 (18.3)
Aspartate aminotransferase increased	0	3 (9.4)	11 (15.7)	23 (15.9)	34 (15.8)	9 (33.3)	46 (16.2)
Alanine aminotransferase increased	0	4 (12.5)	12 (17.1)	23 (15.9)	35 (16.3)	5 (18.5)	44 (15.5)
Skin Reactions and Nail Disorders	4 (40.0)	16 (50.0)	37 (52.9)	63 (43.4)	100 (46.5)	13 (48.1)	133 (46.8)
Rash	1 (10.0)	5 (15.6)	24 (34.3)	19 (13.1)	43 (20.0)	5 (18.5)	54 (19.0)
Pruritus	1 (10.0)	4 (12.5)	6 (8.6)	18 (12.4)	24 (11.2)	4 (14.8)	33 (11.6)

AE=adverse event; DLBCL=diffuse large B-cell lymphoma; LFT=liver function test; MedDRA=Medical Dictionary for Regulatory Activities; s101=study ADCT-402-101; s201=study ADCT-402-201; TEAE=treatment-emergent adverse event
Grouped AEs of particular interest included edema or effusion, LFTs, skin reactions and nail disorders, and Torsades de pointes/QT prolongation/seizure.
The 10% cutoff was based on All Doses. Torsades de pointes/QT prolongation/seizure group did not meet the cutoff.
AEs were coded using MedDRA version 22.0.
Source: ISS Table 1.3.10 (datasets: adae, adsl)

Grade 3 or Higher

The incidence of Grade 3 or higher events in the four AE groups of particular interest (all and those assessed as treatment-related, respectively) was as follows: edema or effusion (4.9% and 4.2%), LFT (19.7% and 16.2%), skin reaction and nail disorders (3.2% and 3.2%), and Torsades de pointes/QT prolongation/seizure (1.4% and 0.4%). Of note, there were no patients with Grade 3 or higher hepatobiliary TEAEs.

The Applicant's Position:

AEs pertaining to edema or effusion, LFTs, and skin reactions have been observed with PBD-based therapies. These did occur in patients treated with loncastuximab tesirine, but were

generally mild to moderate in severity and generally managed with supportive care and dose delay/modification as clinically indicated, consistent with the general tolerability of loncastuximab tesirine. Torsades de pointes/QT prolongation/seizures were not seen in a clinically significant proportion of patients.

The FDA's Assessment:
The information below summarizes the FDA review of adverse events of special interest with loncastuximab tesirine, which include edema or effusion, rash, infection, hepatotoxicity, and inflammatory-related conditions. The summary below will focus on the 145 patients enrolled in the pivotal trial ADCT-402-201.

Edema or Effusion
Edema or effusions are an important identified risk for patients who receive treatment with loncastuximab tesirine. The table below provides a summary of the data for edema or effusion in the ADCT-402-201 population. Using a grouped preferred term combining edema and effusion (excludes localized edema; i.e., nasal edema), of 145 patients in ADCT-402-201, 31% experienced any grade and 5% experienced Grade ≥3 edema or effusion. Edema was the most common preferred term followed by pleural effusion, ascites, and pericardial effusion. For edema, 28% of patients experienced any grade edema with 3% experiencing Grade 3 edema. The median time to onset of any grade edema and Grade 3 edema was 1.3 months and 3.5 months, respectively. Edema, either generalized or local, led to treatment discontinuation in 3% and 2% of patients, respectively. Further, edema led to a dose delay in 5% of patients. Ten patients underwent rechallenge following an adverse event of edema, in which 4 of the 10 patients developed a subsequent edema-related event after rechallenge. For effusions, 11% of patients experienced any grade effusion and Grade ≥3 effusion in 4%. Any grade and Grade 3 pleural effusion were reported in 10% and 2%, respectively and any grade and Grade ≥3 pericardial effusion were reported in 3% and 2%, respectively. The median time to onset for any grade effusion was 1.7 months. Pleural and pericardial effusion led to treatment discontinuation in 2% and 1%, respectively. To further evaluate the incidence of edema or effusions, the FDA analyzed the incidence of hypoalbuminemia. Based on laboratory data, any grade hypoalbuminemia occurred in 38%, with Grade 2 in 15% and Grade 3 in <1%. Notably, the occurrence of edema or effusion with loncastuximab tesirine did not correlate with concurrent hypoalbuminemia.

Table 45: Summary of Edema or Effusions in ADCT-402-201 - FDA Review

Edema or Effusion	**ADCT-402-201 N = 145**
Any grade edema[a]	28%
Edema	25%
Ascites	3%
Grade 3 edema[a]	3%
Median time to onset (months)	
Any Grade (range)	1.3 (1 day to 9.1 months)
Grade 3 (range)	3.5 (9 days to 6 months)
Any grade effusion	11%
Pleural effusion	10%
Pericardial effusion	3%
Grade ≥3 effusion	4%
Pleural effusion	2%
Pericardial effusion	2%
Median time to onset (months)	
Any Grade (range)	1.7 (3 day to 6.7 months)
Grade 3 (range)	3.9 (17 days to 9.1 months)
Treatment discontinuation	10%
Edema	3%
Localized edema	2%
Pleural effusion	2%
Pericardial effusion	1%

Dose delay Edema	 5%
Hypoalbuminemia[b] Any grade Grade 2[c] Grade 3[d]	 38% 15% <1%
[a]Excludes localized edema [b]Based on laboratory data [c]Grade 2 hypoalbuminemia defined as <3 to 2 g/dL [d]Grade 3 hypoalbuminemia defined as <2 g/dL Source: FDA review of ADAE and ADLB datasets	

The most common therapy administered to patients with edema or effusion was diuretic therapy. Some patients with effusions were treated with concomitant corticosteroids.

Based on the data, there is no established standard of treatment for loncastuximab tesirine-associated edema or effusion. Labeling will include a Warning and Precaution for edema and effusion and dose modifications to ensure safe use of the drug. Healthcare providers should be aware that loncastuximab tesirine should be withheld for Grade 2 or higher edema or effusion and dose reduced or discontinued based on the duration and severity.

Cutaneous Reactions

Cutaneous toxicity is an important identified risk with loncastuximab tesirine. The table below provides a summary of the data for cutaneous toxicity in the ADCT-402-201 population. Using a grouped preferred term for rash, of 145 patients in ADCT-402-201, 30% experienced any grade rash and 2% experienced Grade 3 rash. The most common manifestation of rash reported included an erythematous, maculopapular rash. More rare and severe presentations included bullous dermatitis, exfoliative dermatitis, and palmar-plantar erythrodysesthesia syndrome. The median time to onset of any grade rash was 1 month. Rash led to a dose delay of loncastuximab tesirine in 5% of patients. Thirteen patients underwent rechallenge following a cutaneous toxicity event, in which 4 of the 13 patients had a recurrent cutaneous toxicity. Further, loncastuximab tesirine is considered a photosensitizing agent and associated with photosensitivity based on nonclinical evaluation (See Section 5.5.1 and 5.5.5). Clinically, 15 patients (10%) experienced any grade photosensitivity reactions, with 3 patients (2%) experiencing Grade 3 events. In addition, 5 patients (3%) reported skin hyperpigmentation or skin discoloration, which was a finding also noted in the nonclinical data with loncastuximab tesirine (Section 5.5.1)

Table 46: Summary of Cutaneous Toxicity in ADCT-402-201 - FDA Review

Cutaneous toxicity	**ADCT-402-201 N = 145**
Any grade rash	30%
Grade 3 rash	2%
Median time to onset (months) Any Grade (range)	1 (1 day to 3.4 months)
Dose delay Rash	5%
Photosensitivity Any grade Grade 3	10% 2%
Skin discoloration	3%
Source: FDA review of ADAE dataset	

Based on the incidence of Grade 3 rash combined with Grade 3 photosensitivity reactions and the need to inform patients and healthcare providers of the risk, labeling will include a Warning and Precaution for cutaneous reactions and dose modifications to ensure safe use of the drug. Additionally, labeling will include information advising patients to avoid or minimize exposure to direct natural or artificial sunlight and measures to protect skin from exposure.

Infection

Infection is an important identified risk with loncastuximab tesirine use. In the 145 patients in ADCT-402-201, there were 48 patients (33%) with the reported event of infection, with Grade ≥3 infections in 13 patients (9%). There were three deaths attributable to infection. These included sepsis in 2 patients and pneumonia in 1 patient.

Given the concerns for the risk of infection and the incidence of Grade 3-4 neutropenia, labeling will include infection as a Warning and Precaution to ensure safe use of loncastuximab tesirine.

Hepatoxicity

Based on lab-shift analyses, in the 145 patients in ADT-402-201, GGT increased was a common event with 57% of patients experiencing any grade event. Grade 3 GGT increased occurred in 21% and Grade 4 GGT increased in 1%. Any grade transaminase elevation occurred in 41% (AST) and 34% (ALT) of the population, and grade 3-4 toxicities were <1% and 3%, respectively. Additionally, any grade hyperbilirubinemia occurred in 9%, with Grade 3 elevations in 1%. Importantly, the incidence of GGT increased, especially Grade 3 or 4, did not correlate with Grade 3 or 4 AST or ALT or total bilirubin elevation indicative of serious or severe hepatotoxicity. Further, no patients developed drug-induced liver failure or met criteria for Hy's law.

Inflammatory-Related Conditions
Proinflammatory responses have been associated with PBD-containing antibody-drug conjugates as evaluated by Saber et al, 2019 and as was further evaluated by the FDA for loncastuximab tesirine. In collaboration with the Applicant, the FDA and Applicant identified cases of potential inflammatory-related events by identifying preferred terms containing inflammation, "itis," "sis," and other terms associated with inflammation (i.e., pleuritic pain). After exclusion of conditions associated with concurrent events, such as bronchitis being reported during a respiratory tract infection, 3% of patients reported inflammatory-related conditions. The conditions reported included pericarditis, pneumonitis, pleuritis, and dermatitis.

As noted in the nonclinical evaluation of inflammatory-related conditions by Saber et al, these events occur at a low incidence and may include a variety of presentations. Therefore, evaluation of inflammatory-related conditions in ongoing and future trials of loncastuximab tesirine is important to further characterize the risk.

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

Not applicable.

The Applicant's Position:
Not applicable.

The FDA's Assessment:
See Section 8.1.2 for the Applicant's and FDA's review of the COA data submitted with this Application.

8.2.7. Safety Analyses by Demographic Subgroup

Data:
Analyses of safety for age, sex, race, region, and drug formulation were performed. Notable differences are summarized below.

Age
In the 138 DLBCL patients <65 years and the 146 DLBCL patients ≥65 years in all doses combined, for the most common TEAEs, only edema peripheral had a notably higher incidence in older patients, 18.1% vs 30.1%, respectively.

Sex
In the 119 female and 165 male DLBCL patients in all doses combined, for the most common TEAEs, females had a notably higher incidence than males, respectively, for anemia (36.1% vs 22.4%) and vomiting (23.5% vs 9.7%).

Race
Due to the small number of nonwhite patients, comparisons among races were not made because they were not meaningful.

Region
Most Common
In the 145 US and 139 European patients in all doses combined, for the most common TEAEs, US patients had a notably higher incidence than European patients, respectively, for fatigue (46.2% vs 23.0%; note: asthenia 4.1% vs 12.2%), edema peripheral (33.8% vs 14.4%), dyspnea (24.8% vs 7.9%), dizziness (17.2% vs 0.7%), rash maculopapular (12.4% vs 2.2%), and white blood cell count decreased (11.0% vs 0%; note: leukopenia 10.3% vs 5.0%).
A notably lower incidence in the US vs European patients, respectively, was observed for the most common TEAEs of GGT increased (26.2% vs 42.4%), neutropenia (19.3% vs 43.9%; note: neutrophil count decreased was 13.1% vs 0%), and hypomagnesemia (4.8% vs 15.8%).

The clinical relevance of these differences is unclear.

Grade 3 or Higher
In the 145 US and 139 European patients in all doses combined, for the most common Grade 3 or higher TEAEs, US patients had a notably lower incidence of GGT increased vs European patients, 11.7% vs 23.0%, respectively.

The clinical relevance of this difference is unclear.

Two Different Drug Formulations
TEAEs were comparable between the two drug formulations (liquid and lyophilized) used in study ADCT-402-201.

The Applicant's Position:
The safety profile of loncastuximab tesirine was generally similar across different demographic groups. In particular, the TEAE profiles for patients <65 years and ≥65 years were comparable.

The FDA's Assessment:
In general, the FDA agrees with the Applicant's position. However, as noted, there was limited representation of racial and ethnic minorities in the safety population to allow for broad

generalization of the results. In the pivotal trial ADCT-402-201, race was reported in 97% of patients; of these patients, 90% were White, 3% were Black, and 2% were Asian. For ethnicity, 9% were Hispanic or Latino. The tables below provide a summary of the safety data for patients based on race and ethnicity. Importantly, the safety data by race and ethnicity demonstrated a trend with a higher proportion of Grade ≥3 adverse events, Grade 3-4 neutropenia, and TEAEs leading to dose delays (primarily neutropenia) occurring in Black and Hispanic patients compared to White patients, with limited safety data in Asian patients. This reflects an overall limitation in the data as it applies to the US population and a postmarketing requirement was issued to address this concern (Section 13).

Table 47: Summary of Safety by Race or Ethnicity - FDA Review

	SAE	Grade ≥3	Discontinue due to AE	Neutropenia Grade 3-4	Thrombocytopenia Grade 3-4
ADCT-402-201					
Total (N = 145)	39%	72%	23%	30%	18%
White (N = 130)	40%	71%	25%	25%	8%
Black (N = 5)	20%	80%	20%	80%	0
Asian (N = 3)	33%	67%	0	33%	0
Hispanic/Latino (N = 13)	54%	77%	3%	46%	8%
150 µg/kg Dose Pool					
Total (N = 215)	40%	73%	19%	32%	20%
White (N = 197)	41%	72%	20%	28%	20%
Black (N = 7)	29%	86%	29%	71%	14%
Asian (N = 3)	33%	67%	0	33%	0
Hispanic/Latino (N = 17)	47%	71%	18%	35%	6%
Abbreviations: AE, adverse event; SAE, serious adverse event Source: FDA review of ADSL, ADAE and ADLB datasets					

8.2.8. Specific Safety Studies/Clinical Trials

Data:
Not applicable.

The Applicant's Position:
Not applicable.

The FDA's Assessment:
Not applicable.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Data:
Carcinogenicity studies with loncastuximab tesirine or SG3199 have not been conducted.

The Applicant's Position:
In an in vitro micronucleus test and a chromosome aberration assay using human lymphocytes SG3199 was determined to be clastogenic, consistent with its mode of action as a covalent DNA crosslinking agent.

The FDA's Assessment:
See Section 5 for the Applicant's and FDA's review of the nonclinical data. Of the 215 patients in the 150 µg/kg Dose Pool, there was 1 report of non-melanoma skin cancer and 1 report of breast cancer.

Human Reproduction and Pregnancy

Data:
The use of loncastuximab tesirine in pregnant or lactating women has not been studied. Based on its mechanism of action, loncastuximab tesirine can cause embryo-fetal toxicity and/or teratogenicity when administered to a pregnant woman. Loncastuximab tesirine contains a genotoxic component, SG3199.

The Applicant's Position:
Women of reproductive potential and pregnant women should be advised of the potential risk to a fetus.

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

Pediatrics and Assessment of Effects on Growth

Data:
The use of loncastuximab tesirine in pediatric patients has not been studied.

The Applicant's Position:

Safety and effectiveness in pediatric patients have not been established.

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

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data:
There are no data available to determine what the effects of overdose are and whether they can be reversed. No overdoses have been reported as a TEAE in any study (ISS Table 3.3.2). The pharmacologic action of loncastuximab tesirine does not include a therapeutic or side effect profile that might increase the likelihood of misuse for illegal purposes.
The effect of loncastuximab tesirine withdrawal and rebound was not studied.

The Applicant's Position:
Symptomatic treatment and standard supportive care measures for the management of any observed toxicity should be applied.

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

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Data:
Loncastuximab tesirine has not been marketed in any region. No postmarketing data are available.

The Applicant's Position:
Not applicable.

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

Expectations on Safety in the Postmarket Setting

Data:
Toxicities have been adequately represented in the over 400 patients in the studies included in this application and are expected to be similar in the postmarket setting.

The Applicant's Position:
Toxicities appear to have been adequately represented in the studies included in this application. Potential safety concerns beyond the risks conveyed in the proposed labeling are not expected. Routine pharmacovigilance will be conducted in the postmarket setting to monitor for unexpected AEs.

The FDA's Assessment:
In general, the FDA agrees with the Applicant's position. However, the median duration of exposure is limited. In the 145 patients from ADCT-402-201, the median exposure was 3 cycles (range 1 to 15) or 45 days (range 1 to 351) with 34% receiving 5 or more cycles. Therefore, additional data to further characterize long-term safety is warranted and the adverse events of interest, including edema or effusions, cutaneous toxicity, myelosuppression, and infection.

8.2.11. Integrated Assessment of Safety

Data:
Evaluation of the safety profile of loncastuximab tesirine was based on data from five clinical studies involving 401 patients. The primary safety evaluation was based on the Level 1 pooled analyses as these data support the intended indication being sought in the BLA application. The Level 1 pool consisted of a total of 284 patients with relapsed or refractory DLBCL who received loncastuximab tesirine monotherapy, of which 145 patients were from pivotal study ADCT-402-201 and 139 patients were from study ADCT-402-101.

Data from the Level 2 pooled analyses were supportive based on a relevant larger safety database that included total of 363 patients with relapsed or refractory disease who received loncastuximab tesirine monotherapy in three studies as follows: 145 DLBCL patients from pivotal study ADCT-402-201, 183 B-NHL patients from study ADCT-402-101, and 35 B-ALL patients from study ADCT-402-102. Safety data for the 328 B-NHL patients included in the Level 2 pool were generally similar to the data from the Level 1 pool. Given this similarity, the remainder of this discussion will focus on the data from the Level 1 pool of 284 patients with DLBCL treated with loncastuximab tesirine monotherapy.

Dosing and Exposure
In the Phase 1, first-in-human study ADCT-402-101, patients received initial doses of loncastuximab tesirine ranging from 15 to 200 mg/kg. Based on the observation of increased toxicity at the 200 mg/kg dose level and on the fact that a substantial proportion of patients required dose reduction after two cycles, the recommended dose of loncastuximab tesirine used in the pivotal Phase 2 ADCT-402-201 study in patients with relapsed or refractory DLBCL was 150 mg/kg Q3W for two cycles followed by 75 mg/kg Q3W for subsequent cycles.
Of the 284 DLBCL patients in the Level 1 pool, 215 patients received an initial dose of 150 mg/kg. The median treatment duration in all doses combined was 43.0 days (range: 1 to

351 days). The median number of treatment cycles administered was 3.0 cycles (range: 1 to 15 cycles).

Adverse Events

TEAEs were experienced by 98.9% of the 284 DLBCL patients in the Level 1 pool, with 82.4% assessed as treatment-related. Grade 3 or higher TEAEs were experienced by 73.2% of patients, with 51.8% assessed as treatment-related. The most common Grade 3 or higher TEAEs were neutropenia (21.8%), followed by GGT increased (17.3%), thrombocytopenia (15.5%), and anemia (10.9%). Serious TEAEs were experienced by 37.7% of patients, with 12.3% assessed as treatment-related. The most common serious TEAE was pyrexia (3.2%), followed by febrile neutropenia (2.8%) and abdominal pain and hypercalcemia (2.1% each). TEAEs with a fatal outcome were reported in 7.7% of patients, with 3.6% of TEAEs with a fatal outcome being related to progression of lymphoma. Lung infection seen in one patient (0.4%) was the only fatal TEAE assessed as treatment-related.

TEAEs led to treatment withdrawal in 18.3% of the 284 DLBCL patients in the Level 1 pool, with 14.4% assessed as treatment-related. The most common TEAE leading to treatment withdrawal was GGT increased (6.7%), followed by thrombocytopenia (2.1%) and edema peripheral (2.1%). TEAEs required dose modification in 43.7% of patients, with 36.3% assessed as treatment-related. The most common TEAE leading to dose delay was GGT increased (15.1%), followed by neutropenia (9.5%) and thrombocytopenia (6.0%). The most common TEAE leading to dose reduction was GGT increased (2.5%).

Analysis of TEAE groupings known to be associated with the PBD warhead in the 284 DLBCL patient in the Level 1 pool showed that edema or effusion were seen in 38.4% of patients, with 29.6% assessed as treatment-related and 4.9% being Grade 3 or higher. LFT events were seen in 42.6% of patients, with 33.8% assessed as treatment-related and 19.7% being Grade 3 or higher. Skin-related events were seen in 46.8% of patients, with 44.4% assessed as treatment-related and 3.2% being Grade 3 or higher.

In the Level 1 pool, the TEAE profiles for patients <65 years and ≥65 years were comparable, with only edema peripheral having a notably higher incidence in older patients, 18.1% vs 30.1%, respectively. In addition, the TEAE profiles for females and males were comparable, with the only notable differences being that females had a higher incidence than males, respectively, for anemia (36.1% vs 22.4%) and vomiting (23.5% vs 9.7%).

Other Safety Observations

In the 284 DLBCL patients in the Level 1 pool, the majority of patients had maximum postbaseline Grade 2 or lower abnormalities for hematology; LFTs; renal function tests; electrolytes and glucose; and amylase, lipase, or lipid laboratory values. However, notable maximum postbaseline Grade 3 or 4 values were observed for decreases in leukocytes and

neutrophils, platelets, and hemoglobin. Notable maximum postbaseline Grade 3 or 4 values were observed for increases in GGT and glucose, and for decreases in potassium, phosphate, and sodium.

No evidence of clinically significant toxicity for vital signs or depolarization/repolarization of myocardium as measured by ECG was observed and the magnitude of QTc prolongation change from baseline with loncastuximab tesirine peak exposure was not clinically relevant. Loncastuximab tesirine did not exert a clinically relevant ADA induction effect.

The Applicant's Position:
Loncastuximab tesirine was well tolerated. Edema and effusions, skin rash, liver enzyme elevations, and hematologic toxicities were considered likely related to the PBD warhead, as these toxicities have been seen with other PBD compounds including SJG136, rovalpituzumab tesirine, and camidanlumab tesirine (Puzanov et al 2011, Rudin et al 2016, Collins et al 2019, Rudin et al 2017). The majority of these events were mild to moderate in severity. With the exception of laboratory abnormalities, Grade 3 or higher events in these PBD categories were seen in less than 5% of patients. Other AEs were generally similar to those anticipated in lymphoma patients who received antitumor therapy. The AEs were generally managed with dose delay/reduction and supportive care.

The benefits of loncastuximab tesirine outweigh the risks given the antitumor activity, limited therapeutic options for patients with relapsed/refractory DLBCL, and manageable safety profile. The Applicant believes these data support the application for approval at this time.

The FDA's Assessment:
The FDA agrees with the Applicant's position that the safety data demonstrates that loncastuximab tesirine demonstrated a tolerable safety profile in patients with relapsed or refractory large B-cell lymphoma. Although, given the median exposure of 3 cycles in the pivotal trial ADCT-402-201 and 3 cycles in the 150 µg/kg dose pool, there is limited data to support longer-term safety.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:
There are no major statistical issues identified from this submission. The following caveats need to be considered.

- The median DOR was 10.3 months (95% CI: 6.9 to NE). However, 28 (40%) censored events were reported during the study which may substantially affect the interpretation of durability of response. The most common reason for censoring is the new anticancer

treatment started, excluding SCT (17 patients, 24%). Moreover, 25 (36%) responders were censored within 3 months of response duration, including 15 (21%) responders censored due to starting a new anticancer treatment (excluding SCT). Sensitivity analyses on the proportion of patients maintaining response indicated that 36 (51%) responders having a 3 months or longer response, 18 (26%) responders having a 6 months or longer response, and 6 (9%) responders having 12 months or longer response.

- The study also assessed RFS, PFS, OS and PRO. However, these endpoints have limited interpretability in single-arm trials and are therefore considered to be exploratory.

8.4. Conclusions and Recommendations

The FDA's Assessment:

The benefit-risk assessment is favorable for loncastuximab tesirine for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low grade lymphoma, and high-grade B-cell lymphoma.

Efficacy:

Efficacy of loncastuximab tesirine is based on the results from ADCT-402-201, an open-label, multicenter, single-arm trial which included 145 adult patients with relapsed or refractory large B-cell lymphoma after at least 2 prior systemic regimens. Patients received loncastuximab tesirine 150 µg/kg every 3 weeks for 2 cycles, then 75 µg/kg every 3 weeks for subsequent cycles and received treatment until progressive disease, or unacceptable toxicity. The primary endpoint was overall response rate (ORR) as assessed by an Independent Review Committee (IRC) using Lugano 2014 criteria. Among the 145 patients, the median follow-up time was 7.3 months (range 0.3 to 20.2). The ORR per IRC was 48.3% (95% CI 39.9, 56.7), with 24.1% achieving a complete response. The median duration of response (DOR) per Kaplan-Meier was 10.3 months (95% CI 6.9, not evaluable). Notably, of the 70 patients with an objective response, 36% were censored for DOR prior to 3 months.

Safety:

The safety profile of loncastuximab tesirine was supported by analysis of 215 patients administered an initial dose of 150 µg/kg, including the 145 patients from the pivotal trial ADCT-402-201, with relapsed or refractory large B-cell lymphoma.

