CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125388Orig1s108

Trade Name:	ADCETRIS
Generic or Proper Name:	brentuximab vedotin
Sponsor:	Seagen Inc.
Approval Date:	February 12, 2025
Indication:	For treatment of Adult patients with relapsed or refractory large B-cell lymphoma (LBCL), including diffuse large B-cell lymphoma (DLBCL) NOS, DLBCL arising from indolent lymphoma, or high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy who are not eligible for auto-HSCT or CAR T-cell therapy, in combination with lenalidomide and a rituximab product.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

BLA 125388/S-108

SUPPLEMENT APPROVAL

Seagen Inc.
Attention: Xin Wei
Senior Director, Regulatory Affairs
21823 30th Drive SE
Bothell, WA 98021

Dear Ms. Wei:

Please refer to your supplemental biologics license application (sBLA), dated and received May 21, 2024, and your amendments, submitted under section 351(a) of the Public Health Service Act for Adcetris (brentuximab vedotin) for injection.

This Prior Approval supplemental biologics license application provides for a new indication: Adcetris (brentuximab vedotin) in combination with lenalidomide and a rituximab product for the treatment of adult patients with relapsed or refractory large B-cell lymphoma (LBCL), including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS), DLBCL arising from indolent lymphoma, or high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy who are not eligible for autologous hematopoietic stem cell transplantation (auto-HSCT) or chimeric antigen receptor (CAR) T-cell therapy.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF HIGHLIGHTS ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,[1] that is identical to the enclosed labeling (text for the Prescribing Information)

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, please contact David Bak, Regulatory Health Project Manager, at 301-796-6299 or email David.Bak@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Nicholas Richardson, DO, MPH
Deputy Director
Division of Hematologic Malignancies II
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):
- Content of Labeling
  - Prescribing Information

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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

/s/

NICHOLAS C RICHARDSON
02/11/2025 06:48:21 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125388Orig1s108

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ADCETRIS safely and effectively. See full prescribing information for ADCETRIS.

ADCETRIS® (brentuximab vedotin) for injection, for intravenous use
Initial U.S. approval: 2011

WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)
See full prescribing information for complete boxed warning.

JC virus infection resulting in PML and death can occur in patients receiving ADCETRIS (5.9, 6.1).

----------RECENT MAJOR CHANGES ----------

Indications and Usage (1.8)	2/2025
Dosage and Administration (2.1, 2.3, 2.4, 2.5)	2/2025
Warnings and Precautions (5.1)	2/2025

----------INDICATIONS AND USAGE ----------
ADCETRIS is a CD30-directed antibody and microtubule inhibitor conjugate indicated for treatment of:

- Adult patients with previously untreated Stage III or IV classical Hodgkin lymphoma (cHL), in combination with doxorubicin, vinblastine, and dacarbazine (1.1).
- Pediatric patients 2 years and older with previously untreated high risk classical Hodgkin lymphoma (cHL), in combination with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide (1.2).
- Adult patients with classical Hodgkin lymphoma (cHL) at high risk of relapse or progression as post-autologous hematopoietic stem cell transplantation (auto-HSCT) consolidation (1.3).
- Adult patients with classical Hodgkin lymphoma (cHL) after failure of auto-HSCT or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates (1.4).
- Adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL) or other CD30-expressing peripheral T-cell lymphomas (PTCL), including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified (NOS), in combination with cyclophosphamide, doxorubicin, and prednisone (1.5).
- Adult patients with systemic anaplastic large cell lymphoma (sALCL) after failure of at least one prior multi-agent chemotherapy regimen (1.6).
- Adult patients with primary cutaneous anaplastic large cell lymphoma (pcALCL) or CD30-expressing mycosis fungoides (MF) who have received prior systemic therapy (1.7).
- Adult patients with relapsed or refractory large B-cell lymphoma (LBCL), including diffuse large B-cell lymphoma (DLBCL) NOS, DLBCL arising from indolent lymphoma, or high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy who are not eligible for auto-HSCT or CAR T-cell therapy, in combination with lenalidomide and a rituximab product (1.8).

---------- DOSAGE AND ADMINISTRATION ----------

- Administer only as an intravenous infusion over 30 minutes (2.1).
- The recommended dosage as monotherapy for adult patients is 1.8 mg/kg up to a maximum of 180 mg every 3 weeks (2.1).
- The recommended dosage in combination with chemotherapy for adult patients with previously untreated Stage III or IV cHL is 1.2 mg/kg up to a maximum of 120 mg every 2 weeks for a maximum of 12 doses (2.1).
- The recommended dosage in combination with chemotherapy for pediatric patients 2 years and older with previously untreated high risk cHL is 1.8 mg/kg up to a maximum of 180 mg every 3 weeks for a maximum of 5 doses (2.1).
- The recommended dosage in combination with chemotherapy for adult patients with previously untreated PTCL is 1.8 mg/kg up to a maximum of 180 mg every 3 weeks for 6 to 8 doses (2.1).
- The recommended dosage in combination with lenalidomide and a rituximab product for adult patients with relapsed or refractory LBCL is 1.2 mg/kg up to a maximum of 120 mg every 3 weeks (2.1).
- Avoid use in patients with severe renal impairment (2.2)
- Reduce dose in patients with mild hepatic impairment; avoid use in patients with moderate or severe hepatic impairment (2.3).