In 215 patients with relapsed or refractory large B-cell lymphoma, the median duration of treatment was 3 cycles (range 1 to 15) with 30% receiving 5 or more cycles. The most common (≥20%) adverse events, including laboratory abnormalities, were thrombocytopenia, increased gamma-glutamyltransferase, neutropenia, anemia, hyperglycemia, transaminase elevation,

fatigue, hypoalbuminemia, rash, edema, nausea, cough, and musculoskeletal pain. Fatal adverse events occurred in 3%, primarily due to infection. Serious adverse events occurred in 40% and Grade 3 or greater adverse events occurred in 73%. The most common serious adverse events included hypercalcemia, infection, and edema or effusion. The most common Grade 3 or greater adverse events included cytopenias, GGT increased, edema or effusion. Adverse events leading to treatment discontinuation occurred in 19%, most often due to GGT increased, edema, and effusion. Adverse events leading to treatment interruption occurred in 46%, most often due to GGT increased, neutropenia, thrombocytopenia, edema, and rash. Therefore, the primary safety issues identified with loncastuximab tesirine include serious effusions and edema, myelosuppression, infections, and cutaneous toxicity.

Benefit-Risk:

Loncastuximab tesirine has an overall favorable benefit-risk in patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low grade lymphoma, and high-grade B-cell lymphoma. In the 145 patients from ADCT-402-201, the diagnosis was DLBCL not otherwise specified (NOS) in 88% (including 20% with DLBCL arising from low grade lymphoma) and high-grade B-cell lymphoma in 8%. The median number of prior therapies was 3 (range 2 to 7), 63% with refractory disease, 17% with prior stem cell transplant, and 9% with prior chimeric antigen receptor (CAR) T-cell therapy. In this population, the overall response rate of 48% with associated durability and a tolerable safety profile constitutes a meaningful clinical benefit and a favorable benefit-risk. To support accelerated approval, the efficacy data is considered in the context of available therapy for patients with large B-cell lymphoma in the 3rd line setting and beyond. Available therapy includes the chimeric antigen receptor T-cell (CAR-T) therapies, axicabtagene ciloleucel and tisagenlecleucel, with overall response rate of 72% and 50%, respectively, with durability. Although, these therapies have limitations in the general relapsed or refractory large B-cell lymphoma population because of the toxicity profile, the waiting period for CAR-T manufacturing, and restricted availability. Additionally, commonly administered regimens include intensive therapy with platinum, etoposide, and/or cytarabine-based combination regimens (ICE, ESHAP, DHAP) with rituximab or less intensive regimens including gemcitabine, gemcitabine-oxaliplatin, or bendamustine, with rituximab. However, in the 3rd line setting and beyond, these regimens either serve as a bridge to a hematopoietic stem cell transplantation (HSCT) or produce limited responses. Recently, three agents have received accelerated approval for patients with relapsed or refractory diffuse large B-cell lymphoma including polatuzumab vedotin in combination with bendamustine-rituximab, selinexor, and tafasitamab, with overall response rates of 63%, 29%, and 55%, respectively. In the ADCT-402-201 trial population, 71% of patients had received an intensive salvage regimen, HSCT, or CAR-T therapy. Therefore, the overall response rate of 48% with associated durability for loncastuximab tesirine provides data to support a clinically meaningful benefit in the context of available therapy for patients with relapsed or refractory large B-cell lymphoma in the 3rd line setting and beyond.

A notable limitation of the efficacy and safety data include the limited racial and ethnic representation with race reported in 97% of patients in ADCT-402-201; of these patients, 90% were White, 3% were Black, and 2% were Asian. For ethnicity, 9% identified as Hispanic or Latino. Importantly, the safety data by race and ethnicity demonstrated a trend with a higher proportion of Grade ≥3 adverse events, Grade 3-4 neutropenia, and adverse events leading to dose delays occurring in Black and Hispanic patients compared to White patients, with limited safety data in Asian patients. Therefore, characterization of loncastuximab tesirine in broader racial and ethnic population is warranted and informed a post marketing requirement.

The ADCT-402-201 trial enrolled patients with DLBCL not otherwise specified (NOS) in 88% (including 20% with DLBCL arising from low grade lymphoma) and high-grade B-cell lymphoma in 8%. To support inclusion of patients with high grade B-cell lymphoma in an indication, the Applicant provided data from 23 patients with high grade B-cell lymphoma from ADCT-402-101 that demonstrated activity in these patients consistent with the data from the pivotal trial. The indication for loncastuximab tesirine will reflect the subtypes of large B-cell lymphoma enrolled in the pivotal ADCT-402-201 trial.

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

- Treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low grade lymphoma, and high-grade B-cell lymphoma.

Jay Zhao, PhD
Primary Statistical Reviewer

Yu-Te Wu, PhD
Statistical Team Leader

Candis Morrison, PhD, CRNP
Primary Clinical Reviewer

Nicholas Richardson, DO, MPH
Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

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

10 Pediatrics

The Applicant's Position:
A request for a waiver in the age group 0 to 12 months and a request for deferral in the age group 1 to 17 years was submitted in an Initial Pediatric Study Plan in Feb 2020; following FDA review, an Agreed Initial Pediatric Study Plan was submitted to the Agency on 27 Jul 2020, in which FDA's recommendations on the initial plan were incorporated.

The FDA's Assessment:
The FDA agrees with the Applicant's position. The efficacy and safety of loncastuximab tesirine in pediatric patients have not been studied. As noted above, the Applicant submitted an Agreed Initial Pediatric Study Plan that included a deferral for pediatric patients age 1 to 17 years based on the rationale that further efficacy and safety is needed to further inform a potential pediatric study evaluating loncastuximab tesirine in combination in pediatric patients with relapsed or refractory NHL. Thus a PMR was issued based on the Agreed Initial Pediatric Study Plan for loncastuximab tesirine.

11 Labeling Recommendations

The table below summarizes changes to the proposed United States Prescribing Information (USPI). See the final approved USPI for ZYNLONTA (loncastuximab tesirine-lpyl) accompanying the approval letter for more information.

Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
Highlights of Prescribing Information		FDA revised Highlights to align with Format and Content with Selected

Section	Applicant's Proposed Labeling	FDA's proposed Labeling
		Requirements of Prescribing Information (SRPI) as per regulations (21 CFR 201.56 and 21 CFR 201.57 (a)) and FDA Guidances. FDA added the established pharmacologic class (EPC) to the concise indication statement as per 21 CFR 201.57 (a)(6).
1 Indications and Usage	(b) (4)	Modified the Indication to: ZYNLONTA is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of system therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low grade lymphoma, and high-grade B-cell lymphoma. Accelerated approval language modified per recommendations found in the Labeling for Human Prescription Drug and Biological Products Approved Under the Accelerated Approval Regulatory Pathway Guidance for Industry.
2 Dosage and Administration	2.2 Includes premedication administration instructions	*Subsections 2.1-2.4*: FDA modified these subsections

Section	Applicant's Proposed Labeling	FDA's proposed Labeling
	for dexamethasone administration. 2.3 Includes dose delays and modifications instructions in a table for nonhematologic toxicity, neutropenia or thrombocytopenia, and edema or effusion.	for clarity and to replace symbols and abbreviations with intended meaning to prevent misinterpretation. *2.1* Dose calculation updated to use mg/kg rather than mcg/kg. *2.3* Dosage modifications table updated to provide treatment modifications by hematologic and non-hematologic toxicities and specified numeric definitions of thrombocytopenia and neutropenia; edema or effusion and other adverse reactions were described by CTCAE grade. *2.4* Updated dose calculation for patients with body mass index $\geq$ 35 kg/m^2 to use adjusted body weight. Revised the instructions for dilution in infusion bag to highlight that only 5% Dextrose Injection should be used for dilution in the infusion bag.
5 Warnings and Precautions (W&P)	Includes edema or effusion, serious infections, photosensitivity, and embryo-fetal toxicity.	FDA added: W&P *5.2* for Myelosuppression. Modified the title of the W&P for (b) (4) to Cutaneous Reactions and

Section	Applicant's Proposed Labeling	FDA's proposed Labeling
		described not only cases of photosensitivity, but also cases of erythema, and rash (including exfoliative and maculo-papular). Modified the W&P for Embryo-Fetal Toxicity to include the correct duration of contraception for females and males consistent with the Guidance Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations.
6 Adverse Reactions	Summary text provided above adverse drug reaction (ADR) table. Common ADR table included.	Modified this section to align with current OOD labeling practices. Described the pooled safety population of 215 adult patients used to inform the Warnings and Precautions section and based the remaining discussion of safety on the 145 patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who received the recommended dosage. Added a table of laboratory abnormalities and reordered terms in tables to be listed in descending order per 21 CFR 201.57(c)(7)(ii).

Section	Applicant's Proposed Labeling	FDA's proposed Labeling
8 Use in Specific Populations	8.1 and 8.2 Terminology and formatting consistent with current Pregnancy and Lactation Labeling Rule (PLLR) guidance and best labeling practices. 8.3 Provides specific contraception instructions for females and males.	FDA made changes to the format of subsections 8.1-8.3 based on the Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format Guidance. Modified wait times for lactation to equal (b) (4) (3 months) after the last dose. Updated subsection *8.5 Geriatric Use* per the Geriatric Information in Human Prescription Drug and Biological Product Labeling Guidance for Industry.
12 Clinical Pharmacology	Details provided on mechanism of action, pharmacodynamics, and pharmacokinetics.	Updates made to align with current labeling practices and conform with recommendations in the Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format Guidance for Industry. FDA updated subsection *12.2 Pharmacodynamics* with information on the Exposure-Response relationships as per 21 CFR 201.57 (c)(13(i)(B). FDA updated subsection *12.3 Pharmacokinetics* to describe

Section	Applicant's Proposed Labeling	FDA's proposed Labeling
		pharmacokinetic (PK) parameters for only the subset of DLBCL patients.
13 Nonclinical Toxicology		FDA modified product-related findings in subsection *13.2 Animal Toxicology and/or Pharmacology* (initially added by the Applicant) to describe inflammatory-mediated toxicities seen in animal studies, as well as black skin spots potentially related to phototoxicity. This information was added by FDA because of low-incidence findings in patients in clinical trials of (b) (4) that were found to be PBD-related in a meta-analysis of PBD ADCs (Saber et al., 2019).
14 Clinical Studies	Includes description of study ADCT-402-201 design and patient population, overall and complete response rates, and duration of response.	Modified this section to include key patient characteristics in text, rather than tabular format. Inserted median follow-up time. Table 3 (Efficacy Results): -Added results of Partial Response -Included only the primary endpoint of Overall Response Rate (ORR) and Duration of Response (DoR).

Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
		-Footnote added to describe that of 36% of patients who had an objective response were censored prior to 3 months and that 26% of responders had DoR of ≥ 6 months.

The Applicant's Position:
The United States Prescribing Information (USPI) for loncastuximab tesirine meets the regulatory requirements for providing a summary of the essential scientific information needed for its safe and effective use and is consistent with current FDA guidance and best labeling practices.

The FDA's Assessment:
FDA made changes to several sections of the USPI as described above.

Patient Labeling – The FDA's Assessment:
The Patient Prescribing Information (PPI) was reviewed and revised by the FDA's Patient Labeling Team and Review Team. Revisions were made throughout the PPI for consistency with the prescribing information and current labeling policies and practices. For details, refer to the Patient Labeling Team's review filed with BLA 761196.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:
The clinical review team and Division of Risk Management (DRISK) agree that a REMS is not necessary for the safe use of loncastuximab tesirine. There are no additional risk management strategies needed beyond recommended labeling and associated Patient Prescribing Information.

13 Postmarketing Requirements and Commitment

The review team recommends 5 postmarketing requirements (PMR) and 2 postmarketing commitments (PMC). The goal of the postmarketing requirements are to confirm clinical benefit in patients with relapsed or refractory large B-cell lymphoma, further characterize the safety of loncastuximab tesirine, provide information on racial and ethnic minorities consistent with the U.S. large B-cell lymphoma population, determine a safe and appropriate dose in patients with moderate to severe hepatic impairment, and conduct studies in pediatric patients with NHL. The postmarketing commitments are to provide information for the qualification of endotoxin test method for the in-process (b) (4) samples and develop and validate an assay to evaluate the neutralizing capacity of anti-drug antibodies (ADAs) detected in the patient samples

PMR Description
Conduct a randomized, Phase 3 clinical trial to verify and describe the clinical benefit of loncastuximab tesirine-lpyl in patients with relapsed or refractory large B-cell lymphoma. The trial should include sufficient numbers of racial and ethnic minority patients to better reflect the U.S. patient population and allow for interpretation of the results in these patient populations. Patients should be randomized to receive loncastuximab tesirine plus immunotherapy or immunochemotherapy. The primary endpoint should be progression- free survival, with secondary endpoints that include overall survival and objective response rate.

Final Protocol Submission:	03/2020
Trial Completion:	06/2025
Final Report Submission:	12/2025

PMR Description
Conduct a comprehensive analysis evaluating and characterizing the incidence, clinical presentation, management, and outcomes of the potential serious risks of loncastuximab tesirine-associated toxicities of edema, effusion, cutaneous reactions, and inflammatory-

related conditions. Submit an integrated final report from patient-level and pooled analyses of ongoing and completed clinical trials, postmarketing reports and/or literature reports and a comprehensive pharmacovigilance assessment for these potential serious risks.

Draft Analysis Plan Submission	12/2021
Final Analysis Plan Submission:	06/2022
Study Completion:	09/2025
Final Report Submission:	03/2026

PMR Description

Submit an integrated final report containing data from clinical trials to further characterize the exposure of loncastuximab tesirine monotherapy and in combination with immunochemotherapy, the increased risk of severe and serious adverse events, including severe neutropenia, and efficacy among U.S. racial and ethnic minority patients with large B-cell lymphoma. Provide the population pharmacokinetic and exposure-response analyses for both efficacy and safety in the interim report.

Draft Analysis Plan Submission	12/2021
Final Analysis Plan Submission:	06/2022
Interim Report Submission:	03/2025
Study Completion:	09/2025
Final Report Submission:	03/2026

PMR Description

Conduct an open-label, non-randomized, dose-escalation trial to determine a safe and appropriate dosing regimen of loncastuximab tesirine in patients with moderate and severe hepatic impairment, according to the National Cancer Institute Organ Dysfunction Working Group criteria in the target patient population. Collect safety and pharmacokinetic information for loncastuximab tesirine and SG3199 to determine the appropriate starting dose and dosing regimen of loncastuximab tesirine for this population.

Draft Protocol Submission	12/2021
Final Protocol Submission:	09/2022
Trial Completion:	12/2026
Final Report Submission:	06/2027

PMR Description

Conduct a study assessing the efficacy and safety of loncastuximab tesirine in pediatric patients 1 year or older with relapsed or refractory non-Hodgkin lymphoma. The safety

endpoints should determine safety and tolerability of loncastuximab tesirine and identify the recommended dose and schedule. The efficacy endpoints should determine activity as assessed by response rate and durability of response.

Final Protocol Submission	07/2022
Trial Completion:	07/2027
Final Report Submission:	07/2028

PMC Description

Complete the qualification of endotoxin test method for the in-process (b) (4) (b) (4) samples using samples from two additional loncastuximab antibody lots. In addition, complete the qualification of bioburden test method for the in-process samples using samples from two additional loncastuximab antibody lots. The final report should include method qualification reports for endotoxin and bioburden tests.

Final Report Submission	07/2022

PMC Description

Develop and validate an assay to evaluate the neutralizing capacity of anti-drug antibodies (ADAs) detected in the patient samples. The assay should be capable of sensitively detecting neutralizing ADAs in the presence of loncastuximab tesirine levels that are expected to be present in serum at the time of patient sampling. Appropriately bank samples from ongoing clinical trials to evaluate neutralizing antibodies (nAb) in all confirmed ADA-positive samples using the validated assay and correlate with safety and efficacy of loncastuximab tesirine. The final report should include nAb assay validation report and assay standard operating procedure.

Final Report Submission	05/2022

14 Division Director (DHOT) (NME ONLY)

Haleh Saber, PhD, MS
Deputy Division Director (DHOT)

15 Division Director (OCP)

Brian Booth, PhD
Division Director (OCP/DCPI)

16 Division Director (OB)

Thomas Gwise, PhD
Division Director (OB/DBIX)

17 Division Director (Clinical)

Nicole J. Gormley, MD
Division Director (OOD/DHM2)

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

Marc R. Theoret, MD
Acting Supervisory Associate Director (OOD)
Deputy Director (OCE)

19 Appendices

19.1. References

The Applicant's References:

Al-Hamadani M, Habermann TM, Cerhan JR, et al (2015). Non-Hodgkin lymphoma subtype distribution, geodemographic patterns, and survival in the US: A longitudinal analysis of the National Cancer Data Base from 1998 to 2011. Am J Hematol. 90(9):790-795.

Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz H, and Lister T (2014). Recommendations for initial evaluation, staging, and response assessment of Hodgkin and Non-Hodgkin lymphoma: The Lugano classification. J Clin Onc 32(27):3059-3068.

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Hsieh MM, Everhart JE, Byrd-Holt DD, et al. Prevalence of neutropenia in the U.S. population: Age, sex, smoking and ethnic differences. Ann Intern Med. 2007;146:486-492.

Kymriah (tisagenlecleucel) Prescribing Information. May 2018. Novartis Pharmaceuticals Corporation, East Hanover, NJ US.

Monjuvi (tafasitamab-cxix) Prescribing Information. Jul 2020. Morphosys US Inc., Boston, MA US.

Polivy (polatuzumab vedotin-piiq) Prescribing Information. Jun 2019. Genentech, Inc., South San Francisco, CA US.

Puzanov I, Lee W, Chen AP, et al (2011). Phase I pharmacokinetic and pharmacodynamic study of SJG 136, a novel DNA sequence selective minor groove cross linking agent, in advanced solid tumors. Clin Cancer Res 1;17(11):3794 802.

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Saber H, Simpson N, Ricks TK, Leighton JK (2019). An FDA analysis of toxicities associated with PBD-containing antibody-drug conjugates. Regulatory Toxicology and Pharmacology.107:1-8.

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Sehn LH, Gascoyne RD (2015). Diffuse large B-cell lymphoma: optimizing outcome in the context of clinical and biologic heterogeneity. Blood. 125(1):22-32.

Siegel RL, Miller KD, Jemal A. (2019). Cancer statistics, 2019. CA Cancer J Clin. 69(1):7-34.

Xpovio (selinexor) Prescribing Information. Jun 2020. Kayopharm Therapeutics Inc., Newton, MA US.

Yescarta (axicabtagene ciloleucel) Prescribing Information. Jul 2020. Kite Pharma, Inc., Santa Monica, CA US.

The FDA's References:

[1] John A. Hartley (2020): Antibody-drug conjugates (ADCs) delivering pyrrolobenzodiazepine (PBD) dimers for cancer therapy, Expert Opinion on Biological Therapy, DOI: 10.1080/14712598.2020.1776255

[2] Carter, R. H. and R. A. Barrington (2004). "Signaling by the CD19/CD21 complex on B cells." Curr Dir Autoimmun 7: 4-32.

[3] Tedder, T. F. (2009). "CD19: a promising B cell target for rheumatoid arthritis." Nat Rev Rheumatol 5(10): 572-577.

[4] Saber H, Simpson N, Ricks TK, et al. An FDA oncology analysis of toxicities associated with PBD-containing antibody-drug conjugates. Regul Toxicol Pharm. 2019;107:104429.

19.2. Financial Disclosure

The Applicant's Position:
As stated in Section 8.1.2, the Applicant disclosed all financial interests/arrangements with clinical Investigators as per 21 CFR Part 54. None of the Investigators or Sub-investigators involved in the clinical trial (ADCT-402-201) had financial interests to disclose or arrangements that required disclosure. There are no concerns about the integrity of study data based on financial disclosures.

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

Covered Clinical Study (Name and/or Number):* ADCT-402-201

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 256		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements: Not applicable	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided: Not applicable	Yes ☐	No ☐ (Request information from Applicant)

Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: Not applicable	Yes ☐	No ☐ (Request explanation from Applicant)

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

19.3. Nonclinical Pharmacology/Toxicology

Data:
Not applicable.

The Applicant's Position:
Not applicable.

The FDA's Assessment:
Not applicable

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

The FDA's Assessment:

19.4.1. Summary of Bioanalytical Method Validation and Performance

The ADCT-402 drug product consists of an antibody (rB4v1.2) conjugated to a pyrrolobenzodiazepine (PBD) dimer cytotoxic drug (SG3199) through a protease-cleavable valine-alanine linker. The conjugated ADCT-402 drug product is the primary circulating moiety. However, there are measurable concentrations of unconjugated antibody and free SG3199 in circulation. Therefore, analysis was performed to measure:

1) Total loncastuximab tesirine concentration (total unconjugated and conjugated antibody concentration)
2) PBD-conjugated loncastuximab tesirine concentration (SG3199 conjugated antibody concentration)
3) Free SG3199.

Three separate analytical methods were developed for the analyses of the analytes.

Method (b) (4)NL-LML-1656/ (b) (4)-NL-LML-2283: Total Loncastuximab Tesirine
Method (b) (4)NL-LML-1656 (Validation Report: AHD468EL-154683-B) is a ligand binding assay for the determination of total loncastuximab in human serum using an electrochemiluminescence platform. The method is directed to the antibody (rB4v1.2)

component of the ADC and will therefore detect all antibody (rB4v1.2) whether it is conjugated or unconjugated to PBD. The method used a homogenous bridging format with two different mouse anti-idiotypic (anti-ID) antibodies as capture and detection agents. This method was used in study ACDT-402-101 and ADCT-402-201. Method (b) (4)-NL-LML-1656 used the liquid formulation of ADCT-402 drug product to prepare calibration and quality control standards. However, subjects in study ADCT-402-201 were also dosed with the lyophilized formulation of the drug product. For that reason, the two different reference standards were bridged during the conduct of study ADCT-201-201. Method (b) (4) NL-LML-2283 refers to the use of the lyophilized drug product, whereas the liquid drug product is used as the reference standard in Method (b) (4)-NL-LML-1656, otherwise there are no other differences between the two methods.

Methods (b) (4) NL-LML-1656 and (b) (4)-NL-LML-2283 were developed by (b) (4) (b) (4). Method validation assessments for (b) (4)-NL-LML-1656 included precision, accuracy, sensitivity, dilution integrity, dilution linearity, and relevant stability parameters. A summary of the results is included in the table below. Method (b) (4)-NL-LML-1656 Summary.

Table 48: Method (b) (4)-NL-LML-1656 Summary

Sample Volume		20 µL	
Regression		4 parameter logistic	
Weighting factor		$1/y^2$	
Dynamic Range		20-1250 ng/mL	
Calibration standards		20, 40, 65, 120, 220, 400, 700, and 1250 ng/mL	
QC concentrations		50, 250, 1000 ng/mL	
Analyte		Total ADCT-402 (conjugated and unconjugated ADCT-402)	
MRD		1:10	
Lower limit of quantitation		20 ng/mL	
QC Level		LLOQ	Low, Mid, and High
QC Intra-Run Precision Range (%CV)	Run 2	5.6	1.4 - 8.9
	Run 3	3.1	2.8 - 4.8
	Run 4	3.9	3.5 - 6.9
	Run 5	2.4	1.9 - 9.3
	Run 6	3.2	2.3 - 6.8
	Run 7	2.8	4.7 - 7.3
QC Intra-Run Accuracy Range (%Bias)	Run 2	-2.3	-10.6 - 1.5
	Run 3	-1.4	-11.9 - 2.9
	Run 4	7.1	-7.8 - 5.5
	Run 5	4.0	-9.5 - 9.5

	Run 6	-5.0	-6.8 - 2.2
	Run 7	0.7	-15.2 - 8.5
QC Inter-Run Precision Range (%CV)		4.9	4.0 - 6.9
QC Inter-Run Accuracy (%Bias)		-1.5	-10.4 - 5
Dilution Integrity		1:25 dilution up to 25000 ng/mL	
Dilution linearity		3 fold dilutions from 25000 to 11.4 ng/mL were assessed. Prozone effect was observed for concentrations above ULOQ however measured concentrations remained above ULOQ	
Selectivity		Selectivity was determined in normal serum, serum from ALL patients, and serum from NHL patients. All unspiked matrix lots were ≤ 20% of the validated LLOQ. At least 90% of the matrix lots in each group tested were free from interference at 30 and 1000 ng/mL.	
Concomitant drug interference		The following drugs were assessed: duvalumab and ibrutinib	
QC Sample Bench Top Stability		24 hours at room temperature	
QC sample Freeze/Thaw Stability		5 cycles at -20°C and -70°C	
Long Term Stability		402 days at -20°C and -70°C	

During validation of method (b) (4)-NL-LML-1656, unconjugated antibody (rB4v1.2, DAR0) as well as isolated DAR2 and DAR4 fractions were evaluated to ensure the method for total loncastuximab tesirine was able to recognize all fraction types regardless of whether it was conjugated to PBD. The validation showed that all fractions are recognized by the method, however the DAR0 fraction was underestimated at the LLOQ.

Study ADCT-402-101 used method (b) (4)-NL-LML-1656 to analyze 4145 samples in 202 runs. The precision of the QCs was 5.4% to 10.2% and the accuracy was -3.2% to 11%. Eight sample analysis runs were rejected due to failed QC criteria, two sample analysis runs were rejected due to a failed calibration curve, four sample analysis runs were rejected due to preparation errors, one sample analysis run was rejected due to an inconsistent increase in assay signal, and one sample analysis run was rejected due to an inconsistent blank sample response. A total of 560 samples were repeated due to an original result outside the limits of quantitation, an ISR result above the upper limit of quantitation, or the CV of duplicate measurements was above 10%. 8 samples were repeated due to a preparation error and 70 samples were repeated due to a high blank matrix response. A total of 55 samples were repeated in duplicate at the request of the Sponsor due to unexpected results. 23 samples were diluted 50 fold which is above the validated dilution range, however a dilution QC (100,000 ng/mL) with a 100 fold dilution was included in each run with samples diluted above 1:25. 28 samples were analyzed outside of the established long term stability or freeze-thaw stability and the results were included in the bioanalytical report for informational purposes only. Incurred samples reanalysis was performed on 263 samples (~6% of the total number of samples). The absolute relative

difference between the original results and the ISR results was below 30% for 241 of the samples (91.6%).

Study ADCT-402-201 used method (b) (4)-NL-LML-1656 (runs 1-40) and method (b) (4)-NL-LML-2283 (runs 41-77) to analyze 1630 samples. The precision of the QCs was 9.3% to 11.5% and the accuracy was -1.2% to 14.8%. Six sample analysis runs were rejected due to failed QC criteria, one sample analysis run was rejected due to a failing calibration curve, one sample analysis run was rejected due to low signal, and 5 sample analysis runs were rejected due to the use of the wrong detection material. A total of 77 samples were repeated due to an original result outside the limits of quantitation, an ISR result below the limit of quantitation, or the CV of duplicate measurements was above 10%. 12 samples were repeated in duplicate at the request of the Sponsor due to an unexpected result. 14 samples were analyzed outside of the validated long term stability and the results were included in the bioanalytical report for informational purposes only. Incurred sample reanalysis was performed on 165 samples (~10% of the total samples). The absolute relative difference between the original results and the ISR results was below 30% for 156 of the samples (94.5%).

Method (b) (4)NL-LML-1726/ (b) (4)-NL-LML-2284: PBD-conjugated Loncastuximab Tesirine
Method NL-LML-1726 (Validation Report: AHD468EL-154683-D) is a ligand binding assay for the determination of PBD-conjugated loncastuximab tesirine in human serum using an electrochemiluminescence platform. Only antibody (rB4v1.2) that is conjugated with PBD is detected because the capturing antibody is directed to PBD, therefore any unconjugated antibody is not detected. The method used biotinylated mouse anti-PBD antibodies as the capture agent and sulfo-tagged mouse anti-idiotypic (anti-ID) antibodies as the detection agent. This method was used in study ACDT-402-101 and ADCT-402-201. Method (b) (4)-NL-LML-1726 used the liquid formulation of ADCT-402 drug product to prepare the calibration and quality control standards. However, subjects in study ADCT-402-201 were also dosed with the lyophilized formulation of the drug product. For that reason, the two different reference standards were bridged during the conduct of study ADCT-201-201. Method (b) (4)-NL-LML-2284 refers to the use of the lyophilized drug product, whereas the liquid drug product is used as the reference standard in Method (b) (4)-NL-LML-1726, otherwise there are no other differences between the two methods.

Methods (b) (4)-NL-LML-1726 and (b) (4)-NL-LML-2284 were developed by (b) (4) (b) (4). Method validation assessments for (b) (4)-NL-LML-1726 included precision, accuracy, sensitivity, dilution integrity, dilution linearity, and relevant stability parameters. A summary of the results is included in the table below. Method (b) (4)-NL-LML-1726 Summary.

Table 49: Method (b) (4) NL-LML-1726 Summary

Sample Volume	10 uL

Regression		4 parameter logistic	
Weighting factor		$1/y^2$	
Dynamic Range		5.06-3000 ng/mL	
Calibration standards		5.06, 12.6, 31.3, 78, 194, 484, 1200, 3000 ng/mL	
QC concentrations		12, 200, 2400 ng/mL	
Analyte		PBD conjugated ADCT-402	
MRD		1:20	
Lower limit of quantitation		5.06 ng/mL	
QC Level		LLOQ	Low, Mid, and High
QC Intra-Run Precision Range (%CV)	Run 2	1.5	0.9 - 4.2
	Run 3	4.9	1.7 - 4.7
	Run 4	3.4	0.5 - 3.6
	Run 5	2.5	0.9 - 1.6
	Run 6	4.3	1.6 - 4.4
	Run 7	0.6	2.4 - 3.7
QC Intra-Run Accuracy Range (%Bias)	Run 2	-11.5	-8.3 - (-1.9)
	Run 3	-4.1	-11.7 - (-2.2)
	Run 4	16.2	-6.4 - (-1.3)
	Run 5	4.1	-9.7 - (-1.0)
	Run 6	-3.0	-10.3 - (-1.1)
	Run 7	-2.2	-16.3 - (-2.5)
QC Inter-Run Precision Range (%CV)		5.6	2.4 - 4.6
QC Inter-Run Accuracy (% bias)		-12.3	-10.2 - (-1.3)
Dilution Integrity		1:10 dilution up to 30000 ng/mL	
Selectivity		Selectivity was determined in normal serum, serum from ALL patients, and serum from NHL patients. All unspiked matrix lots were $\leq$ 20% of the validated LLOQ. At least 90% of the matrix lots in each group tested were free from interference at 7.5 and 2400 ng/mL.	
Concomitant drug interference		The following drugs were assessed: duvalumab and ibrutinib	
QC Sample Bench Top Stability		24 hours at room temperature	
QC sample Freeze/Thaw Stability		5 cycles at -20 and -70	
Long Term Stability		442 days at -20 and -70	

During validation of method (b) (4)-NL-LML-1726, the potential interference from unconjugated antibody (rB4v1.2, DAR0) was assessed and verified that unconjugated ADCT-402 does not interfere in the assay. The validation also shows that the DAR2 and DAR4 fractions are recognized by the method.

Study ADCT-402-101 used method (b) (4)-NL-LML-1726 to analyze 4142 samples in 205 runs. The precision of the QCs was 4.6% to 14.8% and the accuracy was 0% to 3.3%. 33 sample analysis runs were rejected due to failed QC criteria, three sample analysis runs were rejected due to a failed calibration curve, six sample analysis runs were rejected due to preparation errors, and one sample analysis run was rejected due to an increased response. A total of 280 samples were repeated due to an original result outside the limits of quantitation, an ISR result outside the limit of quantitation, or the CV of duplicate measurements was above 10%. A total of 35 samples were repeated in duplicate at the request of the Sponsor due to unexpected results. Two samples were diluted 20 or 50 fold which is above the validated dilution range, however a dilution QC (120,000 ng/mL) with a 50 fold dilution was included in each run with samples diluted above 1:10. 51 samples were analyzed outside of the established long term stability or freeze thaw stability and the results were included in the bioanalytical report for informational purposes only. Incurred samples reanalysis was performed on 260 samples (~6% of the total number of samples). The absolute relative difference between the original results and the ISR results was below 30% for all samples (100%).

Study ADCT-402-201 used method (b) (4)-NL-LML-1726 (runs 1-37) and method (b) (4)-NL-LML-2284 (runs 38-67) to analyze 1632 samples. The precision of the QCs was 4.4% to 16.2% and the accuracy was 0.5% to 7.1%. Seven sample analysis runs were rejected due to failed QC criteria and two sample analysis runs were rejected because the QC samples had not been bridged. A total of six samples were repeated because the CV of duplicate measurements was above 10%. Six samples were analyzed outside of the validated long term stability and the results were included in the bioanalytical report for informational purposes only. Incurred sample reanalysis was performed on 165 samples (~10% of the total samples). The absolute relative difference between the original results and the ISR results was below 30% for 164 of the samples (99.4%).

Method (b) (4) NL-SML-1769: Free SG3199

Method NL-SML-1769 (Validation Report: AHD469EL-154693-B) is an LC-MS/MS method for the determination of free SG3199 in human serum using a solid-phase extraction method. SG3199-d10 was used as the internal standard. This method was used in study ACDT-402-101 and ADCT-402-201. Method (b) (4)-NL-SML-1769 was developed by (b) (4) (b) (4). Method validation assessments included precision, accuracy, sensitivity, matrix effect, recovery, carryover, dilution integrity, and the relevant stability parameters. A summary of the results is included in the table below. Method (b) (4)-NL-SML-1769 Summary.

Table 50: Method (b) (4)-NL-SML-1769 Summary

Sample Volume	100 µL
Regression	quadratic
Weighting factor	$1/x^2$

Dynamic Range		**25 - 25000 pg/mL**	
Calibration Standards		25, 50, 125, 500, 1250, 5000, 12500, 20000, 25000 pg/mL	
QC concentrations		75, 1250, 20000 pg/mL	
Analyte		SG3199	
Internal Standard		SG3199-d10	
Linearity		$R^2 \geq 0.9976$	
Lower limit of quantitation		25 pg/mL	
% recovery of Analyte		69.0-76.7%	
QC Level		LLOQ	Low, Mid, and High
QC Intra-Run Precision Range (%RSD)	Run 2	2.5	1.3 - 2.2
	Run 3	3.0	1.4 - 2.4
	Run 4	4.8	1.1 - 5.7
QC Intra-Run Accuracy Range (%Bias)	Run 2	0.0	-4.6 - (-1.0)
	Run 3	7.1	-1.2 - (-0.3)
	Run 4	8.5	-3.5 - 2.1
QC Inter-Run Precision Range (%CV		4.9	1.9 - 3.7
QC Inter-Run Accuracy (% Accuracy)		5.2	-3.1 - 2.1
Dilution Integrity		10 fold dilution up to 200000 pg/mL	
Matrix Factor		IS normalized matrix factor of 0.953 at 75 pg/mL with %CV of 4% and 1.03 at 20000 pg/mL with %CV of 2.1%	
Batch Size		not evaluated	
Selectivity		In all cases, SG3199 and SG3199-d10 regions were free from significant interference (≤20.0% of the response of LLOQ and ≤5.0% of internal standard response)	
Carryover		considerable carryover was observed during method validation	
QC Sample Bench Top Stability		20 hours at room temperature	
Processed Sample Stability		147 hours at +10°C	
Reinjection Reproducibility		122 hours at +10°C	
QC sample Freeze/Thaw Stability		5 cycles at -70°C	
Long Term Stability		348 days at -70°C	

The validation also assessed for interference from the conjugated drug product (ADCT-402). The assessment failed for the low QC (75 pg/mL) because the ADCT-402 reference standard also contains a low concentration of free SG3199. The Applicant provided additional data to support the conclusion that there is no significant interference from the ADCT-402 drug product at the low QC. Additionally, benchtop stability assessments were not performed in the presence of ADCT-402 as planned, because of the free SG3199 present in the ADCT-402 reference standard.

The Applicant provided additional development data to support the conclusion that the ADCT-402 is stable during the storage and processing of the subject samples and likely does not impact the measured concentration of SG3199.

Study ADCT-402-101 used method (b) (4)-NL-SML-1769 to analyze 4102 samples in 41 runs. The precision of the QCs was 5.1% to 12.9% and the accuracy was 0.3% to 0.8%. 2 sample analysis runs were rejected due to failed QC criteria. A total of 33 samples were repeated due to internal standard variation and one diluted sample was repeated because the DQCs failed in the run. Incurred samples reanalysis was not performed because too few samples had measurable concentrations (~200 total samples had reportable concentrations above the LLOQ). During method validation, excessive carryover was observed at high concentrations. To monitor carryover during study conduct, 3 blank samples were added after the highest calibration level and all high QC samples. Additionally, a carryover factor was calculated for subject samples during the study to monitor carryover between samples during analysis.

Study ADCT-402-201 used method (b) (4) NL-SML-1769 to analyze 1627 samples in 31 runs. The precision of the QCs was 6.9% to 9.8% and the accuracy was 0.1% to 1.6%. Four sample analysis runs were rejected due to failed QC criteria, one sample analysis run was rejected for preparation errors, and one sample analysis run was rejected due to an instrumental error. 32 samples were repeated due to internal standard variation, results outside of the limit of quantitation, failed dilution QCs, or poor chromatography. 133 samples were analyzed outside of the validated long term stability and the results were included in the bioanalytical report for informational purposes only. Incurred samples reanalysis was not performed because too few samples had measurable concentrations (23 total samples had reportable concentrations above the LLOQ). During method validation, excessive carryover was observed. To monitor carryover during study conduct, 3 blank samples were added after the highest calibration level and all high QC samples. Additionally, carryover was monitored during study conduct by the project manager to ensure subject samples were not impacted.

19.4.2. Summary of Applicant's Population PK Analysis

The Applicant's population PK analyses for loncastuximab tesirine (ADC, total monoclonal antibody [mAb], and its metabolic successor SG3199) were conducted based on 5439 ADC, 5422 total mAb and 5389 SG3199 evaluable concentrations in 328 patients with R/R NHL from Phase 1 Trial ADCT-402-101 (Trial 101) and Phase 2 Trial ADCT-402-201 (Trial 201). The lower limit of quantification (LLOQ) was 0.005 µg/mL for ADC, 0.02 µg/mL for total mAb, and 0.025 ng/mL for SG3199. Approximately 2.5% of ADC, 3.3% of total mAb, and 96% of SG3199 samples were below the LLOQ.

Summary statistics of key baseline continuous and categorical covariates that were evaluated in the population PK analysis are shown in the tables below. The patients had a median (range) age of 65 (20, 94) years, and were primarily White (90%) and with DLBCL (87%). There were 159

(49%), 118 (36%), 50 (15%), and 1 (0.3%) patients with normal renal function, mild, moderate, and severe renal impairment (RI) respectively, according to their creatinine clearance calculated using the Cockcroft-Gault formula. There were 277 (85%) patients with normal hepatic function, 49 (15%) patients with mild hepatic impairment (HI), 1 (0.3%) patient with moderate HI, and no patient with severe HI based on NCI-ODWG criteria. All patients (n = 183) in Trial 101 received liquid formulation, while majority of patients (76%) received the to-be-marketed lyophilized formulation in the registrational Trial 201.

Table 51: Descriptive Statistics of Baseline Continuous Covariates for Patients Included in the Population PK Analysis

	ADCT-402-101 N=183	ADCT-402-201 N=145	Total N=328
Weight (kg)			
N	183	145	328
Mean (SD)	82.2 (22.64)	77.1 (18.71)	80.0 (21.11)
Median	79.6	75.0	78.0
Range	(42.1, 160.5)	(43.9, 152.1)	(42.1, 160.5)
Body mass index (kg/m^2)			
N	181	144	325
Mean (SD)	27.9 (6.59)	26.9 (5.73)	27.5 (6.23)
Median	27.0	26.0	26.6
Range	(16.5, 50.1)	(17.2, 50.5)	(16.5, 50.5)
Body surface area (m^2)			
N	181	144	325
Mean (SD)	1.93 (0.28)	1.86 (0.24)	1.90 (0.27)
Median	1.93	1.86	1.91
Range	(1.36, 2.75)	(1.34, 2.55)	(1.34, 2.75)
Age (yrs)			
N	183	145	328
Mean (SD)	61.7 (14.49)	62.7 (13.63)	62.1 (14.10)
Median	63.0	66.0	64.5
Range	(20.0, 87.0)	(23.0, 94.0)	(20.0, 94.0)
Albumin (g/L)			
N	183	145	328
Mean (SD)	39.70 (4.91)	39.82 (5.33)	39.75 (5.09)
Median	40.00	40.70	40.00
Range	(28.00, 52.00)	(17.00, 49.00)	(17.00, 52.00)
Alanine aminotransferase (U/L)			
N	183	145	328
Mean (SD)	24.3 (23.84)	24.3 (17.46)	24.3 (21.23)
Median	17.0	20.0	19.0
Range	(5.0, 248.0)	(0.9, 130.0)	(0.9, 248.0)
Aspartate aminotransferase (U/L)			
N	183	144	327
Mean (SD)	27.1 (19.45)	25.8 (13.01)	26.5 (16.90)
Median	21.0	22.0	21.0
Range	(10.0, 186.0)	(7.0, 88.0)	(7.0, 186.0)
Creatinine clearance (mL/min)			
N	183	145	328
Mean (SD)	99.7 (44.36)	92.6 (35.58)	96.6 (40.80)
Median	89.2	88.0	88.8

	ADCT-402-101 N=183	ADCT-402-201 N=145	Total N=328
Range	(27.6, 268.3)	(33.8, 211.2)	(27.6, 268.3)
Alkaline phosphatase (U/L)			
N	183	145	328
Mean (SD)	98.9 (56.73)	100.2 (49.53)	99.5 (53.59)
Median	83.0	90.0	86.0
Range	(13.0, 541.0)	(2.9, 376.0)	(2.9, 541.0)
Total bilirubin (µmol/L)			
N	183	145	328
Mean (SD)	8.088 (4.82)	8.509 (3.99)	8.274 (4.47)
Median	6.840	7.353	7.000
Range	(2.907, 32.490)	(1.710, 27.360)	(1.710, 32.490)
Lactate Dehydrogenase (U/L)			
N	183	145	328
Mean (SD)	562.3 (1002.39)	425.9 (364.71)	502.0 (788.93)
Median	323.0	297.0	313.0
Range	(109.0, 9348.0)	(133.0, 2498.0)	(109.0, 9348.0)
Tumor Area (cm^2)			
N	180	141	321
Mean (SD)	61.3 (119.77)	33.2 (45.77)	49.0 (95.58)
Median	34.1	18.7	25.4
Range	(1.2, 1237.2)	(1.3, 299.4)	(1.2, 1237.2)
Lymphocytes (10^9 Cell/L)			
N	183	145	328
Mean (SD)	3.5 (25.14)	1.0 (1.04)	2.4 (18.81)
Median	0.7	0.7	0.7
Range	(0.1, 330.3)	(0.0, 9.2)	(0.0, 330.3)

Source: Population PK Analysis Report, Table 6.

Table 52: Descriptive Statistics of Baseline Categorical Covariates for Patients Included in the Population PK Analysis

	ADCT-402-101 N=183	ADCT-402-201 N=145	Total N=328
Dose			
N	183	145	328
15 µg/kg	4 (2.2%)	0 (0.0%)	4 (1.2%)
30 µg/kg	4 (2.2%)	0 (0.0%)	4 (1.2%)
60 µg/kg	4 (2.2%)	0 (0.0%)	4 (1.2%)
90 µg/kg	5 (2.7%)	0 (0.0%)	5 (1.5%)
120 µg/kg	42 (23.0%)	0 (0.0%)	42 (12.8%)
150 µg/kg	88 (48.1%)	145 (100%)	233 (71.0%)
200 µg/kg	36 (19.7%)	0 (0.0%)	36 (11.0%)

	ADCT-402-101 N=183	ADCT-402-201 N=145	Total N=328
Sex			
N	183	145	328
Men	114 (62.3%)	85 (58.6%)	199 (60.7%)
Women	69 (37.7%)	60 (41.4%)	129 (39.3%)
Race			
N	181	145	326
White	164 (90.6%)	130 (89.7%)	294 (90.2%)
Black or African American	11 (6.1%)	5 (3.4%)	16 (4.9%)
Asian	3 (1.7%)	3 (2.1%)	6 (1.8%)
Other	3 (1.7%)	7 (4.8%)	10 (3.1%)
Race category			
N	181	145	326
White	164 (90.6%)	130 (89.7%)	294 (90.2%)
Non-White	17 (9.4%)	15 (10.3%)	32 (9.8%)
Age			
N	183	145	328
<65 yr	99 (54.1%)	65 (44.8%)	164 (50.0%)
≥65 yr	84 (45.9%)	80 (55.2%)	164 (50.0%)
Weight			
N	183	145	328
<65 kg	45 (24.6%)	37 (25.5%)	82 (25.0%)
65 to 85 kg	70 (38.3%)	66 (45.5%)	136 (41.5%)
≥85 kg	68 (37.2%)	42 (29.0%)	110 (33.5%)
Creatinine clearance category			
N	183	145	328
≥90 mL/min	90 (49.2%)	69 (47.6%)	159 (48.5%)
≥60 - <90 mL/min	66 (36.1%)	52 (35.9%)	118 (36.0%)
≥30 - <60 mL/min	26 (14.2%)	24 (16.6%)	50 (15.2%)
≥15 - <30 mL/min	1 (0.5%)	0 (0.0%)	1 (0.3%)
Hepatic dysfunction			
N	183	144	327
Normal	155 (84.7%)	122 (84.7%)	277 (84.7%)
Mild dysfunction	27 (14.8%)	22 (15.3%)	49 (15.0%)
Moderate dysfunction	1 (0.5%)	0 (0.0%)	1 (0.3%)
Baseline ECOG score			
N	183	145	328
0	54 (29.5%)	58 (40.0%)	112 (34.1%)
1	106 (57.9%)	78 (53.8%)	184 (56.1%)
2	21 (11.5%)	9 (6.2%)	30 (9.1%)
3	2 (1.1%)	0 (0.0%)	2 (0.6%)

	ADCT-402-101 N=183	ADCT-402-201 N=145	Total N=328
Disease subtype			
N	183	145	328
DLBCL	139 (76.0%)	145 (100%)	284 (86.6%)
Others	44 (24.0%)	0 (0.0%)	44 (13.4%)
Drug Formulation			
N	183	145	328
Liquid	183 (100%)	35 (24.1%)	218 (66.5%)
Lyophilized	0 (0.0%)	110 (75.9%)	110 (33.5%)
Anti-drug Antibody			
N	172	140	312
Pre-existing	5 (2.9%)	1 (0.7%)	6 (1.9%)
Post-dose Positive	1 (0.6%)	0 (0.0%)	1 (0.3%)
Other [a]	166 (96.5%)	139 (99.3%)	305 (97.8%)

Source: Population PK Analysis Report, Table 7.

The Applicant's model development was initiated with an integrated two-compartment model with linear clearance (CL) for structural model development for ADC and total mAb using PK data from Phase 1 trial only. The Phase 1 trial provided PK data in a wider dosing range than Phase 2 data, and hence was more informative. After the structural model was established, pooled PK data from Phase 1 and Phase 2 trials were used to develop the base PK model. Selected covariates were assessed at both screening and stepwise forward selection/backward elimination steps. After the final covariate model was determined, the SG3199 model component was added because SG3199 was considered to have little impact on both structural model selection and covariate modeling. The final model was validated by visual predictive check (VPC) and bootstrap. The final population PK model was used to derive individual PK exposure metrics in patients with NHL for subsequent exposure-response (E-R) analysis.

Final PK Models for ADC and total mAb

A two-compartment linear model with a linear CL and time-dependent CL (DELT) in parallel was chosen as the final structural model of ADC, and total mAb. The covariate analysis identified 5 statistically significant covariates, including body weight (BW), ECOG, albumin, and sex on linear CL, disease status and albumin on DELT, sex on first-order rate constant of DELT decrease over time (K_{des}), as well as BW and sex on volume of central compartment (V_1). The inclusion of these covariates reduced between-subject variability (BSV) for CL by 13.3%, BSV for V1 by 15.6%, and BSV for DELT by 15.5%.

The population PK parameters of the final models for ADC and total mAb are presented in the table below. The parameter estimates of the final population PK model were in close agreement to the median values of 104 resampled bootstrapping runs (Table 54), which demonstrated good stability of the final PK model.

Table 53: PK Parameter Estimates from Final ADC Population PK Model

Parameters	Symbol	Estimate (%RSE)
CL (L/day)	θ1	0.218 (8.6)
WT on CL	θ10	0.438 (45.5)
ECOG on CL	θ13	0.275 (44.4)
ALBU on CL	θ14	-0.406 (83.7)
SEX on CL	θ20	-0.170 (45.5)
V1 (L)	θ2	3.86 (4.1)
WT on V1	θ15	0.539 (25.9)
SEX on V1	θ21	-0.0792 (69.1)
CL_{dec} (L/day)	θ3	0.0441 (11)
V2 (L)	θ4	3.53 (fixed)
DELT (L/day)	θ5	0.117 (18.1)
PTST on DELT	θ18	11.45 (28.9)
ALBU on DELT	θ28	-7.18 (11.4)
Q (L/day)	θ6	1.16 (fixed)
K_{des} (1/day)	θ7	0.0347 (16.2)
SEX on K_{des}	θ23	0.652 (69.5)
BSV of CL (%CV)	η1	44.9 (9.7)
BSV of V1 (%CV)	η2	31.8 (9.7)
BSV of CL_{dec} (%CV)	η3	89.4 (6.4)
BSV of V2 (%CV)	η4	54 (12.1)
BSV of DELT (%CV)	η5	149.4 (13)
BSV of Q (%CV)	η6	129.6 (12.2)
BSV of K_{des} (%CV)	η7	97.3 (25.7)
BOV of CL (%CV)	η8	25.7 (fixed)
BOV of V1 (%CV)	η11	32.7 (fixed)
BOV of CL_{dec} (%CV)	η14	57.1 (fixed)
BOV of V2 (%CV)	η17	24.9 (fixed)
ADD ERR1 (%CV)	θ8	21.1 (0.5)
ADD ERR2 (%CV)	θ9	22.2 (0.5)

Key: ADD ERR1= additive error of PBD-conjugated Ab on a log scale; ADD ERR2= additive error of Total Ab on a log scale; CL= linear clearance; CL_{dec}= deconjugation clearance; CV= coefficient of variation; BSV= between-subject variability; BOV= between-occasion variability; partially time-dependent clearance = DELT*exp(-Kdes*t); Q=inter-compartmental clearance; %RSE = %relative standard error; V_1= volume of distribution in the central compartment; V_2= volume of distribution in the peripheral compartment; WT= body weight; PTST= disease subtype; ALBU= albumin;

Note: The objective function value= - 15096.39. Condition number = 104.24. Condition number was calculated as the ratio of the largest to smallest eigenvalue of correlation matrix of estimate. The typical values (TV) of PK parameters, $TVCL = 0.218 \cdot \left(\frac{WT}{78.0}\right)^{0.438} \cdot \left(\frac{ALB}{40.0}\right)^{-0.406} \cdot ECOG_{CL} \cdot SEX_{CL}$, where $ECOG_{CL}$ is a shift factor of 1 for ECOG=0 patients, and 1 + 0.275 for ECOG>0 patients, and SEX_{CL} is a shift factor of 1 for male patients, and 1 - 0.17 for female patients. $TVV1 = 3.86 \cdot \left(\frac{WT}{78.0}\right)^{0.539} \cdot SEX_{V1}$, where SEX_{V1} is a shift factor of 1 for male patients and $1 - 0.0792$ for female patients. $TVDELT = 0.117 \cdot \left(\frac{ALBU}{40.0}\right)^{-7.18} \cdot PTST_{DELT}$, where $PTST_{DELT}$ is a shift factor of 1 for DLBCL patients, and 1 + 11.45 for non-DLBCL patients, and TVKdes = 0.0347* SEX_{KDES}, where SEX_{KDES} is a shift factor of 1 for male, and 1 + 0.652 for female.