----------DOSAGE FORMS AND STRENGTHS ----------
For injection: 50 mg lyophilized powder in a single-dose vial (3).

----------CONTRAINDICATIONS----------
Concomitant use with bleomycin due to pulmonary toxicity (4).

----------WARNINGS AND PRECAUTIONS ----------

- Peripheral neuropathy: Monitor patients for neuropathy and institute dose modifications accordingly (5.1).
- Anaphylaxis and infusion reactions: If an infusion reaction occurs, interrupt the infusion. If anaphylaxis occurs, immediately discontinue the infusion (5.2).
- Hematologic toxicities: Monitor complete blood counts. Monitor for signs of infection. Manage using dose delays and growth factor support (5.3).
- Serious infections and opportunistic infections: Closely monitor patients for the emergence of bacterial, fungal or viral infections (5.4).
- Tumor lysis syndrome: Closely monitor patients with rapidly proliferating tumor or high tumor burden (5.5).
- Hepatotoxicity: Monitor liver enzymes and bilirubin (5.8).
- Pulmonary toxicity: Monitor patients for new or worsening symptoms (5.10).
- Serious dermatologic reactions: Discontinue if Stevens-Johnson syndrome or toxic epidermal necrolysis occurs (5.11).
- Gastrointestinal complications: Monitor patients for new or worsening symptoms (5.12).
- Hyperglycemia: Monitor patients for new or worsening hyperglycemia. Manage with anti-hyperglycemic medications as clinically indicated (5.13).
- Embryo-Fetal toxicity: Can cause fetal harm. Advise females of reproductive potential and males with female partners of reproductive potential of the potential risk to a fetus and to use effective contraception (5.14, 8.1, 8.3).

----------ADVERSE REACTIONS ----------
The most common adverse reactions (≥20%) are peripheral neuropathy, nausea, fatigue, musculoskeletal pain, constipation, diarrhea, vomiting, pyrexia, upper respiratory tract infection, mucositis, abdominal pain, and rash.
The most common laboratory abnormalities (≥20%) are decreased neutrophils, increased creatinine, decreased hemoglobin, decreased lymphocytes, increased glucose, increased alanine aminotransferase (ALT), and increased aspartate aminotransferase (AST) (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Seagen Inc. at 1-855-473-2436 or FDA at 1-800-FDA-1088 or www.fda.gov/Safety/MedWatch.

---------- DRUG INTERACTIONS ----------
Concomitant use of strong CYP3A4 inhibitors or inducers has the potential to affect the exposure to monomethyl auristatin E (MMAE) (7.1).

----------USE IN SPECIFIC POPULATIONS----------

- Moderate or severe hepatic impairment or severe renal impairment: MMAE exposure and adverse reactions are increased (6, 7, 8.6, 8.7).
- Lactation: Advise women not to breastfeed (8.2).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 2/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

JC virus infection resulting in PML and death can occur in patients receiving ADCETRIS *[see Warnings and Precautions (5.9), Adverse Reactions (6.1)]*.

1 INDICATIONS AND USAGE

1.1 Previously Untreated Stage III or IV Classical Hodgkin Lymphoma (cHL), in Combination with Chemotherapy

ADCETRIS is indicated for the treatment of adult patients with previously untreated Stage III or IV cHL, in combination with doxorubicin, vinblastine, and dacarbazine.

1.2 Previously Untreated High Risk Classical Hodgkin Lymphoma (cHL), in Combination with Chemotherapy

ADCETRIS is indicated for the treatment of pediatric patients 2 years and older with previously untreated high risk cHL, in combination with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide.

1.3 Classical Hodgkin Lymphoma (cHL) Consolidation

ADCETRIS is indicated for the treatment of adult patients with cHL at high risk of relapse or progression as post-autologous hematopoietic stem cell transplantation (auto-HSCT) consolidation.

1.4 Relapsed Classical Hodgkin Lymphoma (cHL)

ADCETRIS is indicated for the treatment of adult patients with cHL after failure of auto-HSCT or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates.

1.5 Previously Untreated Systemic Anaplastic Large Cell Lymphoma (sALCL) or Other CD30-Expressing Peripheral T-cell Lymphomas (PTCL), in Combination with Chemotherapy

ADCETRIS is indicated for the treatment of adult patients with previously untreated sALCL or other CD30-expressing PTCL, including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified (NOS), in combination with cyclophosphamide, doxorubicin, and prednisone.

1.6 Relapsed Systemic Anaplastic Large Cell Lymphoma (sALCL)

ADCETRIS is indicated for the treatment of adult patients with sALCL after failure of at least one prior multi-agent chemotherapy regimen.