Source: Population PK Analysis Report, Table 10.

Table 54: Bootstrap Validation of Population Pharmacokinetics Parameters of ADCT-402 PBD-Conjugated Antibody and Total Antibody

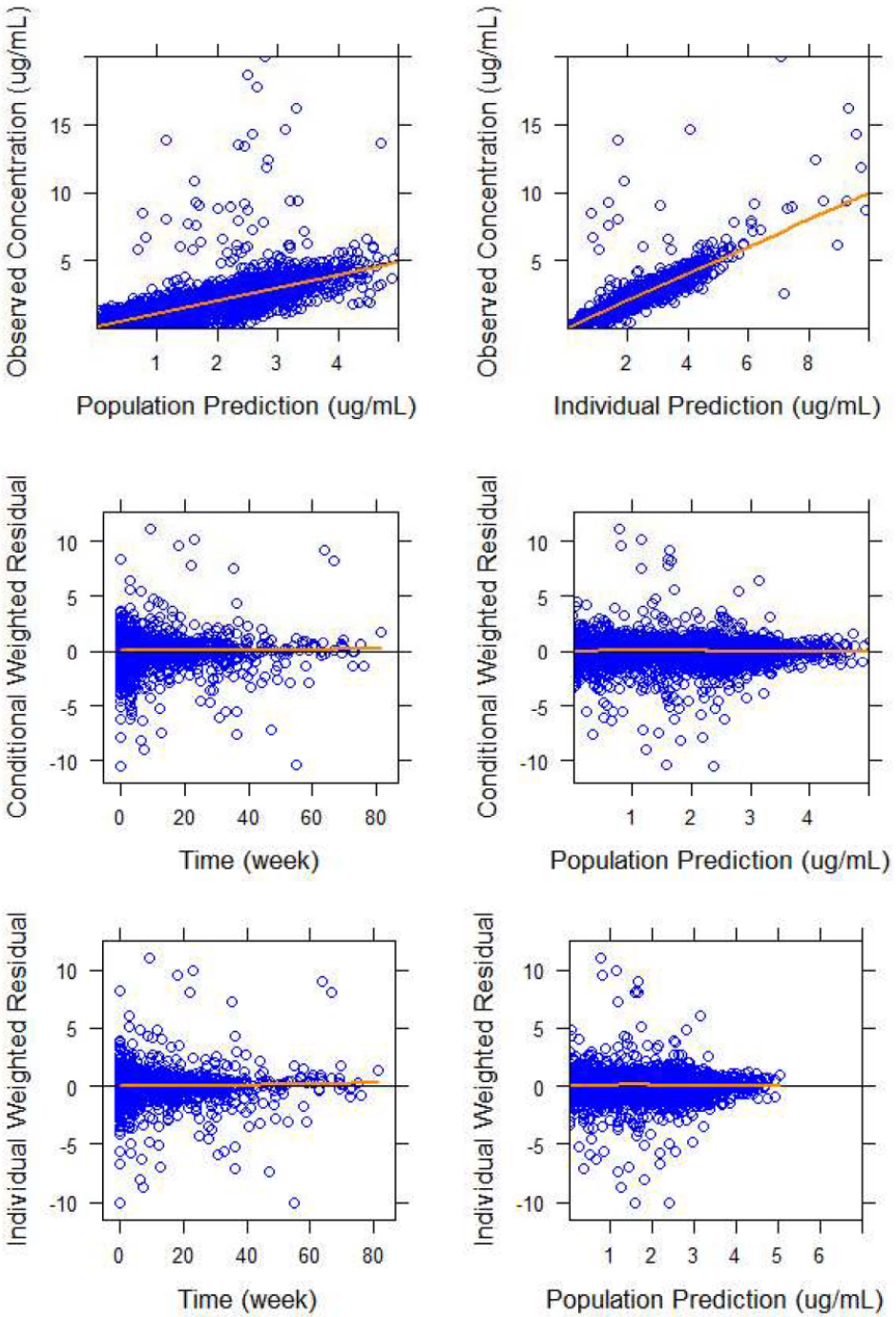
Parameters [a]	Symbol	Estimate (%RSE) [b]	Bootstrap Median (95% CI) [c]
CL (L/day)	θ1	0.218 (8.6)	0.212 (0.182 - 0.241)
WT on CL	θ10	0.438 (45.5)	0.494 (0.181 - 0.781)
ECOG on CL	θ13	0.275 (44.2)	0.286 (0.164 - 0.493)
ALBU on CL	θ14	-0.41 (83.7)	-0.42 (-0.86 - -0.03)
SEX on CL	θ20	-0.1699 (45.5)	-0.1199 (-0.3037 - 0.0122)
V1 (L)	θ2	3.86 (4.1)	3.94 (3.67 - 4.30)
WT on V1	θ15	0.5 (25.9)	0.6 (0.4 - 0.7)
SEX on V1	θ21	-0.0792 (69.1)	-0.0974 (-0.1827 - 0.0272)
CL_{dec} (L/day)	θ3	0.0441 (11)	0.0437 (0.0379 - 0.0478)
V2 (L)	θ4	3.53 (fixed)	3.53 (fixed)
DELT (L/day)	θ5	0.117 (18.1)	0.110 (0.068 - 0.151)
PTST on DELT	θ18	11.45 (28.9)	10.53 (4.23 - 20.69)
ALBU on DELT	θ28	-7.18 (11.4)	-6.12 (-7.20 - -4.08)
Q (L/day)	θ6	1.16 (fixed)	1.16 (fixed)
K_{des} (1/day)	θ7	0.0347 (16.2)	0.0348 (0.0213 - 0.0605)
SEX on K_{des}	θ23	0.652 (69.5)	0.652 (0.014 - 2.015)
BSV of CL (%CV)	η1	44.9 (9.7)	43.4 (31.5 - 57.4)
BSV of V1 (%CV)	η2	31.8 (9.7)	31.8 (24.6 - 42.9)
BSV of CL_{dec} (%CV)	η3	89.4 (6.4)	88.0 (44.1 - 129.6)
BSV of V2 (%CV)	η4	54 (12.1)	53.0 (42.0 - 64.8)
BSV of DELT (%CV)	η5	149.4 (13)	148.4 (130.7 - 181.7)
BSV of Q (%CV)	η6	129.6 (12.2)	129.2 (116.5 - 144.9)
BSV of K_{des} (%CV)	η7	97.3 (25.7)	98.8 (85.4 - 117.5)
BOV of CL (%CV)	η8	25.7 (fixed)	25.7 (fixed)
BOV of V1 (%CV)	η11	32.7 (fixed)	32.7 (fixed)
BOV of CL_{dec} (%CV)	η14	57.1 (fixed)	57.1 (fixed)
BOV of V2 (%CV)	η17	24.9 (fixed)	24.9 (fixed)
ADD ERR1 (%CV)	θ8	21.1 (0.5)	21.0 (16.9 - 24.6)
ADD ERR2 (%CV)	θ9	22.2 (0.5)	22.2 (18.0 - 26.1)

[a] Definition of covariate factors are listed in Section 2.5
[b] run235
[c] run235bs bootstrap replicated at least 100 times.

Source: Population PK Analysis Report, Attachment 38.

The goodness-of-fit plots for ADC (Figure 9) and total mAb (Figure 10), and visual predictive check (VPC) plots stratified by sex for ADC (Figure 11) and total mAb (Figure 12) indicate that the final population PK model adequately describes the ADC and total mAb data.

Figure 9: Goodness of Fit Diagnostic Plots of ADC for the Final Population PK Model



Source: Population PK Analysis Report, Attachment 26.

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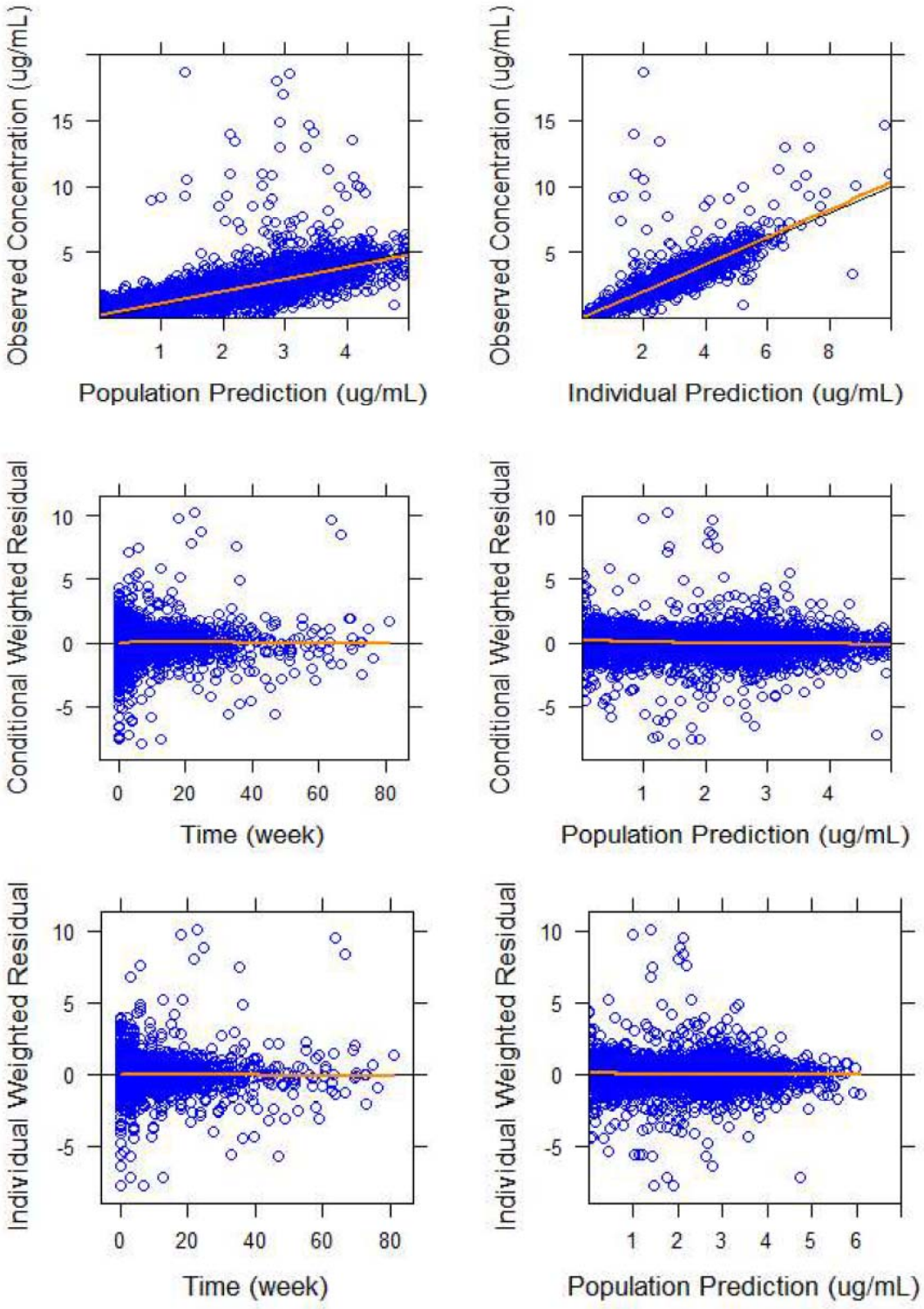
Figure 10: Goodness of Fit Diagnostic Plots of total mAb for the Final Population PK Model



Source: Population PK Analysis Report, Attachment 26.

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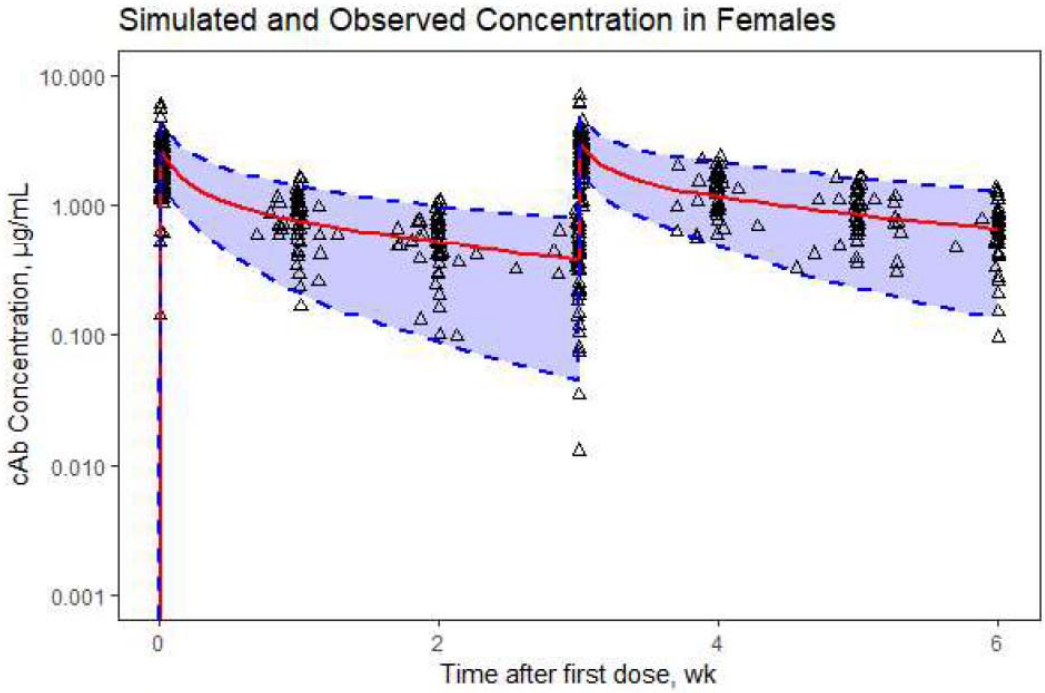
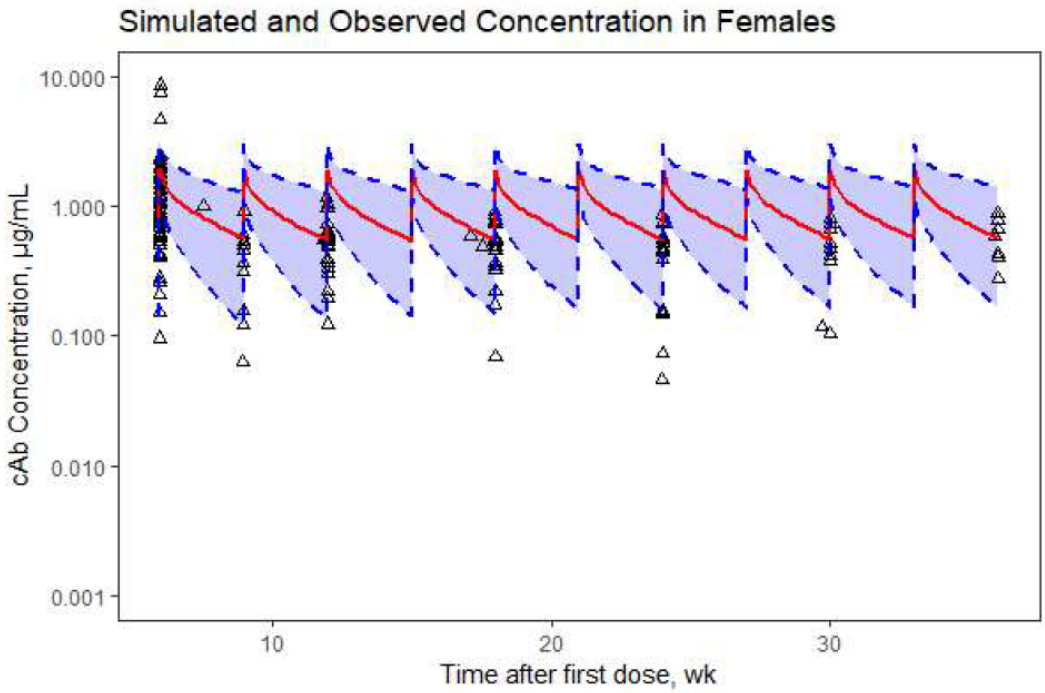
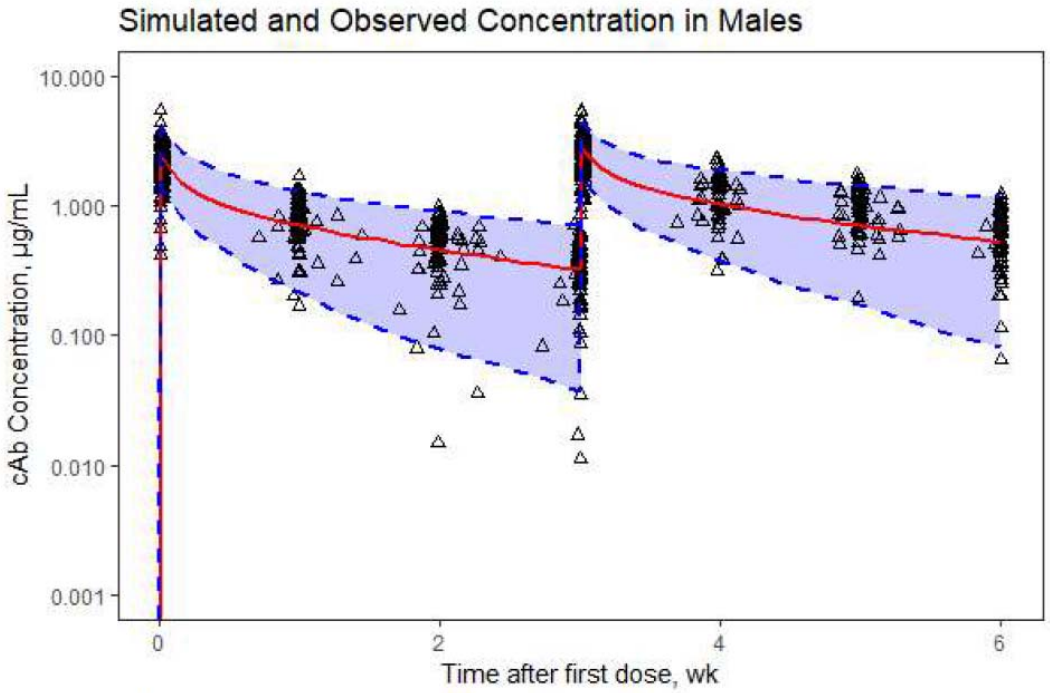
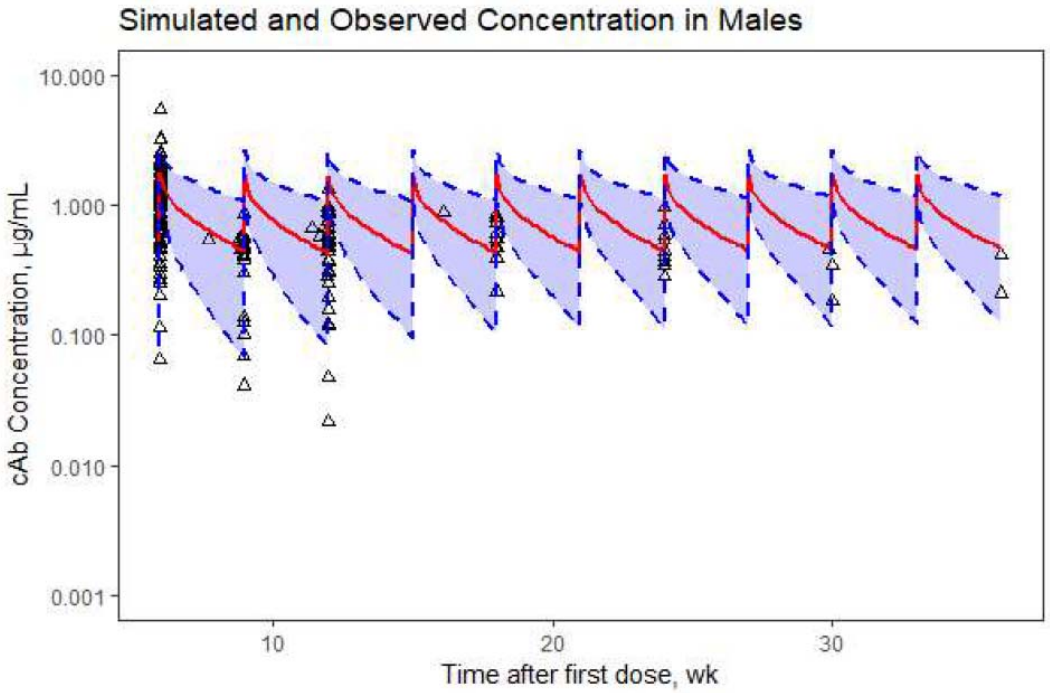
Figure 11: Visual Predictive Check of ADC Concentrations from Trial 201 for the Final PPK Model by Sex





* The solid red line represents the median model-predicted values, and the dashed blue line indicate the model-predicted 95% confidence interval. The black triangle markers represent observed PK data.

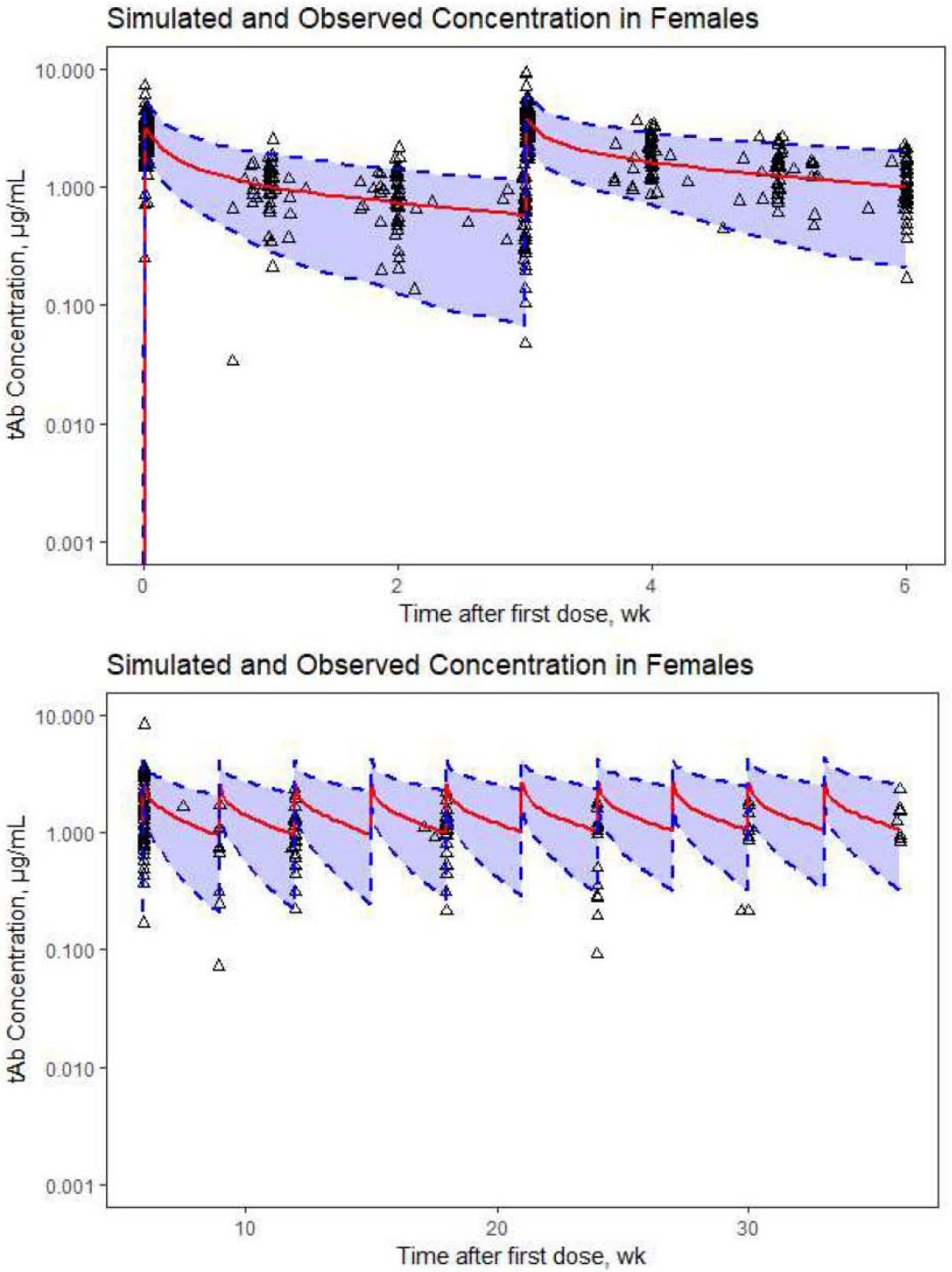




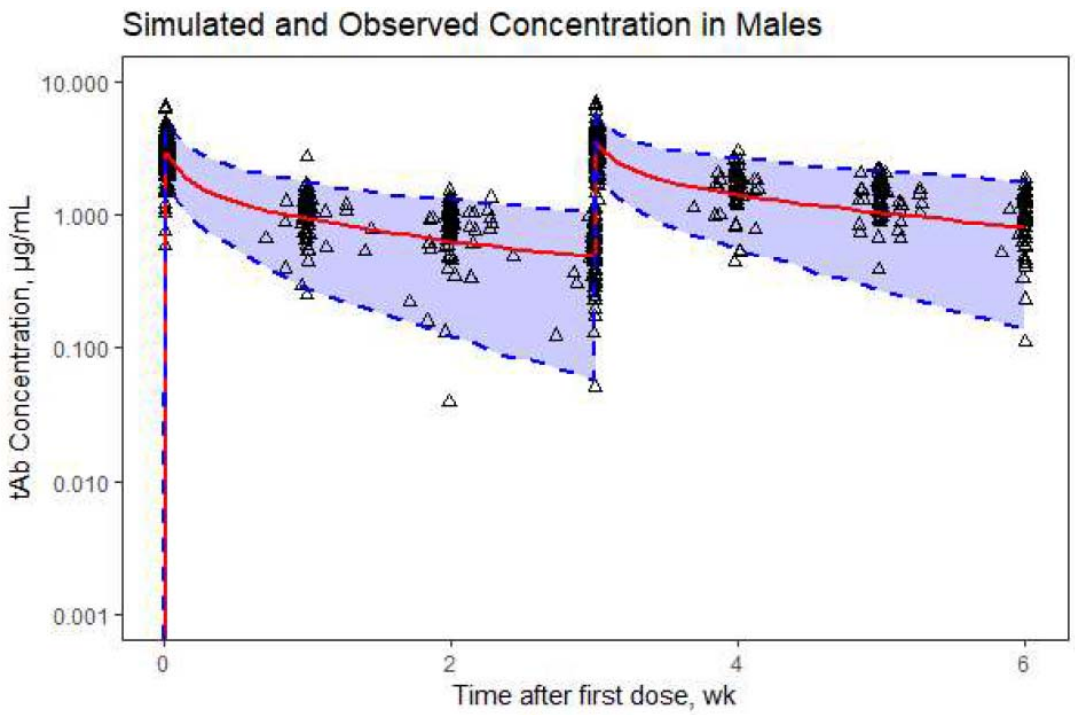
* The solid red line represents the median model-predicted values, and the dashed blue line indicate the model-predicted 95% confidence interval. The black triangle markers represent observed PK data.

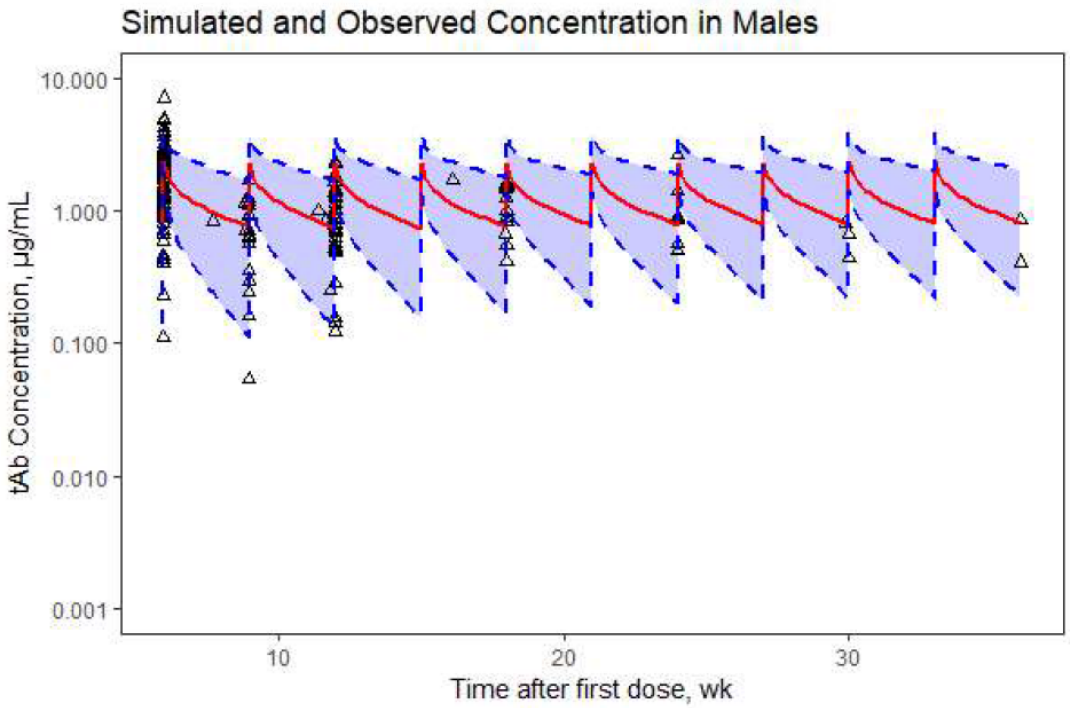
Source: Population PK Analysis Report, Attachment 35.

Figure 12: Visual Predictive Check of Total mAb Concentrations from Trial 201 for the Final PPK Model by Sex



* The solid red line represents the median model-predicted values, and the dashed blue line indicate the model-predicted 95% confidence interval. The black triangle markers represent observed PK data.





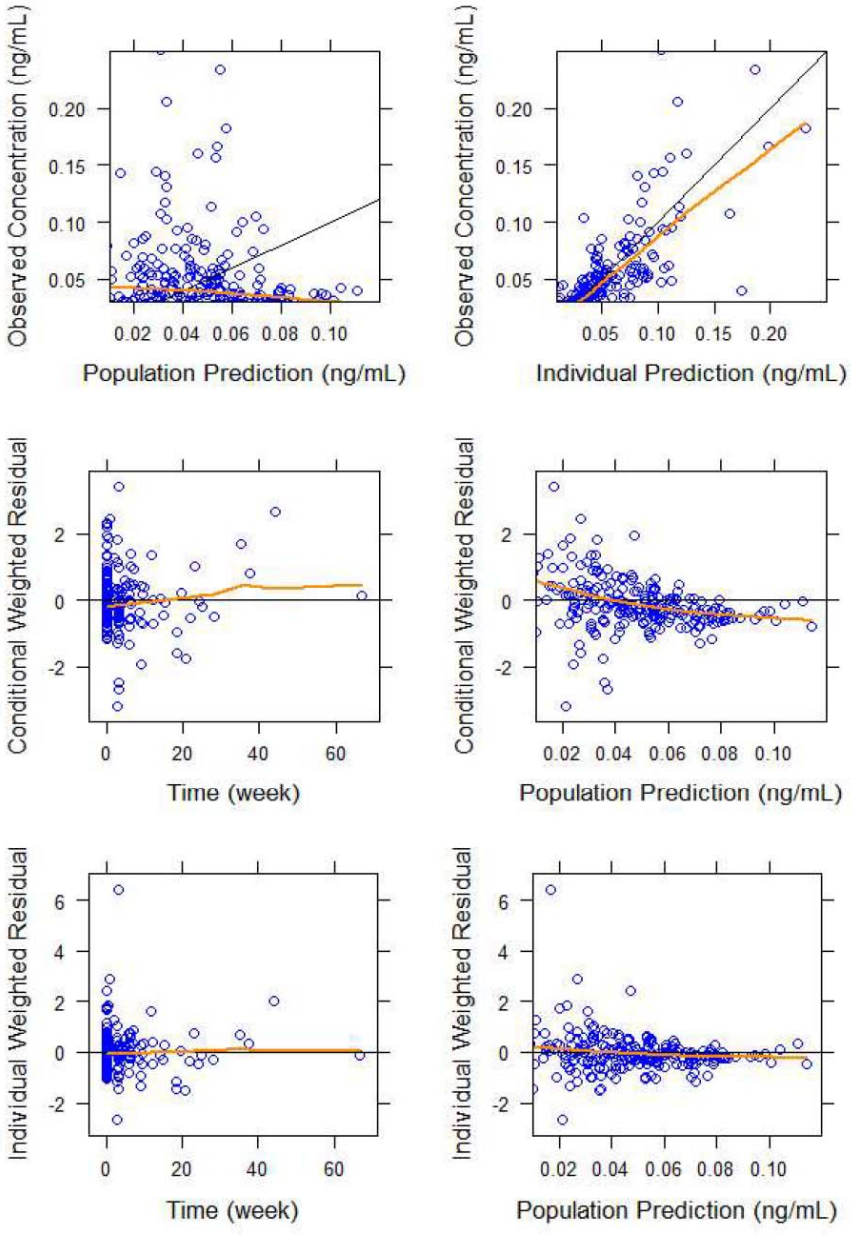
* The solid red line represents the median model-predicted values, and the dashed blue line indicate the model-predicted 95% confidence interval. The black triangle markers represent observed PK data.

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

Final PK Model of SG3199

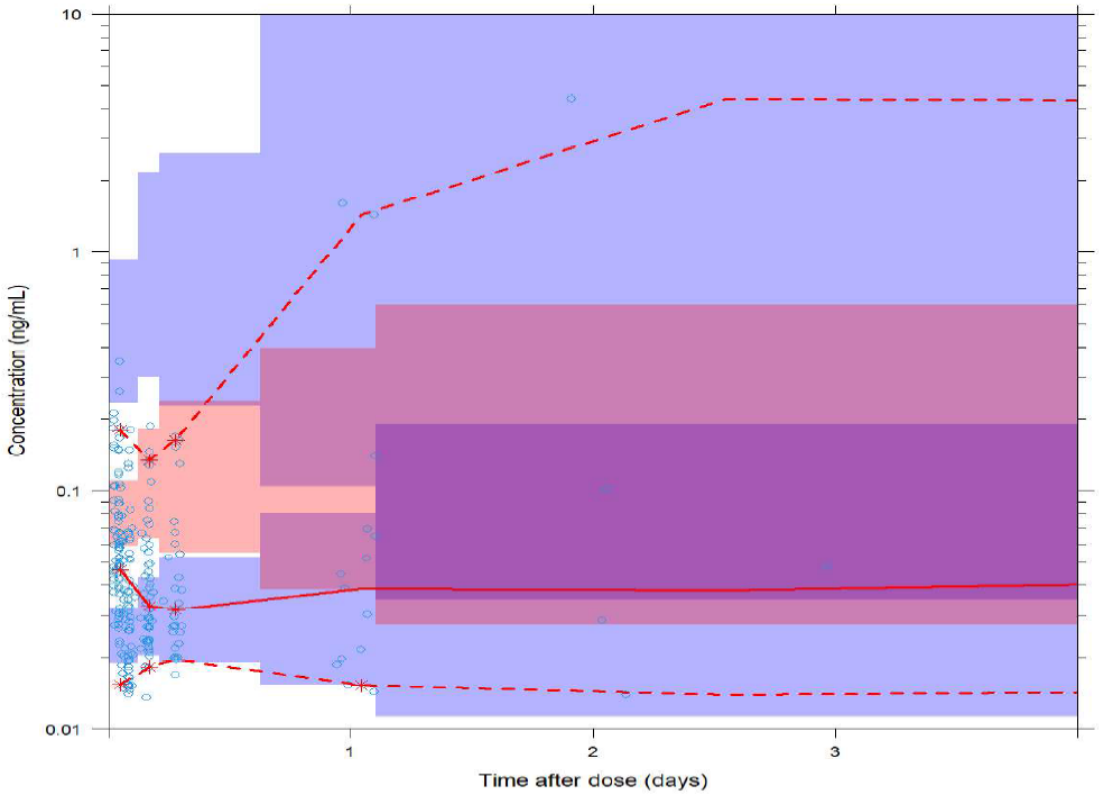
The PK of SG3199 was described with a linear one-compartment model linked to ADC, where the input rate of SG3199 was governed by the first-order degradation of ADC. The clearance for SG3199 (CL_{SG}) were estimated to be 1.9 L/day (RSE: 16.6%) with a BSV of 124.9%. The volume of distribution for SG3199 (V_5) was estimated to be 0.0492 L (RSE: 23.0%). The goodness-of-fit plots and VPC plots for the final SG3199 PK model are presented in Figure 13 and Figure 14, respectively.

Figure 13: Goodness of Fit Plots for Final SG3199 Population PK Model



Source: Population PK Analysis Report, Attachment 32.

Figure 14: VPC for Final SG3199 Population PK Model

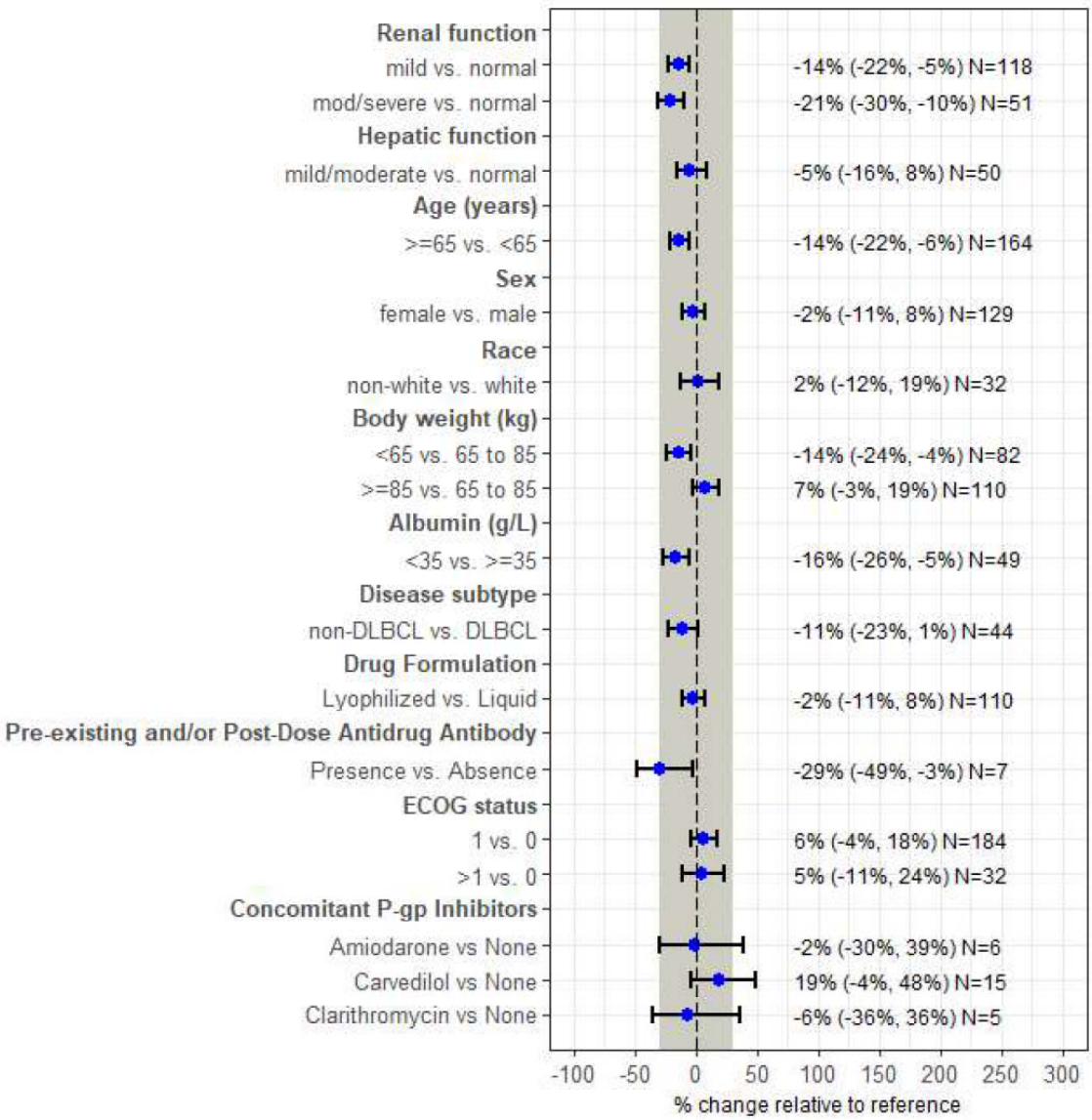


Source: Population PK Analysis Report, Attachment 35.

Based on the final ADC population PK model, post-hoc ADC PK exposures were compared in subgroups based on simulation assuming that all subjects received 150 µg/kg loncastuximab Q3W for two cycles, and 75 µg/kg Q3W for remaining cycles in the same dosing schedules as in Trial 201. The forest plots of subgroup analyses on the corresponding percent change relative to reference values of model-predicted Cycle 1 ADC Cmax and Cavg are presented in Figure 15 and Figure 16, respectively. The median Cycle 1 Cavg of ADC in patients with abnormally low albumin (n=49) is 52% lower than that in patients with normal albumin (n=279). Simulations indicated that the dosage adjustment to 220 ug/kg Q3W x 2, 110 ug/kg Q3W thereafter for patients with abnormally low albumin is expected to achieve a generally comparable exposure (14% lower) to those with normal albumin. ADC exposures in patients with mild/moderate hepatic impairment (n=50) was 42% lower than that in patients with normal hepatic function. Lower drug exposure in hepatic impaired patients is not expected, and it could be explained by other factors such as disease subtype and below normal serum albumin level. No clinically important influence of mild to moderate renal impairment (30≤ CRCL <90 mL/min), age, sex, race, BW, drug formulation, pre-

existing and/or post-dose ADA, ECOG performance status, or concomitant P-gp inhibitors on ADC exposures were observed in patients with DLBCL after loncastuximab dose was adjusted by BW.

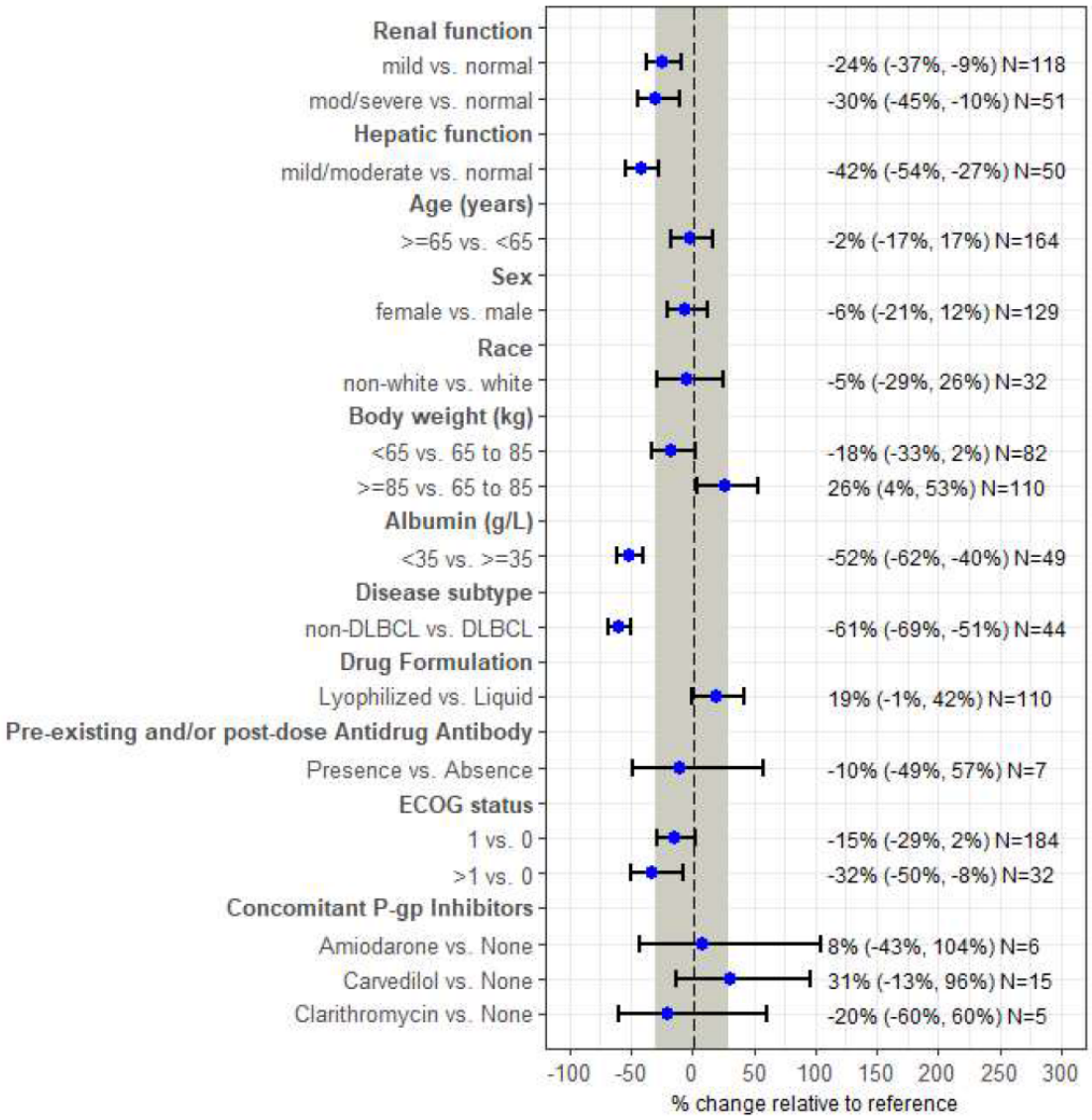
Figure 15: Forest Plot of Subgroup Analyses on Percent Change Relative to Reference Value of Model-Predicted Cycle One Peak ADCT-402 PBD-Conjugated Antibody Concentration



Key: Solid blue circle represents mean and error bar represents 95% confidence interval. Dashed line represents reference value of 0. Numbers represent ratio, confidence interval, and number of patients in the comparison groups. Gray shaded region represents ±30% from reference value. ECOG=Eastern Cooperative Oncology Group disease status at the baseline; DLBCL= Diffuse Large B-cell Lymphoma. Note: Analyses assumed that all patients received 150 µg/kg ADCT-402 30 min IV infusion once every 3 weeks. Peak concentration was derived as the post-infusion concentration of the 1th dose. The number of patients in the reference group for each covariate: normal renal function (N=159); normal hepatic function (N=277); age <65 yr (N=164); male (N=199); white (N=294); body weight from 65 to 85 kg (N=136); DLBCL (N=284); ECOG=0 (N=112); albumin from 35 to 52 g/L (N=279); liquid drug form (N=218); absence of anti-drug antibody (N=305); no concomitant P-gp inhibitors (N=302). Three body weight subgroups are 42.1 to 65 kg, 65 to 85 kg, and 85 to 160.5 kg. Two albumin subgroups are 17 to 34 g/L, 35 to 52 g/L.

Source: Population PK Analysis Report, Figure 9.

Figure 16: Forest Plot of Subgroup Analyses on Percent Change Relative to Reference Value of Model-Predicted Cycle One Cavg ADCT-402 PBD-Conjugated Antibody Concentration

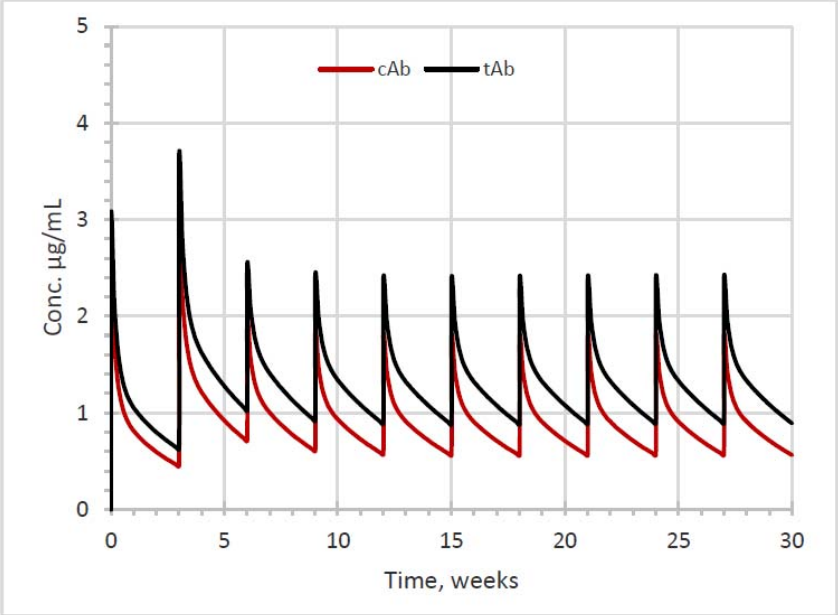


Key: Solid blue circle represents mean and error bar represents 95% confidence interval. Dashed line represents reference value of 0. Numbers represent ratio, confidence interval, and number of patients in the comparison groups. Gray shaded region represents ±30% from reference value. ECOG=Eastern Cooperative Oncology Group disease status at the baseline; DLBCL= Diffuse Large B-cell Lymphoma. Note: Analyses assumed that all patients received 150 µg/kg ADCT-402 30 min IV infusion once every 3 weeks. The number of patients in the reference group for each covariate: normal renal function (N=159); normal hepatic function (N=277); age <65 yr (N=164); male (N=199); white (N=294); body weight from 65 to 85 kg (N=136); DLBCL (N=284); ECOG=0 (N=112); albumin from 35 to 52 g/L (N=279); liquid drug form (N=218); absence of anti-drug antibody (N=305); no concomitant P-gp inhibitors (N=302). Three body weight subgroups are 42.1 to 65 kg, 65 to 85 kg, and 85 to 160.5 kg. Two albumin subgroups are 17 to 34 g/L, 35 to 52 g/L.