1.7 Relapsed Primary Cutaneous Anaplastic Large Cell Lymphoma (pcALCL) or CD30-Expressing Mycosis Fungoides (MF)

ADCETRIS is indicated for the treatment of adult patients with pcALCL or CD30-expressing MF who have received prior systemic therapy.

1.8 Relapsed or Refractory Large B-Cell Lymphoma (LBCL)

ADCETRIS in combination with lenalidomide and a rituximab product is indicated for the treatment of adult patients with relapsed or refractory LBCL, including diffuse large B-cell lymphoma (DLBCL) NOS, DLBCL arising from indolent lymphoma, or high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy who are not eligible for auto-HSCT or chimeric antigen receptor (CAR) T-cell therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended ADCETRIS dosage is provided in Table 1. Administer ADCETRIS as a 30-minute intravenous infusion.

For recommended dosage for patients with renal or hepatic impairment, see *Dosage and Administration (2.2 and 2.3)*.

For dosing instructions of combination agents administered with ADCETRIS, see *Clinical Studies (14.1, 14.2, and 14.5)* and the manufacturer's prescribing information.

Table 1: Recommended ADCETRIS Dosage

Indication	Recommended Dose*	Frequency and Duration
Adult patients with previously untreated Stage III or IV classical Hodgkin lymphoma	1.2 mg/kg up to a maximum of 120 mg in combination with chemotherapy	Administer every 2 weeks until a maximum of 12 doses, disease progression, or unacceptable toxicity
Pediatric patients with previously untreated high risk classical Hodgkin lymphoma	1.8 mg/kg up to a maximum of 180 mg in combination with chemotherapy	Administer every 3 weeks with each cycle of chemotherapy for a maximum of 5 doses
Adult patients with classical Hodgkin lymphoma consolidation	1.8 mg/kg up to a maximum of 180 mg	Initiate ADCETRIS treatment within 4-6 weeks post-auto-HSCT or upon recovery from auto-HSCT Administer every 3 weeks until a maximum of 16 cycles, disease progression, or unacceptable toxicity
Adult patients with relapsed classical Hodgkin lymphoma	1.8 mg/kg up to a maximum of 180 mg	Administer every 3 weeks until disease progression or unacceptable toxicity
Adult patients with previously untreated systemic ALCL or other CD30-expressing peripheral T-cell lymphomas	1.8 mg/kg up to a maximum of 180 mg in combination with chemotherapy	Administer every 3 weeks with each cycle of chemotherapy for 6 to 8 doses
Adult patients with relapsed Systemic ALCL	1.8 mg/kg up to a maximum of 180 mg	Administer every 3 weeks until disease progression or unacceptable toxicity
Adult patients with relapsed primary cutaneous ALCL or CD30-expressing mycosis fungoides	1.8 mg/kg up to a maximum of 180 mg	Administer every 3 weeks until a maximum of 16 cycles, disease progression, or unacceptable toxicity

Indication	Recommended Dose*	Frequency and Duration
Adult patients with relapsed or refractory LBCL	1.2 mg/kg up to a maximum of 120 mg in combination with lenalidomide and rituximab†	Administer every 3 weeks until disease progression, or unacceptable toxicity

* The dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg.
† Starting with cycle 2, rituximab intravenous treatment could be substituted with rituximab and hyaluronidase human via subcutaneous injection every 3 weeks.

2.2 Recommended Dosage in Patients with Renal Impairment

No dosage adjustment is required for mild renal impairment (CrCL greater than 50-80 mL/min) and moderate renal impairment (CrCL 30-50 mL/min).
Avoid use in patients with severe (CrCL less than 30 mL/min) renal impairment *[see Warnings and Precautions (5.6)]*.

2.3 Recommended Dosage in Patients with Hepatic Impairment

Adult patients with previously untreated Stage III or IV classical Hodgkin lymphoma

Reduce the dosage of ADCETRIS to 0.9 mg/kg up to a maximum of 90 mg every 2 weeks for patients with mild hepatic impairment (Child-Pugh A).

Avoid use in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment *[see Warnings and Precautions (5.7)]*.

Adult patients with relapsed or refractory LBCL

Reduce the dosage of ADCETRIS to 0.9 mg/kg up to a maximum of 90 mg every 3 weeks for patients with mild hepatic impairment (total bilirubin ≤ upper limit of normal [ULN] and aspartate transaminase [AST] > ULN, or total bilirubin >1 to 1.5 × ULN and any AST).

Avoid use in patients with moderate and severe hepatic impairment (total bilirubin >1.5 × ULN) *[see Warnings and Precautions (5.7)]*.

Hepatic impairment is defined per the National Cancer Institute Organ Dysfunction Working Group.

All other indications

Reduce the dosage of ADCETRIS to 1.2 mg/kg up to a maximum of 120 mg every 3 weeks for patients with mild hepatic impairment (Child-Pugh A).

Avoid use in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment *[see Warnings and Precautions (5.7)]*.

2.4 Recommended Prophylactic Medications

In adult patients with previously untreated Stage III or IV cHL who are treated with ADCETRIS + doxorubicin, vinblastine, and dacarbazine (AVD), administer G-CSF beginning with Cycle 1.

In pediatric patients with previously untreated high risk cHL who are treated with ADCETRIS + doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide (AVEPC), administer G-CSF beginning with Cycle 1.

In adult patients with previously untreated PTCL who are treated with ADCETRIS + cyclophosphamide, doxorubicin, and prednisone (CHP), administer G-CSF beginning with Cycle 1.

In adult patients with relapsed or refractory LBCL who are treated with ADCETRIS + lenalidomide + rituximab, administer G-CSF beginning with Cycle 1.

2.5 Dosage Modifications for Adverse Reactions

Table 2: Dosage Modifications for Peripheral Neuropathy or Neutropenia in Adult Patients *[see Warnings and Precautions (5.1, 5.3)]*

Recommended ADCETRIS Dosage from Table 1*	Monotherapy or Combination Therapy	Severity†	Dosage Modification
Peripheral Neuropathy			
1.2 mg/kg up to a maximum of 120 mg every 2 weeks	In combination with chemotherapy	Grade 2	Reduce dose to 0.9 mg/kg up to a maximum of 90 mg every 2 weeks.
		Grade 3	Hold ADCETRIS dosing until improvement to Grade 2 or lower. Restart at 0.9 mg/kg up to a maximum of 90 mg every 2 weeks. Consider modifying the dose of other neurotoxic chemotherapy agents.
		Grade 4	Discontinue dosing.
1.2 mg/kg up to a maximum of 120 mg every 3 weeks	In combination with lenalidomide and rituximab	Grade 2	Sensory neuropathy: If resolves to Grade 1 or lower before the next scheduled dose, resume at the same dose level. If Grade 2 persists at the next scheduled dose, reduce one dose level. Motor neuropathy: Reduce dosage to 0.9 mg/kg up to a maximum of 90 mg every 3 weeks.
		Grade 3	Sensory neuropathy: Hold ADCETRIS dosing until improvement to Grade 2 or lower, then restart treatment at a reduced dosage of 0.9 mg/kg up to a maximum of 90 mg every 3 weeks. Motor neuropathy: Discontinue dosing.
		Grade 4	Discontinue dosing.

Recommended ADCETRIS Dosage from Table 1*	Monotherapy or Combination Therapy	Severity†	Dosage Modification
1.8 mg/kg up to a maximum of 180 mg every 3 weeks	As monotherapy	New or worsening Grade 2 or 3	Hold dosing until improvement to baseline or Grade 1. Restart at 1.2 mg/kg up to a maximum of 120 mg every 3 weeks.
		Grade 4	Discontinue dosing.
	In combination with chemotherapy	Grade 2	Sensory neuropathy: Continue treatment at same dose. Motor neuropathy: Reduce dose to 1.2 mg/kg up to a maximum of 120 mg every 3 weeks.
		Grade 3	Sensory neuropathy: Reduce dose to 1.2 mg/kg, up to a maximum of 120 mg every 3 weeks. Motor neuropathy: Discontinue dosing.
		Grade 4	Discontinue dosing.
Neutropenia			
1.2 mg/kg up to a maximum of 120 mg every 2 weeks	In combination with chemotherapy	Grade 3 or 4	Administer G-CSF prophylaxis for subsequent cycles for patients not receiving primary G-CSF prophylaxis.
1.2 mg/kg up to a maximum of 120 mg every 3 weeks	In combination with lenalidomide and rituximab	Grade 3 or 4	Hold dosing until improvement to baseline or Grade 2 or lower. Reduce/discontinue lenalidomide dose per prescribing information. Administer G-CSF prophylaxis for subsequent cycles for patients not receiving primary G-CSF prophylaxis.
1.8 mg/kg up to a maximum of 180 mg every 3 weeks	In combination with chemotherapy	Grade 3 or 4	Administer G-CSF prophylaxis in subsequent cycles for patients not receiving primary G-CSF prophylaxis.

Recommended ADCETRIS Dosage from Table 1*	Monotherapy or Combination Therapy	Severity†	Dosage Modification
1.8 mg/kg up to a maximum of 180 mg every 3 weeks	As monotherapy	Grade 3 or 4	Hold dosing until improvement to baseline or Grade 2 or lower. Consider G-CSF prophylaxis for subsequent cycles.
		Recurrent Grade 4 despite G-CSF prophylaxis	Consider discontinuation or dose reduction to 1.2 mg/kg up to a maximum of 120 mg every 3 weeks.

* The dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg.
† Grades based on National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.