Source: Population PK Analysis Report, Figure 11.

The typical parameter estimates of the final population PK model was used to simulate a concentration-time profiles of total mAb and ADC at 150 g/kg loncastuximab tesirine IV infusion Q3W for 2 cycles, followed by 75 g/kg Q3W thereafter (Figure 17). The ratio of the steady state peak concentration of ADC after Q3W dosing of 75 µg/kg loncastuximab tesirine and the peak concentration after the first dose was 1.26.

Figure 17: Typical Pharmacokinetic Profiles of ADCT-402 Total Antibody, and PBD-conjugated Antibody

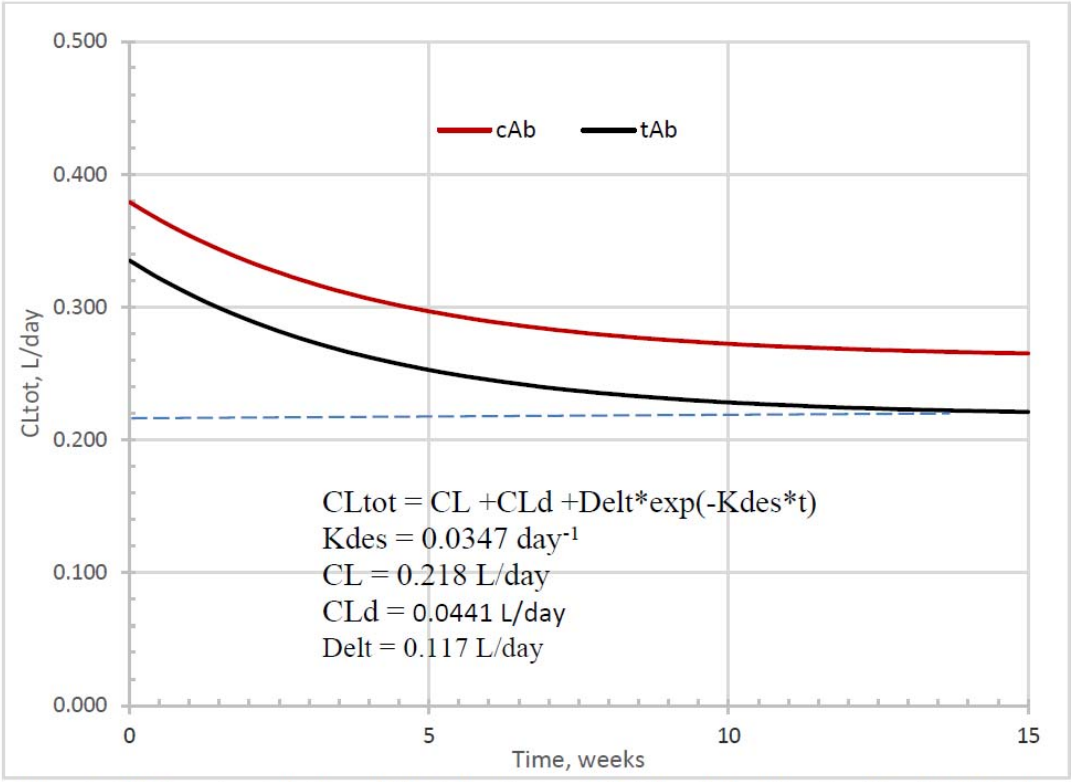


* Red line for PBD-conjugated Ab, and black line for total Ab

Source: Population PK Analysis Report, Figure 12.

As part of the clearance of loncastuximab is time-dependent, the dynamics of the total clearance profiles of loncastuximab ADC and total mAb is presented in Figure 18. The time-dependent clearance declined exponentially at the rate of 0.0347 per day (K_{des}), and approached to zero in ~ 15 weeks. The total clearance of total Ab approached 0.218 L/day in ~15 weeks.

Figure 18: Predicted Total Clearance Versus Time Profiles of ADCT-402 Total Antibody and PBD-conjugated Ab



* Red line for PBD-conjugated Ab, and black line for total Ab. Blue dashed line for CL of 0.218 L/day

Source: Population PK Analysis Report, Figure 13.

Reviewer's Comments: *The Applicant's population PK models were generally able to describe the observed concentration-time profiles of ADC and total mAb following the administration of loncastuximab tesirine ranged from 15 to 200 µg/kg Q3W or Q6W in patients with R/R NHL. Although there appears to be some underprediction for C_{max}, the final PK models are acceptable to generate the main post-hoc exposure metrics, i.e. C_{avg}, and C_{min} of ADC in Cycles 1, 2, and 3 for exposure-efficacy and safety analyses. The time-dependent total clearance for loncastuximab ADC generally approached the steady state in ~10 weeks (Figure 18), suggesting no further dose reduction is needed after Cycle 3.*

The Applicant's final population PK model for SG3199 is not acceptable as the estimated volume of distribution (0.0492 L) was much lower than the extracellular fluid volume. This is mainly because ~96% of SG3199 PK samples were below the LLOQ of 0.025 ng/mL and thus removed from the population PK analysis. Therefore, SG3199 exposure-efficacy and safety analyses should be based on SG3199 observed PK data, rather than the derived PK metrics from the model.

Covariate analysis revealed that body weight was significant covariate for CL and V_1 of ADC, which supports the BW-based dosing regimen. Although Cycle 1 Cavg of ADC in patients with abnormally low albumin was found 52% lower than that in patients with normal albumin, this may be due to some other confounding factors in correlation with albumin. In addition, no clinically significant difference in loncastuximab exposures were found between patients with normal liver function and patients with mild hepatic impairment. As such, no dose adjustment is recommended for patients with abnormally low albumin or mild hepatic impairment. Loncastuximab exposures were also not clinically significantly altered by sex, age (20 to 94 years), race (white vs. black), mild to moderate renal impairment, pre-existing and/or post-dose ADA, ECOG performance status (0, 1, or 2), or concomitant P-gp inhibitors after the dose was adjusted by body weight. Therefore, no dose adjustment is needed for the above-mentioned specific populations. There are insufficient PK data from the limited number of patients in Asian and other racial subgroups to inform the need of dose adjustment for these specific patient populations.

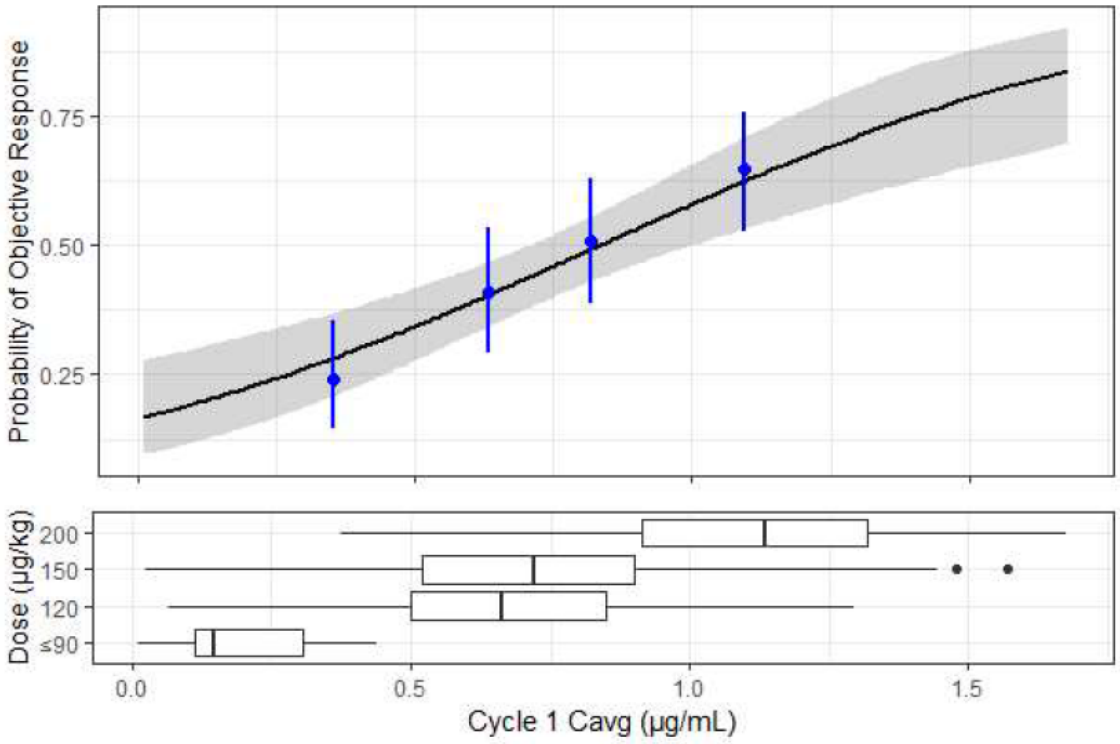
19.4.3. Summary of Applicant's Exposure-Response Analysis

Summary of Applicant's Exposure-Response for Efficacy

The Applicant conducted the E-R analyses for efficacy endpoints (i.e., ORR, OS, and DOR) for ADC exposure measures in patients with DLBCL (n=282) following the administration of loncastuximab tesirine 15 – 200 µg/kg Q3W or Q6W in Trials 101 and 201.

A quartile plot for ADC Cycle 1 Cavg and univariate logistic regression as base model was used to evaluate the exposure response relationship for ORR as presented in Figure 19. The final multivariate model identified Cycle 1 Cavg, baseline tumor sum of area, and disease phenotype (selected high risk vs. other) as the predictors of ORR. Estimates of odds ratio (95% CI) for each predictor in the final model are presented in Table 55. The odds of objective response increased by 6.09-fold for 1 µg/mL increase in Cycle 1 Cavg (1.20-fold for 0.1 µg/mL increase in Cycle 1 Cavg). The odds of objective response decreased by 0.985-fold for 1 cm^2 increase in baseline tumor sum of area, and 0.48-fold for selected high risk disease phenotypes. Figure 20 presents the estimated odds ratios relative to reference value for Cycle 1 Cavg and each covariate. A patient with Cycle 1 Cavg of 1.3 µg/mL (95^{th} percentile) has a 2.82-fold increase in odds of objective response in comparison to a patient with Cycle 1 Cavg of 0.725 µg/mL (median).

Figure 19: Observed and Model-Predicted Overall Response Rate from the Logistic Regression Base Model by PBD-Conjugated Ab Cycle 1 Cavg and the Distribution of PBD-Conjugated Ab Cycle 1 Cavg (µg/mL) by Dose Levels in DLBCL Patients



Key: The solid blue circles (vertical line segments) represent the observed objective response rate (95% CI, Clopper-Pearson method) for each quartile of Cycle 1 C_{avg}. The solid black line and shaded grey area represent the predicted objective response rate (95% CI) from a univariate logistic regression using individual patient level Cycle 1 C_{avg}.

Note: The quartile ranges for Cycle 1 C_{avg} were: 1st quartile (0.0120 to 0.504 µg/mL), 2nd quartile (0.506 to 0.723 µg/mL), 3rd quartile (0.727 to 0.941 µg/mL), and 4th quartile (0.943 to 1.68 µg/mL).

Source: Exposure-Response Analyses Report, Figure 8.

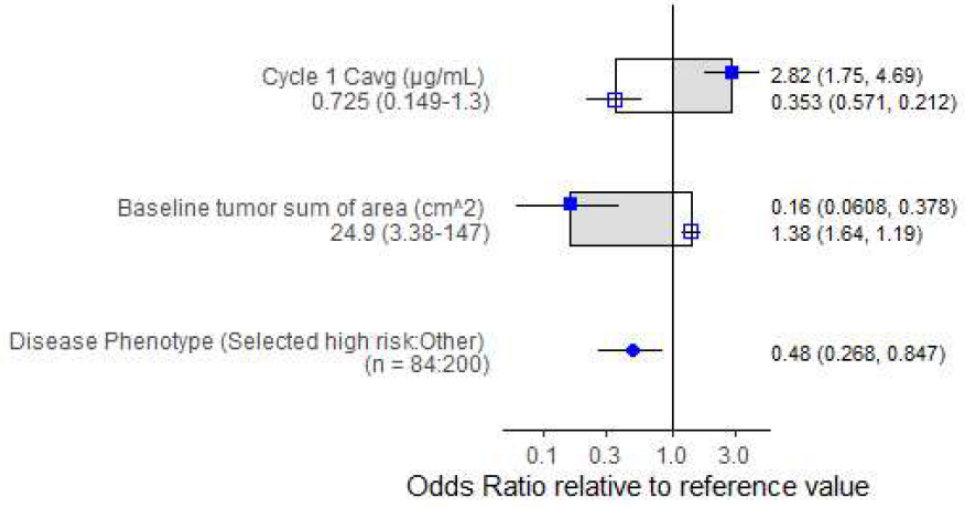
Table 55: Estimates of Odds Ratio (95% CI) from the Final Logistic Regression Model for Overall Response Rate with PBD-Conjugated Ab Cycle 1 Cavg

	Estimate	Odds Ratio (95% CI)	p-value
Intercept	-0.746	-	-
Cycle 1 C_{avg} (µg/mL)	1.81	6.09 (2.65, 14.7)	0.000035
Baseline tumor sum of area (cm^2)	-0.015	0.985 (0.977, 0.992)	0.0000813
Selected high risk disease phenotype	-0.733	0.48 (0.268, 0.847)	0.0122

Key: CI= confidence interval.
Note: AIC = 346.

Source: Exposure-Response Analyses Report, Table 13.

Figure 20: Estimated Odds Ratios Relative to Reference from the Final Logistic Regression Model for Overall Response Rate with PBD-Conjugated Ab Cycle 1 Cavg



Key: CI=confidence interval; P05=5th percentile; P95=95th percentile.
For continuous covariates, solid blue squares (horizontal lines) represent estimated odds ratio (95% CI) of P95 relative to the median (reference) value, and hollow blue squares (horizontal lines) represent estimated odds ratio (95% CI) of P05 relative to the median (reference) value. For categorical covariates, solid blue circles (horizontal lines) represent estimated odds ratio (95% CI) relative to the reference group. Numbers to left of forest plot represent median (P05-P95) for continuous covariates and subject count (comparison:reference) for categorical covariates. Numbers to right of forest plot represent odds ratio relative to reference value (95% CI).

Source: Exposure-Response Analyses Report, Figure 9.

The Applicant's multivariate analysis for OS using Cox proportional hazard model included the following covariates with a significant effect ($p<0.01$) on OS: baseline albumin, bulky disease (bulky v. other), and hepatic function (mild/moderate impairment v. normal), aside from Cycle 1 Cavg. Parameter estimates from the final Cox proportional hazards model for OS are presented in Table 56. The hazard of death decreased by 39% for 1 µg/mL increase in Cycle 1 Cavg (4.76% for 0.1 µg/mL increase in Cycle 1 Cavg) and 7% for 1 g/L increase in baseline albumin. The hazard of death increased by 213% with bulky tumor, and 90% with mild/moderate hepatic impairment.

Table 56: Parameter estimates from the Final Cox Proportional Hazards Model for Overall Survival with PBD-Conjugated Ab Cycle 1 Cavg in DLBCL Patients

	Predictor Stat	HR (95% CI)	p-value	HR P05: Median (95% CI)	HR P95: Median (95% CI)
Cycle 1 C_{avg} (µg/mL)	0.722 (0.148-1.3)	0.614 (0.379, 0.994)	0.0472	1.32 (1, 1.75)	0.755 (0.572, 0.997)
Baseline albumin (g/L)	40 (31.1-48)	0.929 (0.899, 0.96)	0.000011	1.94 (1.44, 2.6)	0.554 (0.426, 0.721)
Hepatic function	Mild/Moderate impairment: Normal (n = 44:237)	1.9 (1.29, 2.8)	0.0011		
Bulky disease	Bulky: Other (n = 26:256)	3.13 (2.01, 4.88)	4.31E-7		

Key: CI=confidence interval; HR=hazard ratio; P05=5th percentile; P95=95th percentile. Median (P05-P95) is presented for continuous predictors and count of comparator: reference is provided for categorical predictors under Predictor Stat.

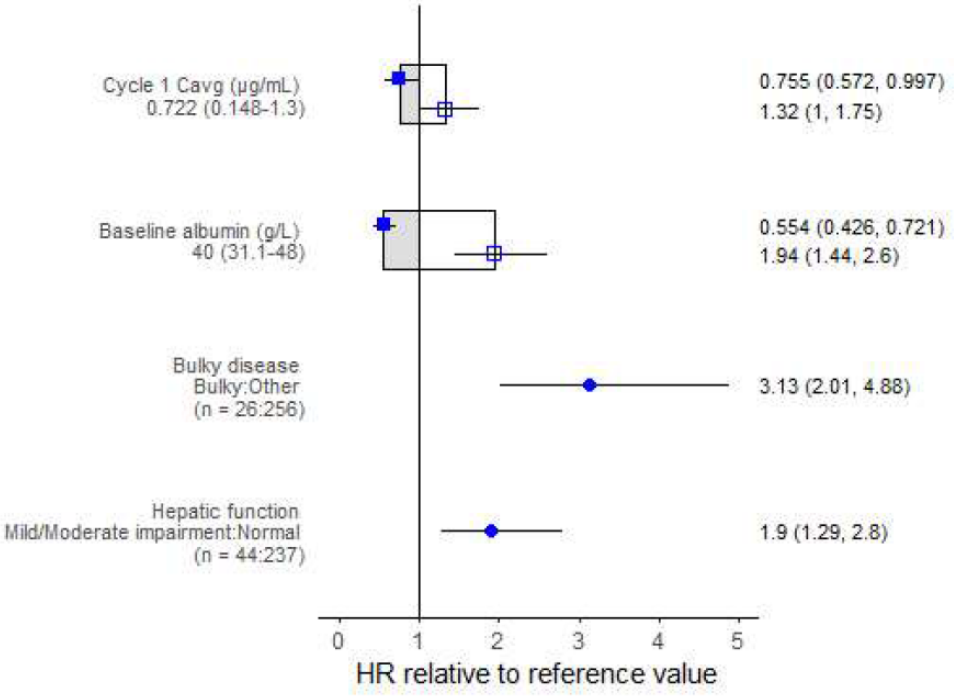
Note: Likelihood ratio test, p-value = 4E-14.

Source: Exposure-Response Analyses Report, Table 11.

Figure 21 presents the estimated hazard ratios from the final model relative to reference value for Cycle 1 Cavg and each covariate. A patient with Cycle 1 Cavg of 1.3 µg/mL (95th percentile) has a 24.5% reduction in risk of death compared to a patient with Cycle 1 Cavg of 0.722 µg/mL (median).

The relative hazard for death decreased with increasing Cycle 1 Cavg as presented in Figure 22. Patients in the 50th and 75th percentiles of Cycle 1 Cavg (0.725 and 0.941 µg/mL, respectively) had a risk of death reduced by approximately 29% and 36% relative to patients with the minimum Cycle 1 Cavg (0.0120 µg/mL). Figure 22 also presents the distribution of Cycle 1 Cavg by dose levels.

Figure 21: Estimated Hazard Ratios Relative to Reference from the Final Cox Proportional Hazards Model for Overall Survival with PBD-Conjugated Ab Exposure in DLBCL Patients

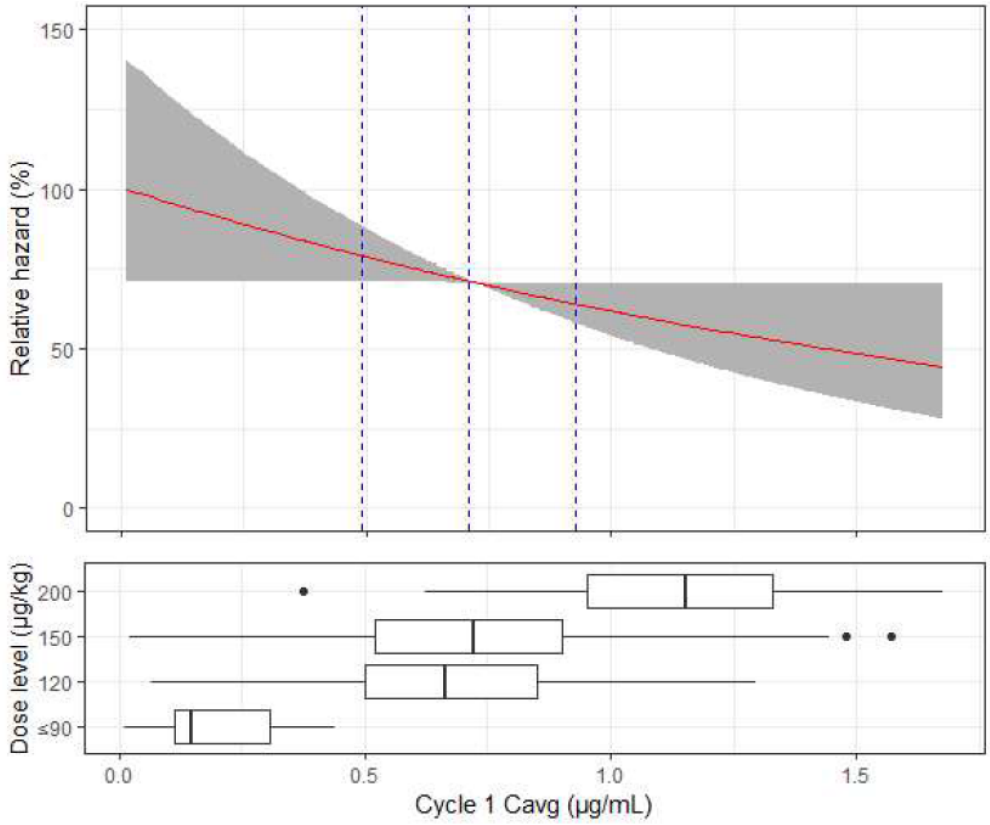


Key: CI=confidence interval; HR=hazard ratio; P05=5th percentile; P95=95th percentile. For continuous covariates, solid blue squares (horizontal lines) represent estimated hazard ratio (95% CI) of P95 relative to the median (reference) value, and hollow blue squares (horizontal lines) represent estimated hazard ratio (95% CI) of P05 relative to the median (reference) value. For categorical covariates, solid blue circles (horizontal lines) represent estimated hazard ratio (95% CI) relative to the reference group. Numbers to left of forest plot represent median (P05-P95) for continuous covariates and subject count (comparison:reference) for categorical covariates. Numbers to right of forest plot represent HR relative to reference value (95% CI).

Note: Likelihood ratio test, p-value = 4E-14.

Source: Exposure-Response Analyses Report, Figure 5.

Figure 22: Relative Hazard of Overall Survival from the Cox Proportional Hazards Model at Different Levels of PBD-Conjugated Ab Cycle 1 Cavg (µg/mL) and the Distribution of PBD-Conjugated Ab Cycle 1 Cavg (µg/mL) by Dose Levels in DLBCL Patients



Key: The solid red line represents the point estimate, and gray shaded areas represent 95% confidence interval. Blue vertical dotted lines separate the quartiles of Cycle 1 average concentration (C_{avg}). The minimum Cycle 1 C_{avg} (0.0120 µg/mL) of the combined data from Studies ADCT-402-101 and ADCT-402-201 were used as the reference values. Hazard ratio and its 95% confidence interval were estimated based on a Cox proportional hazards model with Cycle 1 C_{avg}, baseline albumin, bulky disease (bulky v. not bulky), and hepatic function (normal v. mild/moderate impairment). The quartiles for Cycle 1 C_{avg} were: 1st quartile (0.0120 to 0.504 µg/mL), 2nd quartile (0.506 to 0.722 µg/mL), 3rd quartile (0.723 to 0.941 µg/mL), and 4th quartile (0.943 to 1.68 µg/mL).

Source: Exposure-Response Analyses Report, Figure 6.

Univariate Cox PH models were performed for DOR and the results indicated no significant relationship between ADC exposures and DOR at significance level of 0.05. The estimated 95% confidence intervals of the hazard ratio from all of the univariate cox models for DOR included 1, indicating no effect of exposure on DOR.

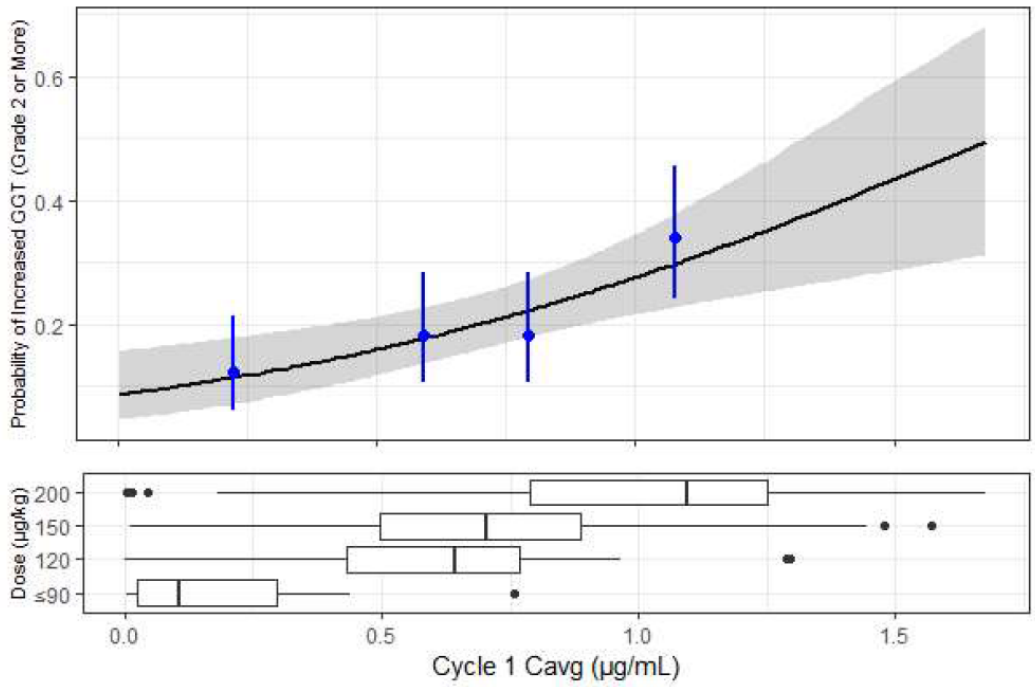
Reviewer's Comments: *The Applicant's exposure-efficacy analyses for ORR, OS and DOR in patients with DLBCL following the administration of loncastuximab tesirine 15 – 200 µg/kg Q3W or Q6W appear acceptable.*

Summary of Applicant's Exposure-Response for Safety

The exposure-safety analysis was conducted in 328 patients (284 patients with DLBCL and 44 patients with other B-NHL subtypes) from Trials 101 and 201. Univariate logistic regression with estimated PK metrics as predictors for TEAE categories were performed to aid in model selection. The occurrence of TEAEs of grade 2 or more for increased GGT, skin and nail, and LFT consistently showed significant relationships with Cavg and Cmin for Cycles 1, 2, and 3.

Increased GGT showed the most significant relationships with Cavg and Cmin from each cycle ($p<0.01$), and Cycle 1 Cavg was the most significant predictor for the occurrence of increased GGT based on the univariate analysis. The quartile plot for Cycle 1 Cavg and univariate logistic regression as base model was used to explore graphically the exposure response relationship for increased GGT (grade ≥2) as presented in Figure 23.

Figure 23: Observed and Predicted Probability of Increased GGT of Grade ≥2 from the Logistic Regression Base Model by Cycle 1 Cavg and the Distribution of Cycle 1 Cavg (µg/mL) by Dose Levels in All Patients



Key: The solid blue circles (vertical line segments) represent the observed proportion of patients (95% CI, Clopper-Pearson method) with increased GGT of grade 2 or more for each quartile of Cycle 1 C_{avg}. The solid black line and shaded grey area represent the predicted probability (95% CI) of increased GGT of grade 2 or more from a univariate logistic regression using individual patient level Cycle 1 C_{avg}.

Note: The quartile ranges for Cycle 1 C_{avg} were: 1st quartile (0.0120 to 0.462 µg/mL), 2nd quartile (0.463 to 0.700 µg/mL), 3rd quartile (0.702 to 0.918 µg/mL), and 4th quartile (0.919 to 1.68 µg/mL).

Source: Exposure-Response Analyses Report, Figure 10.

Estimates of odds ratio (95% CI) for each predictor in the final multivariate logistic regression model are presented in Table 57. The odds of having increased GGT (grade ≥2) increased by 3.73-fold for 1 µg/mL increase in Cycle 1 Cavg, 2.75-fold for non-white patients, 1.02-fold for 1 U/L increase in baseline ALT, 2.69-fold for patients with bulky tumor, 4.12-fold for patients with previous chemotherapy treatment. Figure 24 presents the estimated odds ratios relative to reference value for Cycle 1 Cavg and each covariate in the final logistic model. A patient with Cycle 1 Cavg of 1.28 µg/mL (95th percentile) has a 2.15-fold increase in odds of increased GGT (grade ≥2) in comparison to a patient with Cycle 1 Cavg of 0.7 µg/mL (median).

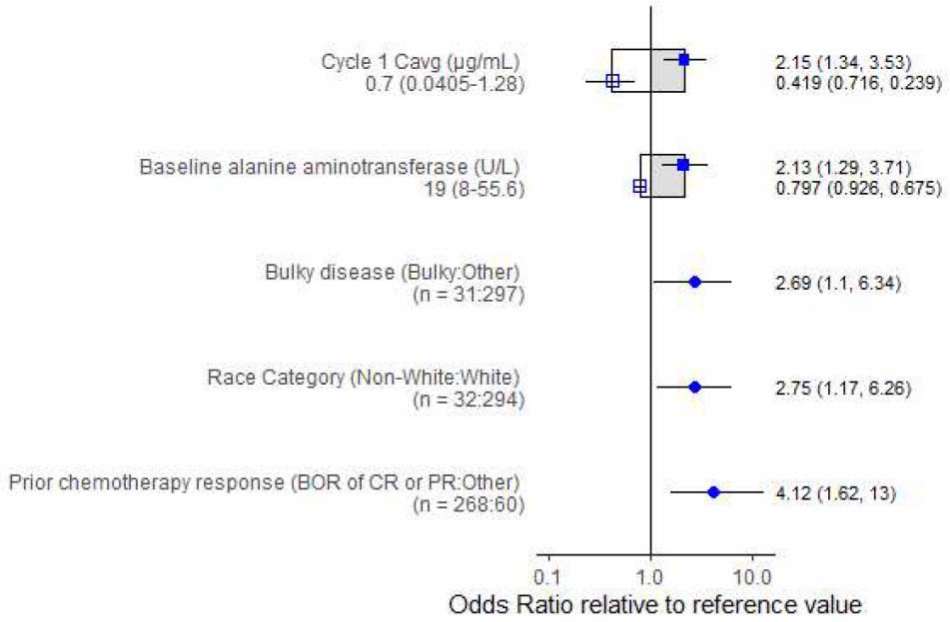
Table 57: Estimates (95% CI) from the Final Logistic Regression Model for Loncastuximab Tesirine Exposure Response Relationship with Increased GGT of Grade ≥2

	Estimate	Odds Ratio (95% CI)	p-value
Intercept	-4.3	-	-
Cycle 1 C_{avg} (µg/mL)	1.32	3.73 (1.66, 8.74)	0.00181
Race category	1.01	2.75 (1.17, 6.26)	0.0172
Alanine aminotransferase (U/L)	0.0207	1.02 (1.01, 1.04)	0.00554
Bulky disease	0.99	2.69 (1.1, 6.34)	0.0255
Prior chemotherapy response	1.41	4.12 (1.62, 13)	0.00683

Key: CI= confidence interval.
Note: AIC = 311.

Source: Exposure-Response Analyses Report, Table 15.

Figure 24: Estimated Odds Ratios Relative to Reference from the Final Logistic Regression Model for Loncastuximab Tesirine Exposure Response Relationship with Increased GGT of Grade ≥2

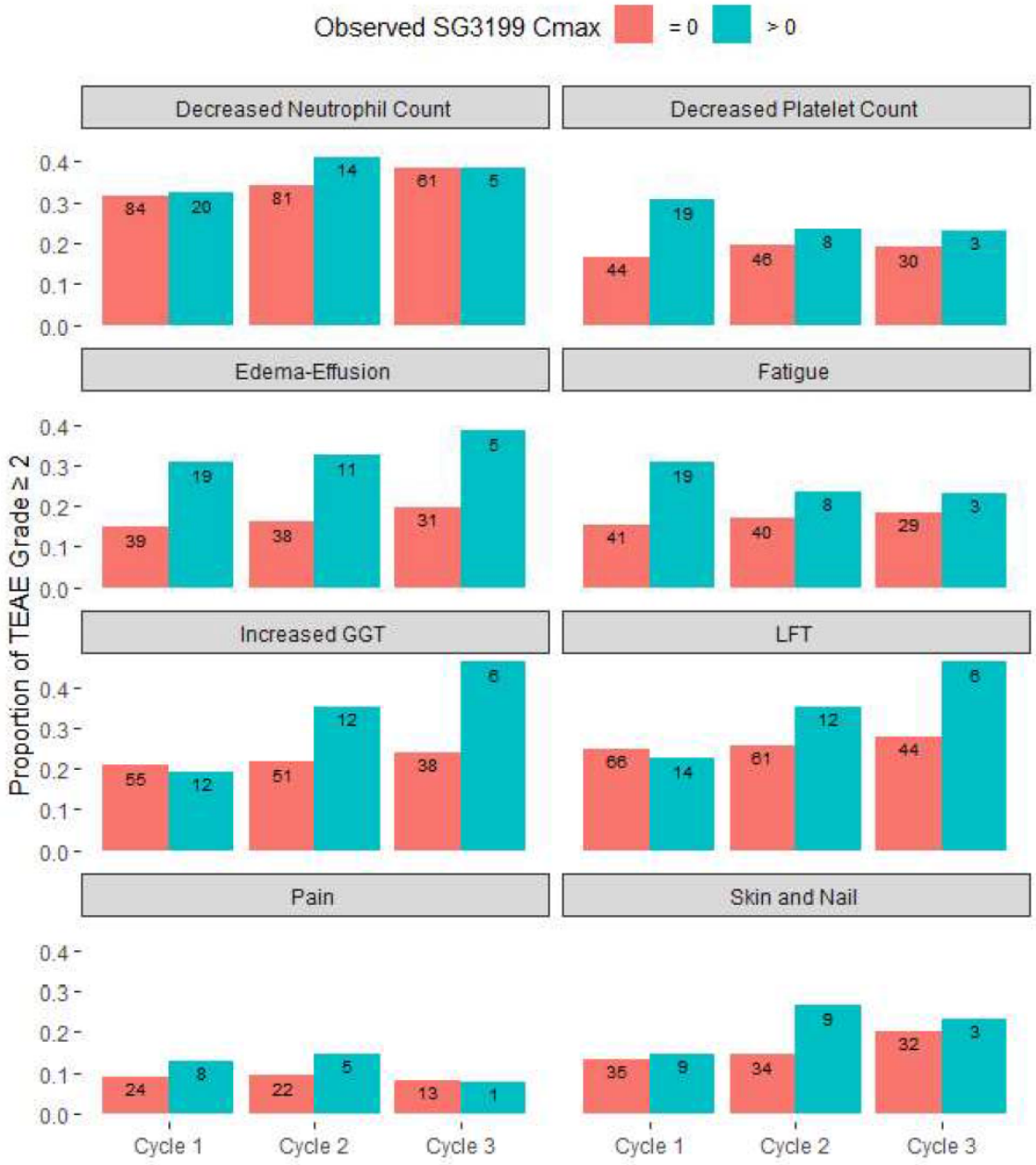


Key: CI=confidence interval; P05=5th percentile; P95=95th percentile. For continuous covariates, solid blue squares (horizontal lines) represent estimated odds ratio (95% CI) of P95 relative to the median (reference) value, and hollow blue squares (horizontal lines) represent estimated odds ratio (95% CI) of P05 relative to the median (reference) value. For categorical covariates, solid blue circles (horizontal lines) represent estimated odds ratio (95% CI) relative to the reference group. Numbers to left of forest plot represent median (P05-P95) for continuous covariates and subject count (comparison:reference) for categorical covariates. Numbers to right of forest plot represent odds ratio relative to reference value (95% CI).

Source: Exposure-Response Analyses Report, Figure 11.

Due to a low number of patients with measurable levels of SG3199 concentration, the Applicant explored a comparison of TEAE (grade ≥2) occurrence between patients with no measurable SG3199 and patients with measurable SG3199 concentrations. Proportions of patients having TEAE (grade ≥2) with or without measurable SG3199 concentrations by cycle are presented in Figure 25. There seemed to be a higher proportion of patients with TEAEs (grade 2 or more) of decreased platelet count, edema-effusion, fatigue, and skin and nail for patients with measurable SG3199 concentration in Cycles 1, 2 and 3.

Figure 25: Proportion of Patients with TEAE (Grade ≥2) by SG3199 Exposure and Cycle in Studies ADCT-402-101 and ADCT-402-201



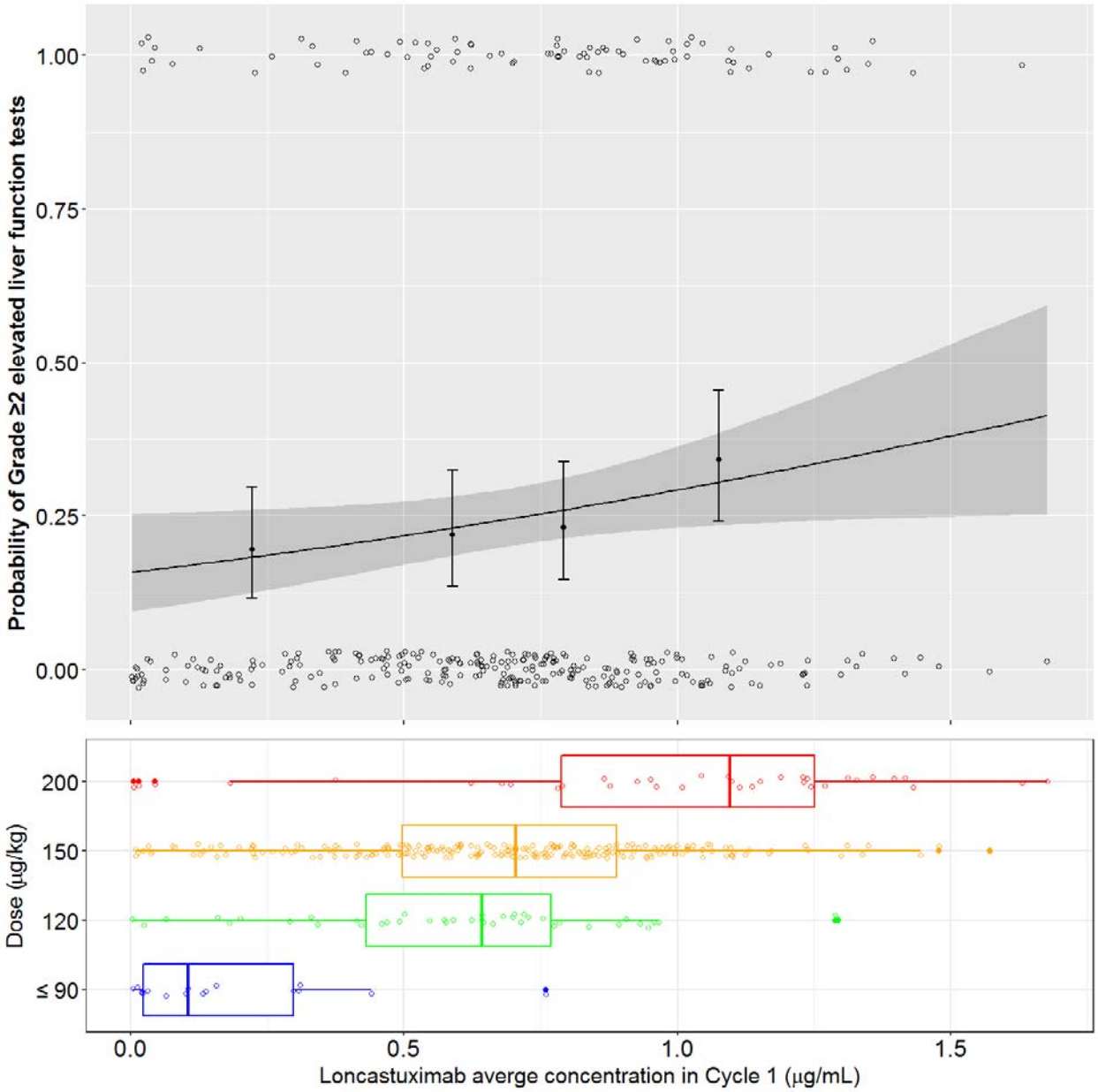
Note: Proportion of patients is defined by cycle and by two observed SG3199 C_{max} groups, non-measurable (= 0) and measurable (> 0).

Source: Exposure-Response Analyses Report, Figure 4.

Reviewer's Comments: *The Applicant's E-R analyses for safety measures appear acceptable. The Reviewer also conducted independent multivariate E-R analyses for additional safety measures using loncastuximab Cmax, Cavg and Cmin in Cycles 1, 2 and 3 from 328 patients in Trials 101 and 201. Since the E-R relationships were consistent across different loncastuximab PK metrics, only the E-R results using loncastuximab Cavg in Cycle 1 are presented below.*

The E-R analyses showed that Grade ≥2 elevated LFTs were associated with Cycle 1 loncastuximab Cavg (Figure 26) with no other significant covariates at p<0.05 (Table 58).

Figure 26: Observed and Predicted Probability of elevated LFTs of Grade ≥2 from the Logistic Regression Base Model by Cycle 1 Cavg and the Distribution of Cycle 1 Cavg (µg/mL) by Dose Levels in All Patients



Source: Reviewer's analysis.

Table 58: Estimates (95% CI) from the Final Logistic Regression Model for Loncastuximab Tesirine Exposure Response Relationship with elevated LFTs of Grade ≥2

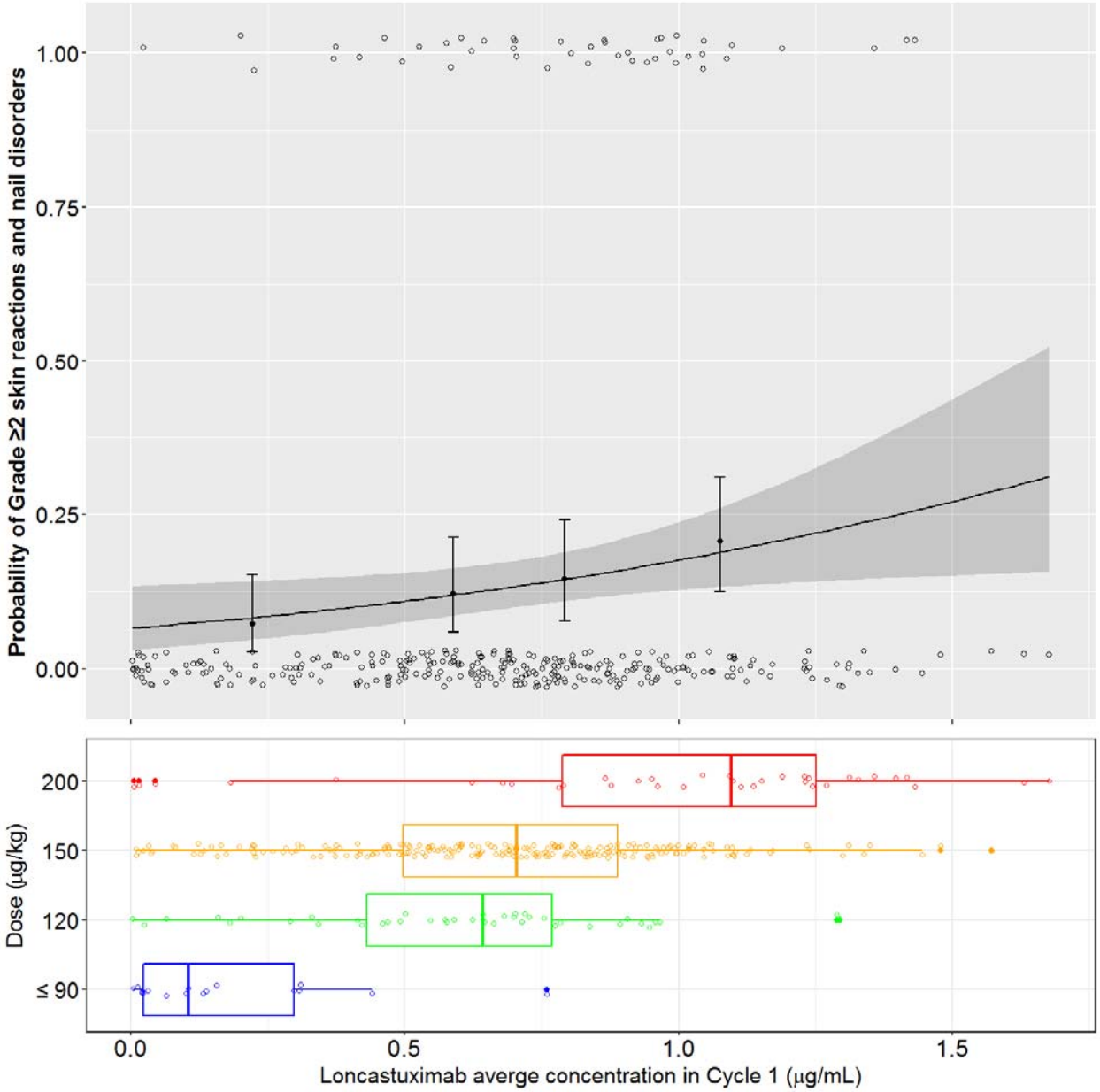
Parameter	Estimate	SE	95% CI	Z value	P value

Intercept (β_0)	-1.67	0.30	(-2.26, -1.08)	-5.56	2.67×10^{-8}
Cavg	0.79	0.37	(0.59, 1.52)	2.12	3.41×10^{-2}

Source: FDA's analysis.

Grade ≥2 skin reactions and nail disorders were associated with Cycle 1 loncastuximab Cavg (Figure 27) with pre-existing ADA as a significant covariate at p<0.05 (Table 59).

Figure 27: Observed and Predicted Probability of Skin Reactions and Nail Disorders of Grade ≥2 from the Logistic Regression Base Model by Cycle 1 Cavg and the Distribution of Cycle 1 Cavg (µg/mL) by Dose Levels in All Patients



Source: Reviewer's analysis.

Table 59: Estimates (95% CI) from the Final Logistic Regression Model for Loncastuximab Tesirine Exposure Response Relationship with Skin Reactions and Nail Disorders of Grade ≥2

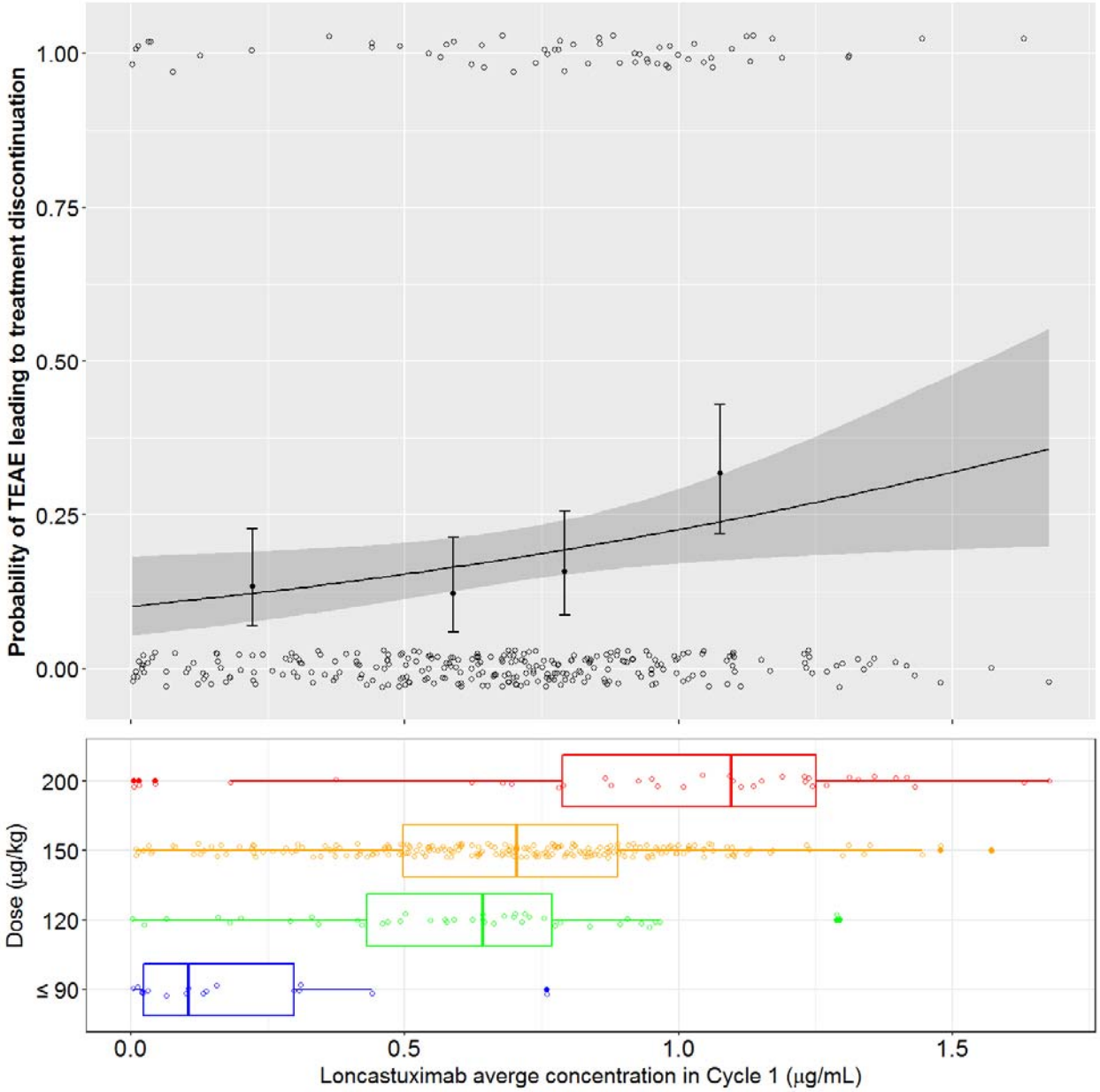
Parameter	Estimate	SE	95% CI	Z value	P value

Intercept (β_0)	-2.75	0.41	(-3.56, -1.94)	-6.69	2.17×10^{-11}
Cavg	1.13	0.48	(0.19, 2.06)	2.36	1.85×10^{-2}
Pre-existing ADA	2.65	0.90	(0.89, 4.41)	2.95	3.17×10^{-3}

Source: FDA's analysis.