Table 3: Dosage Modifications for Peripheral Neuropathy or Neutropenia in Pediatric Patients

Recommended ADCETRIS Dosage from Table 1*	Severity	Dosage Modification
Peripheral Neuropathy†		
1.8 mg/kg up to a maximum of 180 mg every 3 weeks	Grade 2†	Reduce dose of vincristine per prescribing information. Continue dosing with ADCETRIS. If neuropathy improves to Grade ≤1 by day 8 of next cycle, then resume vincristine at full dose.
	Grade 3†	Discontinue vincristine. <u>First Occurrence:</u> Hold ADCETRIS dosing until improvement to ≤ Grade 2 then restart at 1.2 mg/kg up to a maximum of 120 mg. <u>Second Occurrence:</u> Hold until improvement to ≤ Grade 2 then restart at 0.8 mg/kg up to a maximum of 80 mg. <u>Third Occurrence:</u> Discontinue ADCETRIS.
	Grade 4†	Discontinue ADCETRIS and vincristine.
Neutropenia		
1.8 mg/kg up to a maximum of 180 mg every 3 weeks	Grade 3 or 4	Reduce dose to 1.2 mg/kg up to a maximum of 120 mg every 3 weeks in patients who are unable to start a cycle >5 weeks after the start of the previous cycle (>2-week delay) due to neutropenia.

* The dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg.
† Peripheral neuropathy was assessed using the Balis scale.

2.6 Instructions for Preparation and Administration

Administration

- Administer ADCETRIS as an intravenous infusion only.
- **Do not mix ADCETRIS with, or administer as an infusion with, other medicinal products.**

Reconstitution

- Follow procedures for proper handling and disposal of hazardous drugs[1].
- Use appropriate aseptic technique for reconstitution and preparation of dosing solutions.
- Determine the number of 50 mg vials needed based on the patient's weight and the prescribed dose *[see Dosage and Administration (2.1)].*
- Reconstitute each 50 mg vial of ADCETRIS with 10.5 mL of Sterile Water for Injection to yield a single-dose solution containing 5 mg/mL brentuximab vedotin.
- Direct the stream toward the wall of vial and not directly at the cake or powder.
- Gently swirl the vial to aid dissolution. **DO NOT SHAKE**.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The reconstituted solution should be clear to slightly opalescent, colorless, and free of visible particulates.
- Following reconstitution, dilute immediately into an infusion bag. If not diluted immediately, store the solution refrigerated at 2°C to 8°C (36°F to 46°F) and use within 24 hours of reconstitution. **DO NOT FREEZE.**
- Discard any unused portion left in the vial.

Dilution

- Calculate the required volume of 5 mg/mL reconstituted ADCETRIS solution needed.
- Withdraw this amount from the vial and immediately add it to an infusion bag containing 0.9% Sodium Chloride Injection, USP, 5% Dextrose Injection or Lactated Ringer's Injection to achieve a final concentration of 0.4 mg/mL to 1.8 mg/mL brentuximab vedotin.
- Gently invert the bag to mix the solution.
- Following dilution, infuse the ADCETRIS solution immediately. If not used immediately, store the solution refrigerated at 2°C to 8°C (36°F to 46°F) and use within 24 hours of reconstitution. **DO NOT FREEZE.**

3 DOSAGE FORMS AND STRENGTHS

For injection: 50 mg of brentuximab vedotin as a sterile, white to off-white lyophilized, preservative-free cake or powder in a single-dose vial for reconstitution.

4 CONTRAINDICATIONS

ADCETRIS is contraindicated with concomitant bleomycin due to pulmonary toxicity (e.g., interstitial infiltration and/or inflammation) *[see Adverse Reactions (6.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Peripheral Neuropathy

ADCETRIS treatment causes a peripheral neuropathy that is predominantly sensory. Cases of peripheral motor neuropathy have also been reported. ADCETRIS-induced peripheral neuropathy is cumulative.

In studies of ADCETRIS as monotherapy, 62% of patients experienced any grade of peripheral neuropathy. The median time to onset was 3 months (range, 0–12). Of the patients who experienced neuropathy, 62% had complete resolution, 24% had partial improvement, and 14% had no improvement at their last evaluation. The median time from onset to resolution or improvement was 5 months (range, 0–45). Of the patients with ongoing neuropathy (38%), 71% had Grade 1, 24% had Grade 2, and 4% had Grade 3.

In ECHELON-1 (Study 5), 67% of patients treated with ADCETRIS + AVD experienced any grade of peripheral neuropathy. The median time to onset of any grade was 2 months (range, 0–7), of Grade 2 was 3 months (range, 0–6) and of Grade 3 was 4 months (range, <1–7). By the time of the primary analysis, 43% of affected patients had complete resolution, 24% had partial improvement, and 33% had no improvement at their last evaluation. The median time from onset to resolution or improvement of any grade was 2 months (range, 0–32).

At the updated analysis of ECHELON-1, 72% of the patients who experienced peripheral neuropathy had complete resolution, 14% had partial improvement, and 14% had no improvement. The median time to partial improvement was 2.9 months (range, <1–50), and the median time to complete resolution was 6.6 months (range, <1–67). Of the patients with ongoing neuropathy (28%), 57% had Grade 1, 30% had Grade 2, 12% had Grade 3, and <1% had Grade 4.

In ECHELON-2 (Study 6), 52% of patients treated with ADCETRIS + CHP experienced new or worsening peripheral neuropathy of any grade (by maximum grade, 34% Grade 1, 15% Grade 2, 3% Grade 3, <1% Grade 4). The peripheral neuropathy was predominantly sensory (94% sensory, 16% motor) and had a median onset time of 2 months (range, <1–5). At last evaluation, 50% had complete resolution of neuropathy, 12% had partial improvement, and 38% had no improvement. The median time to resolution or improvement overall was 4 months (range, 0–45). Of patients with ongoing neuropathy (50%), 72% had Grade 1, 25% had Grade 2, and 3% had Grade 3.

In AHOD1331 (Study 7), 20% of pediatric patients treated with ADCETRIS + AVEPC experienced peripheral neuropathy of any grade (7% Grade 3, <1% Grade 4). Peripheral neuropathy was predominantly sensory. Of the patients who experienced peripheral neuropathy, 81% experienced sensory neuropathy and 29% experienced motor neuropathy.

In ECHELON-3 (Study 8), 27% of patients treated with ADCETRIS + lenalidomide + a rituximab product experienced peripheral neuropathy of any grade (by maximum grade, 14% Grade 1, 7% Grade 2, 5% Grade 3). The peripheral neuropathy was predominantly sensory and had a

median onset time of 3 months (range, <1-10). Peripheral neuropathy resulted in ADCETRIS dose reduction in 6% of treated patients, and permanent discontinuation in 4.5%. At last evaluation, 7% of the patients who experienced peripheral neuropathy had complete resolution of neuropathy, 10% had partial improvement, and 83% had no improvement. The median time to resolution was 2 months (range <1-3). The median time to improvement was 4 months (range, 3-4). Of patients who experienced peripheral neuropathy, 93% had ongoing peripheral neuropathy (47% had Grade 1, 33% had Grade 2, and 13% had Grade 3).

Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain, or weakness. Patients experiencing new or worsening peripheral neuropathy may require a delay, change in dose, or discontinuation of ADCETRIS *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)]*.

5.2 Anaphylaxis and Infusion Reactions

Infusion-related reactions, including anaphylaxis, have occurred with ADCETRIS. Monitor patients during infusion. If anaphylaxis occurs, immediately and permanently discontinue administration of ADCETRIS and administer appropriate medical therapy. If an infusion-related reaction occurs, interrupt the infusion and institute appropriate medical management. Patients who have experienced a prior infusion-related reaction should be premedicated for subsequent infusions. Premedication may include acetaminophen, an antihistamine, and a corticosteroid.

5.3 Hematologic Toxicities

Fatal and serious cases of febrile neutropenia have been reported with ADCETRIS. Prolonged (≥1 week) severe neutropenia and Grade 3 or Grade 4 thrombocytopenia or anemia can occur with ADCETRIS.

Start primary prophylaxis with G-CSF beginning with Cycle 1 for adult patients who receive ADCETRIS in combination for previously untreated Stage III or IV cHL or previously untreated PTCL or relapsed or refractory LBCL, and pediatric patients who receive ADCETRIS in combination with chemotherapy for previously untreated high risk cHL *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)]*.

Monitor complete blood counts prior to each dose of ADCETRIS. Monitor more frequently for patients with Grade 3 or 4 neutropenia. Monitor patients for fever. If Grade 3 or 4 neutropenia develops, consider dose delays, reductions, discontinuation, or G-CSF prophylaxis with subsequent ADCETRIS doses *[see Dosage and Administration (2.2, 2.3)]*.

5.4 Serious Infections and Opportunistic Infections

Serious infections and opportunistic infections such as pneumonia, bacteremia, and sepsis or septic shock (including fatal outcomes) have been reported in patients treated with ADCETRIS. Monitor patients closely during treatment for the emergence of possible bacterial, fungal, or viral infections.

5.5 Tumor Lysis Syndrome

Patients with rapidly proliferating tumor and high tumor burden may be at increased risk of tumor lysis syndrome. Monitor closely and take appropriate measures.

5.6 Increased Toxicity in the Presence of Severe Renal Impairment

The frequency of ≥ Grade 3 adverse reactions and deaths was greater in patients with severe renal impairment compared to patients with normal renal function. Due to higher MMAE exposure, ≥Grade 3 adverse reactions may be more frequent in patients with severe renal impairment compared to patients with normal renal function. Avoid the use of ADCETRIS in patients with severe renal impairment [creatinine clearance (CrCL) <30 mL/min] *[see Use in Specific Populations (8.6)].*

5.7 Increased Toxicity in the Presence of Moderate or Severe Hepatic Impairment

The frequency of ≥ Grade 3 adverse reactions and deaths was greater in patients with moderate and severe hepatic impairment compared to patients with normal hepatic function. Avoid the use of ADCETRIS in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment *[see Use in Specific Populations (8.7)]*.

5.8 Hepatotoxicity

Fatal and serious cases of hepatotoxicity have occurred in patients receiving ADCETRIS. Cases were consistent with hepatocellular injury, including elevations of transaminases and/or bilirubin. Cases have occurred after the first dose of ADCETRIS or after ADCETRIS rechallenge. Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications may also increase the risk. Monitor liver enzymes and bilirubin. Patients experiencing new, worsening, or recurrent hepatotoxicity may require a delay, change in dose, or discontinuation of ADCETRIS.