TEAE leading to treatment discontinuation were associated with Cycle 1 loncastuximab Cavg (Figure 28) with baseline creatinine clearance (CRCL) as a significant covariate at p<0.05 (Table 60).

Figure 28: Observed and Predicted Probability of TEAE Leading to Treatment Discontinuation from the Logistic Regression Base Model by Cycle 1 Cavg and the Distribution of Cycle 1 Cavg (µg/mL) by Dose Levels in All Patients



Source: Reviewer's analysis.

Table 60: Estimates (95% CI) from the Final Logistic Regression Model for Loncastuximab Tesirine Exposure Response Relationship with TEAE Leading to Treatment Discontinuation

Parameter	Estimate	SE	95% CI	Z value	P value

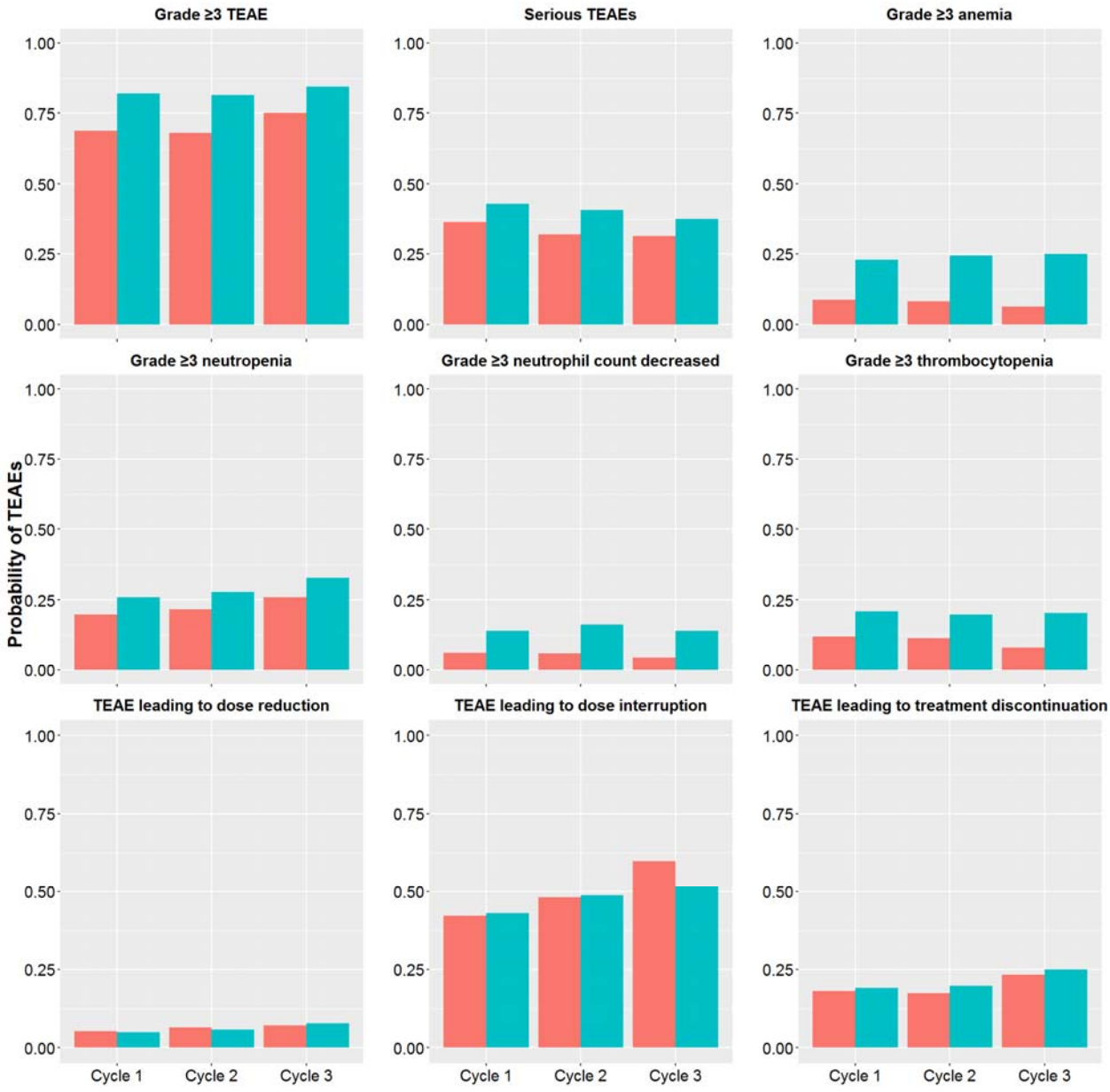
Intercept (β_0)	-1.46	0.47	(-2.39, -0.54)	-3.10	1.92×10^{-3}
Cavg	1.11	0.43	(0.27, 1.95)	2.59	9.63×10^{-3}
Baseline CRCL	-0.0089	0.0042	(-0.017, -0.00072)	-2.14	3.30×10^{-2}

Source: FDA's analysis.

Overall, there was no significant E-R relationship for Grade ≥ 2 edema or effusion, Grade ≥ 2 pain, Grade ≥ 2 decreased neutrophil count, Grade ≥ 2 decreased platelet count, Grade ≥ 2 fatigue, Grade ≥ 3 TEAE, serious TEAE, Grade ≥ 3 anemia, Grade ≥ 3 neutropenia, Grade ≥ 3 neutrophil count decreased, Grade ≥ 3 thrombocytopenia, TEAE leading to dose reduction, or TEAE leading to dose interruption.

The Reviewer also explored a comparison of some additional TEAEs occurrence between patients with no measurable SG3199 and patients with measurable SG3199 concentrations (Figure 29). There seemed to be a higher proportion of patients with Grade ≥ 3 overall TEAEs, serious TEAE, Grade ≥ 3 of anemia, neutropenia, neutrophil count decreased, and thrombocytopenia in patients with measurable SG3199 in Cycles 1, 2 and 3. Further quantitative logistic regression analysis could not be conducted, due to the limited measurable SG3199 concentrations (<5%).

Figure 29: Proportion of Patients with TEAE by SG3199 Exposure and Cycle in Studies ADCT-402-101 and ADCT-402-201



Source: Reviewer's analysis.

19.5. Grouped Preferred Terms Used in Safety Analyses Conducted by FDA

The FDA's Assessment:
The following table presents the FDA grouped preferred terms used for the safety analyses with this application.

Note: Not all listed Preferred Terms (PT) appear in the BLA datasets.

FDA Grouped PT	Included in Grouping	Not Included
Abdominal pain	All PTs containing "abdominal pain", Abdominal discomfort, Abdominal tenderness, Epigastric discomfort, Gastrointestinal pain	Abdominal distension
Acute kidney injury	Acute kidney injury, Acute prerenal failure, Acute renal failure, Renal injury	Azotemia, Hypercreatinemia
Anemia	All PTs containing "anemia", RBC count decreased, hemoglobin decreased	
Atrial fibrillation or flutter	Atrial fibrillation, Atrial flutter, Cardiac flutter	
Bruising	All PTs containing "bruise," "contusion," or "ecchymosis"	Petechiae, Purpura, Increased tendency to bruise
Cardiac arrhythmias	High-level group term, "Cardiac arrhythmias"	
Cardiac failure	All PTs containing "cardiac failure", Congestive cardiomyopathy, Cardiomyopathy, Left ventricular failure, Cor pulmonale, Cardiopulmonary failure, Cardiogenic shock, Ischemic cardiomyopathy	
Cataract	All PTs containing "cataract"	
Chest pain	Chest discomfort, Chest pain, Angina pectoris	Noncardiac chest pain, musculoskeletal chest pain
Colitis	Colitis, Colitis microscopic, Colitis ulcerative, Colitis erosive, Enterocolitis, Enterocolitis hemorrhagic	Enteritis, Enterocolitis infectious
Cough	All PTs containing "Cough"	
Cytomegalovirus infection	Cytomegalovirus infection, Cytomegalovirus viremia	
Diarrhea	Diarrhea, Diarrhea hemorrhagic, Defecation urgency	Post procedural diarrhea
Dizziness	All PTs containing "Dizziness" or "Vertigo"	
Dyspnea	All PTs containing "Dyspnea"	

FDA Grouped PT	Included in Grouping	Not Included
Edema	Edema, Generalized edema, Face edema, Swelling face, Peripheral swelling, Swelling, Edema peripheral, Fluid overload, Fluid retention, Pulmonary edema, Acute pulmonary edema, Pulmonary congestion, Ascites	Edema blister, Localized sites of edema or swelling (e.g., Localized edema, Lip edema, Nasal edema, Periorbital edema, Eye swelling, breast edema, testicular edema)
Fatigue	Asthenia, Fatigue, Lethargy	
Febrile neutropenia	Febrile neutropenia, Febrile bone marrow aplasia, Neutropenic infection, Neutropenic sepsis* * Note: Neutropenic sepsis is counted under both the "febrile neutropenia" and "sepsis" PTs	
Gastroenteritis	Gastroenteritis and specific types (e.g. viral), Enterocolitis infectious, Enterococcal infection, Enterococcal bacteremia	Gastroenteritis radiation, Gastritis
Gastrointestinal hemorrhage	All PTs containing "Gastrointestinal hemorrhage", Gastric hemorrhage, Gastric ulcer hemorrhage, Large intestinal ulcer hemorrhage, Hematochezia, Hematemesis, Intestinal hemorrhage, Intestinal hemorrhage, Melena, Hemorrhoidal hemorrhage, Rectal hemorrhage, Small intestinal hemorrhage	
Headache	All PTs containing "headache", Migraine	
Hemorrhage	All PTs containing "hemorrhage" or "hemorrhagic", all PTs contained in FDA's "Gastrointestinal hemorrhage" grouping, Menorrhagia, Hemarthrosis, Hemoptysis, Hematuria, Epistaxis	Petechiae, Purpura, FDA's grouping for "Bruising," Tumor hemorrhage
Hemorrhage intracranial	Includes but is not limited to: Hemorrhage intracranial, Subdural hematoma, Subdural hemorrhage, Cerebral hemorrhage, Hemorrhagic stroke, Subarachnoid hemorrhage	
Hepatitis	All PTs containing "hepatitis", Hepatocellular injury, Hepatotoxicity, Drug-induced liver injury, Liver injury	FDA's "Transaminase elevation" grouping, PTs containing "Hepatic failure", Hepatic encephalopathy
Herpesvirus infection	High-level group term, "Herpes viral infection"	
Hyperbilirubinemia	Blood bilirubin increased, Hyperbilirubinemia, Jaundice	
Hypertension	Hypertension, Essential hypertension, Blood pressure increased, Blood pressure systolic increased	
Hypotension	Hypotension, Diastolic hypotension, Orthostatic hypotension, Blood pressure decreased	
Leukocytosis[a]	Leukocytosis, Hyperleukocytosis, White blood cell count increase	

FDA Grouped PT	Included in Grouping	Not Included
Lower respiratory tract infection	**Narrow grouping (main analysis):** Combine specific site of infection with other descriptors of that infection, for example combine "lower respiratory tract infection bacterial" with lower respiratory tract infection," "bronchitis viral" under "bronchitis," and "pneumonia" with other related PTs as defined in separate entries. **Broad grouping:** All PTs containing "bronchitis" or "lower respiratory tract infection", All PTs in "Pneumonia" grouping, Bronchiolitis, Lung infection, Tracheobronchitis, infective exacerbation of bronchiectasis, lower respiratory tract congestion, lower respiratory tract inflammation	Bronchiectasis
Musculoskeletal pain	Back pain, Musculoskeletal chest pain, Noncardiac chest pain, Musculoskeletal pain, Musculoskeletal discomfort, Limb discomfort, Myofascial pain syndrome, Neck pain, Pain in extremity, Myalgia, Spinal pain	Arthralgia, Musculoskeletal stiffness
Myocardial ischemia or infarction	Acute myocardial infarction, Myocardial ischemia, Angina unstable, Acute coronary syndrome, Myocardial infarction, Coronary artery stenosis or occlusion	Angina pectoris, Troponin I increased
Nausea	All terms containing "nausea", Retching	Procedural nausea
Neutropenia	Neutropenia, Neutrophil count decreased, Granulocytopenia, Agranulocytosis	Febrile neutropenia
Neuropathy peripheral	All PTs containing both "Neuropathy" and "Peripheral," sensory disturbance, paresthesia, polyneuropathy, selected cases of neuralgia, selected cases of hypoethesia, and muscular weakness if localized	
Nonmelanoma skin cancer	Squamous cell carcinoma of skin, Basal cell carcinoma, Bowen's disease, Basosquamous carcinoma, Lip squamous cell carcinoma	
Pneumonia	All PTs containing "pneumonia", including within another word (e.g., bronchopneumonia), All PTs containing "pulmonary infection," Bronchopulmonary aspergillosis, Lung infiltration, Lung consolidation, lung infection	Respiratory tract infection, Lower respiratory tract infection
Pneumonitis	Pneumonitis, Acute respiratory distress syndrome, Interstitial lung disease, Respiratory tract inflammation	
Rash	All PTs containing "rash", All PTs containing "dermatitis" except as noted, Drug eruption, Drug reaction with eosinophilia and systemic symptoms, Erythema, Erythema multiforme, Generalized erythema, Toxic skin eruption, Palmar erythema, Palmoplantar keratoderma, Palmar-plantar erythrodysesthesia syndrome, Skin reaction, Skin toxicity, Stevens-Johnson syndrome, Toxic epidermal necrolysis, acute generalized exanthematous pustulosis	All PTs containing "Eczema", Dermatitis atopic, Dermatitis contact, Neurodermatitis, Seborrheic dermatitis, Actinic keratosis, Folliculitis, Urticaria, Lichen planus, Herpes

FDA Grouped PT	Included in Grouping	Not Included
		dermatitis, Acarodermatitis, Vaccination site rash, Photodermatosis
Respiratory tract infection	PT "Respiratory tract infection" + specific types (e.g. respiratory tract infection viral, all PTs containing "influenza" or "parainfluenza,"respiratory syncytial virus infection, Human metapneumovirus, Sinobronchitis	FDA grouping for "Upper respiratory tract infection" and "Lower respiratory tract infection"
Sepsis	All PTs containing "Bacteremia" or "Sepsis", including within another word (e.g., urosepsis), Septic shock * Note: Neutropenic sepsis is counted under both the "febrile neutropenia" and "sepsis" PTs	
Supraventricular tachycardia	High-level term, "Supraventricular arrhythmias"	
Taste disorder	Taste disorder, Dysgeusia, Hypogeusia, Ageusia	
Thrombocytopenia	Thrombocytopenia, Platelet count decreased	PTs with "thrombocytopenic purpura"
Thrombosis or thromboembolism	All PTs containing "thrombosis" except as noted, Peripheral embolism, Pulmonary embolism	Superficial thrombosis, Air embolism, embolism, septic embolism
Transaminase elevation	Alanine aminotransferase increased, Aspartate aminotransferase increased, Alanine aminotransferase, Aspartate aminotransferase, Transaminase increased, Hypertransaminasemia, Hepatic enzyme increased	PTs under FDA's "Hepatitis" grouping, PTs containing "hepatic failure", Hepatic function abnormal
Upper respiratory tract infection	Broad grouping: Except as noted, all PTs containing "upper respiratory tract infection," "upper respiratory infection," "sinusitis," "laryngitis," "tonsillitis," or "pharyngitis," including within another word (e.g. nasopharyngitis), all PTs containing "rhinitis" except as noted, Rhinorrhea, Rhinovirus infection, Human rhinovirus test positive, alpha hemolytic streptococcal infection, upper respiratory tract inflammation, upper respiratory tract congestion	PTs containing the descriptor "allergic" (e.g., Rhinitis allergic), Rhinorrhea, Reflux laryngitis
Urinary tract infection	All PTs containing "cystitis" or "urinary tract infection", Pyelonephritis, Kidney infection	
Ventricular arrhythmia	High-level term, "Ventricular arrhythmias and cardiac arrest"	
Xerosis	Dry skin, Dry eye, Dry mouth, Xerosis	

[a] Grouping for other lab-related AEs is similar, e.g., hyperglycemia = hyperglycemia + blood glucose increased, hypokalemia = hypokalemia + blood potassium decreased, lymphopenia = lymphopenia + lymphocyte count decreased

BLA 761196 Zynlonta (loncastuximab tesirine-lpyl)
ADC Therapeutics SA

Assessment Aid Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Natalie Simpson, PhD	OOD/DHOT	Sections: 5	**Select one:** ☑ Authored ☐ Approved
	Signature: Natalie Simpson -S D g tal y signed by Natalie Simpson -S DN c US, o U.S. Government, ou HHS, ou FDA, ou People, 0.9.2342.19200300.100.1.1 2000576562, cn Natalie Simpson -S Date 2021.04.06 15 56 26 -04'00'			
Nonclinical Team Leader (Acting)	Brenda Gehrke, PhD	OOD/DHOT	Sections: 5	**Select one:** ☑ Authored ☑ Approved
	Signature: Brenda Gehrke -S Digitally signed by Brenda Gehrke -S DN c US, o U.S. Government, ou HHS, ou FDA, ou People, cn Brenda Gehrke -S, 0.9.2342.19200300.100.1.1 0012062023 Date 2021.04.06 12 23 21 -04'00'			
Nonclinical Team Deputy Division Director	Haleh Saber, PhD, MS	OOD/DHOT	Sections: 5, 14	**Select one:** ☐ Authored ☑ Approved
	Signature: Haleh Saber -S Digitally signed by Haleh Saber -S DN c US, o U.S. Government, ou HHS, ou FDA, ou People, cn Haleh Saber -S, 0.9.2342.19200300.100.1.1 1300212858 Date 2021.04.06 12 19 18 -04'00'			
OSIS Reviewer	Amanda Lewin, PhD	OTS/OSIS	Sections: 6, 19.4	**Select one:** ☑ Authored ☐ Approved
	Signature: Amanda E. Lewin -S Digitally signed by Amanda E. Lewin -S DN c US, o U.S. Government, ou HHS, ou FDA, ou People, 0.9.2342.19200300.100.1.1 2002000530, cn Amanda E. Lewin -S Date 2021.04.09 16 09 13 -04'00'			
OSIS Team Leader	Gopa Biswas, PhD	OTS/OSIS	Sections: 6, 19.4	**Select one:** ☑ Authored ☑ Approved
	Signature: Gopa Biswas -S Dig tally signed by Gopa Biswas -S DN c US, o U.S. Government, ou HHS, ou FDA, ou People, cn Gopa Biswas -S, 0.9.2342.19200300.100.1.1 2000342781 Date 2021.04.16 09 14 36 -04'00'			
Pharmacometrics Reviewer	Liang Li, PhD	OCP/DPM	Sections: 6, 19.4	**Select one:** ☑ Authored ☐ Approved
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Pharmacometrics Team Leader	Lian Ma, PhD	OCP/DPM	Sections: 6, 19.4	**Select one:** ☑ Authored ☑ Approved
	Signature: Lian Ma -S Digitally signed by Lian Ma -S DN c US, o U.S. Government, ou HHS, ou FDA, ou People, cn Lian Ma -S, 0.9.2342.19200300.100.1.1 2000825336 Date 2021.04.06 11 56 03 -04'00'			
Clinical Pharmacology Reviewer	Krithika Arun Shetty, PhD	OCP/DCPI	Sections: 6, 19.4	**Select one:** ☑ Authored ☐ Approved
	Signature: Krithika-arun Shetty -S Digitally signed by Krithika-arun Shetty -S DN c US, o U.S. Government, ou HHS, ou FDA, ou People, 0.9.2342.19200300.100.1.1 2002698440, cn Krithika-arun Shetty -S Date 2021.04.06 12 01 52 -04'00'			

BLA 761196 Zynlonta (loncastuximab tesirine-lpyl)
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Clinical Pharmacology Team Leader	Ruby Leong, PharmD	OCP/DCPI	Sections: 6, 19.4	**Select one:** ☑ Authored ☑ Approved
	Signature: Ruby Leong -S3 — Digitally signed by Ruby Leong -S3 DN c US, o U.S. Government, ou HHS, ou FDA, ou People, cn Ruby Leong -S3, 0.9.2342.19200300.100.1.1 2000548953 Date 2021.04.06 13:40:03 -04'00'			
Clinical Pharmacology Division Director	Brian Booth, PhD	OCP/DCPI	Sections: 6, 15, 19.4	**Select one:** ☐ Authored ☑ Approved
	Signature: Brian P. Booth -S — Digitally signed by Brian P. Booth -S DN c US, o U.S. Government, ou HHS, ou FDA, ou People, cn Brian P. Booth -S, 0.9.2342.19200300.100.1.1 1300137436 Date 2021.04.08 08:51:02 -04'00'			
Statistical Reviewer	Jay Zhao, PhD	OB/DBIX	Sections: 7, 8	**Select one:** ☑ Authored ☐ Approved
	Signature: Jian Zhao -S — Dig tally signed by Jian Zhao -S DN c US, o U.S. Government, ou HHS, ou FDA, ou People, cn Jian Zhao -S, 0.9.2342.19200300.100.1.1 2003071296 Date 2021.04.06 16:00:39 -04'00'			
Statistical Team Leader	Yu-te Wu, PhD	OB/DBIX	Sections: 7, 8	**Select one:** ☑ Authored ☑ Approved
	Signature: Yute Wu -S — Digitally signed by Yute Wu -S DN c US, o U.S. Government, ou HHS, ou FDA, ou People, cn Yute Wu -S, 0.9.2342.19200300.100.1.1 1300389006 Date 2021.04.06 14:04:47 -04'00'			
Division Director (OB)	Thomas Gwise, PhD	OB/DBIX	Sections: 7, 8, 16	**Select one:** ☐ Authored ☑ Approved
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Clinical Reviewer	Candis Morrison, PhD, CRNP	OOD/DHM2	Sections: 2, 3, 4, 7, 8, 9, 10, 12, 13, 19.2	**Select one:** ☑ Authored ☐ Approved
	Signature: Candis Morrison -S — Digitally signed by Candis Morrison -S DN c US, o U.S. Government, ou HHS, ou FDA, ou People, 0.9.2342.19200300.100.1.1 2001366518, cn Candis Morrison -S Date 2021.04.07 07:26:52 -04'00'			
Associate Director for Labeling (Acting)	Elizabeth Everhart, MSN, RN, ACNP	OOD	Sections: 11	**Select one:** ☑ Authored ☑ Approved
	Signature: Elizabeth E. Everhart -S — D gitally s gned by El zabeth E. Everhart -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.23 2.19200300.100.1.1=2000363858, cn=Elizabeth E. Everhart -S Da e: 2021.0 06 12: 8: 7 -0 '00'			
Cross-Disciplinary Team Leader (CDTL)/Clinical Team Leader	Nicholas Richardson, DO, MPH	OOD/DHM2	Sections: All	**Select one:** ☑ Authored ☑ Approved
	Signature: Nicholas C. Richardson -S — Digitally signed by N cholas C. Richardson -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.23 2.19200300.100.1.1=20020 0136, cn=Nicholas C. Richardson -S Date: 2021.0 .20 05:59:22 -0 '00'			

BLA 761196 Zynlonta (loncastuximab tesirine-lpyl)
ADC Therapeutics SA

Division Director (Clinical)	Nicole Gormley, MD	OOD/DHM2	Sections: All	**Select one:** ☐ Authored ☑ Approved
	Signature: Nicole J. Gormley -S Digitally signed by Nicole J. Gormley -S DN c US, o U.S. Government, ou HHS, ou FDA, ou People, 0.9.2342.19200300.100.1.1 0012754803, cn Nicole J. Gormley -S Date 2021.04.16 09 37 21 -04 00'			
Supervisory Associate Director for Clinical Oncology (Acting)	Marc Theoret, MD	OOD	Sections: All	**Select one:** ☐ Authored ☑ Approved
	Signature: See appended signature page below			

OOD: Office of Oncologic Diseases
DHOT: Division of Hematology, Oncology, Toxicology
OTS: Office of Translational Sciences
OSIS: Office of Study Integrity and Surveillance
OCP: Office of Clinical Pharmacology
DPM: Division of Pharmacometrics
DTPM: Division of Translational and Precision Medicine (DTPM)
DCPI: Division of Cancer Pharmacology I
OB: Office of Biostatistics
DBIX: Division of Biometrics IX
DHM2: Division of Hematologic Malignancies 2

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/s/

JENNIFER J LEE
04/23/2021 09:00:06 AM

NICHOLAS C RICHARDSON
04/23/2021 09:11:32 AM

MARC R THEORET
04/23/2021 11:08:43 AM
My signature indicates that I have considered the FDA assessments and recommendations included in this Review in determining the regulatory action.