5.9 Progressive Multifocal Leukoencephalopathy

Fatal cases of JC virus infection resulting in PML have been reported in ADCETRIS-treated patients. First onset of symptoms occurred at various times from initiation of ADCETRIS therapy, with some cases occurring within 3 months of initial exposure. In addition to ADCETRIS therapy, other possible contributory factors include prior therapies and underlying disease that may cause immunosuppression. Consider the diagnosis of PML in any patient presenting with new-onset signs and symptoms of central nervous system abnormalities. Hold ADCETRIS dosing for any suspected case of PML and discontinue ADCETRIS dosing if a diagnosis of PML is confirmed.

5.10 Pulmonary Toxicity

Fatal and serious events of noninfectious pulmonary toxicity including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome (ARDS), have been reported. Monitor patients for signs and symptoms of pulmonary toxicity, including cough and dyspnea. In the event of new or worsening pulmonary symptoms, hold ADCETRIS dosing during evaluation and until symptomatic improvement.

5.11 Serious Dermatologic Reactions

Fatal and serious cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with ADCETRIS. If SJS or TEN occurs, discontinue ADCETRIS and administer appropriate medical therapy.

5.12 Gastrointestinal Complications

Fatal and serious events of acute pancreatitis have been reported. Other fatal and serious gastrointestinal (GI) complications include perforation, hemorrhage, erosion, ulcer, intestinal obstruction, enterocolitis, neutropenic colitis, and ileus. Lymphoma with preexisting GI involvement may increase the risk of perforation. In the event of new or worsening GI symptoms, including severe abdominal pain, perform a prompt diagnostic evaluation and treat appropriately.

5.13 Hyperglycemia

Serious events of hyperglycemia, such as new-onset hyperglycemia, exacerbation of pre-existing diabetes mellitus, and ketoacidosis (including fatal outcomes) have been reported in ADCETRIS-treated patients. In studies of ADCETRIS monotherapy, 8% of patients experienced any grade hyperglycemia, with 6% experiencing Grade 3 or 4 hyperglycemia. The median time to onset for any grade or Grade 3 or 4 was 1 month (range, 0-10). Hyperglycemia occurred more frequently in patients with high body mass index or diabetes. Monitor serum glucose and if hyperglycemia develops, administer anti-hyperglycemic medications as clinically indicated.

5.14 Embryo-Fetal Toxicity

Based on the mechanism of action and findings in animals, ADCETRIS can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of ADCETRIS in pregnant women. In animal reproduction studies, brentuximab vedotin caused embryo-fetal toxicities, including significantly decreased embryo viability, and fetal malformations at maternal exposures that were similar to the clinical dose of 1.8 mg/kg every three weeks.

Advise females of reproductive potential to use effective contraception during ADCETRIS treatment and for 2 months after the last dose of ADCETRIS. Advise male patients with female partners of reproductive potential to use effective contraception during ADCETRIS treatment and for 4 months after the last dose of ADCETRIS. Advise a pregnant woman of the potential risk to the fetus *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Peripheral Neuropathy *[see Warnings and Precautions (5.1)]*
- Anaphylaxis and Infusion Reactions *[see Warnings and Precautions (5.2)]*
- Hematologic Toxicities *[see Warnings and Precautions (5.3)]*
- Serious Infections and Opportunistic Infections *[see Warnings and Precautions (5.4)]*
- Tumor Lysis Syndrome *[see Warnings and Precautions (5.5)]*
- Increased Toxicity in the Presence of Severe Renal Impairment *[see Warnings and Precautions (5.6)]*

- Increased Toxicity in the Presence of Moderate or Severe Hepatic Impairment *[see Warnings and Precautions (5.7)]*
- Hepatotoxicity *[see Warnings and Precautions (5.8)]*
- Progressive Multifocal Leukoencephalopathy *[see Warnings and Precautions (5.9)]*
- Pulmonary Toxicity *[see Warnings and Precautions (5.10)]*
- Serious Dermatologic Reactions *[see Warnings and Precautions (5.11)]*
- Gastrointestinal Complications *[see Warnings and Precautions (5.12)]*
- Hyperglycemia *[see Warnings and Precautions (5.13)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data below reflect exposure to ADCETRIS in 931 adult patients with cHL including 662 patients who received ADCETRIS in combination with chemotherapy in a randomized controlled trial, 269 who received ADCETRIS as monotherapy (167 in a randomized controlled trial and 102 in a single arm trial), and 296 pediatric patients with high risk cHL who received ADCETRIS in combination with chemotherapy. Data summarizing ADCETRIS exposure are also provided for 347 patients with T-cell lymphoma, including 223 patients with PTCL who received ADCETRIS in combination with chemotherapy in a randomized, double-blind, controlled trial; 58 patients with sALCL who received ADCETRIS monotherapy in a single-arm trial; and 66 patients with pcALCL or CD30-expressing MF who received ADCETRIS monotherapy in a randomized, controlled trial. ADCETRIS was administered intravenously at a dose of either 1.2 mg/kg every 2 weeks in combination with AVD, 1.8 mg/kg every 3 weeks in combination with AVEPC in pediatric patients, 1.8 mg/kg every 3 weeks in combination with CHP, or 1.8 mg/kg every 3 weeks as monotherapy.

The most common adverse reactions (≥20%) with monotherapy in adult patients were peripheral neuropathy, fatigue, upper respiratory tract infection, musculoskeletal pain, nausea, diarrhea, pyrexia, rash, and cough.

The most common laboratory abnormalities (≥20%) with monotherapy in adult patients were decreased neutrophils, increased creatinine, increased glucose, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), decreased lymphocytes, decreased hemoglobin, and decreased platelets.

The most common adverse reactions (≥20%) with combination therapy in adult patients were peripheral neuropathy, nausea, fatigue, musculoskeletal pain, constipation, diarrhea, mucositis, vomiting, abdominal pain, pyrexia, alopecia, upper respiratory tract infection, and rash.

The most common laboratory abnormalities (≥20%) with combination therapy in adult patients were decreased neutrophils, increased creatinine, decreased hemoglobin, decreased lymphocytes, increased ALT, increased AST, increased glucose, and increased uric acid.

The most common Grade ≥3 adverse reactions (≥5%) in combination with AVEPC in pediatric patients were neutropenia, anemia, thrombocytopenia, febrile neutropenia, stomatitis, and infection.

Previously Untreated Stage III or IV Classical Hodgkin Lymphoma (Study 5: ECHELON-1)

ADCETRIS in combination with AVD was evaluated for the treatment of previously untreated patients with Stage III or IV cHL in a randomized, open-label, multicenter clinical trial of 1334 patients. Patients were randomized to receive up to 6 cycles of ADCETRIS + AVD or ABVD on Days 1 and 15 of each 28-day cycle. The recommended starting dose of ADCETRIS was 1.2 mg/kg intravenously over 30 minutes, administered approximately 1 hour after completion of AVD therapy. A total of 1321 patients received at least one dose of study treatment (662 ADCETRIS + AVD, 659 ABVD). The median number of treatment cycles in each study arm was 6 (range, 1–6); 76% of patients on the ADCETRIS + AVD arm received 12 doses of ADCETRIS *[see Clinical Studies (14.1)]*.

After 75% of patients had started study treatment, the use of prophylactic G-CSF was recommended with the initiation of treatment for all ADCETRIS + AVD treated patients, based on the observed rates of neutropenia and febrile neutropenia *[see Dosage and Administration (2.2)]*. Among 579 patients on the ADCETRIS + AVD arm who did not receive G-CSF primary prophylaxis beginning with Cycle 1, 96% experienced neutropenia (21% with Grade 3; 67% with Grade 4), and 21% had febrile neutropenia (14% with Grade 3; 6% with Grade 4). Among 83 patients on the ADCETRIS + AVD arm who received G-CSF primary prophylaxis beginning with Cycle 1, 61% experienced neutropenia (13% with Grade 3; 27% with Grade 4), and 11% experienced febrile neutropenia (8% with Grade 3; 2% with Grade 4).

Serious adverse reactions were reported in 43% of ADCETRIS + AVD-treated patients and 27% of ABVD-treated patients. The most common serious adverse reactions in ADCETRIS + AVD-treated patients were febrile neutropenia (17%), pyrexia (7%), neutropenia and pneumonia (3% each).

Adverse reactions that led to dose delays of one or more drugs in more than 5% of ADCETRIS + AVD-treated patients were neutropenia (21%) and febrile neutropenia (8%) *[see Dosage and Administration (2.2)]*. Adverse reactions led to treatment discontinuation of one or more drugs in 13% of ADCETRIS + AVD-treated patients. Seven percent of patients treated with ADCETRIS + AVD discontinued due to peripheral neuropathy.

There were 9 on-study deaths among ADCETRIS + AVD-treated patients; 7 were associated with neutropenia, and none of these patients had received G-CSF prior to developing neutropenia.

Table 4: Adverse Reactions Reported in ≥10% of ADCETRIS + AVD-Treated Patients in Previously Untreated Stage III or IV Classical Hodgkin Lymphoma (Study 5: ECHELON-1)

	ADCETRIS + AVD Total N = 662 % of patients			ABVD Total N = 659 % of patients		
Body System Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Blood and lymphatic system disorders						
Anemia*	98	11	<1	92	6	<1
Neutropenia*	91	20	62	89	31	42
Febrile neutropenia	19	13	6	8	6	2
Gastrointestinal disorders						
Constipation	42	2	-	37	<1	<1
Vomiting	33	3	-	28	1	-
Diarrhea	27	3	<1	18	<1	-
Stomatitis	21	2	-	16	<1	-
Abdominal pain	21	3	-	10	<1	-
Nervous system disorders						
Peripheral sensory neuropathy	65	10	<1	41	2	-
Peripheral motor neuropathy	11	2	-	4	<1	-
General disorders and administration site conditions						
Pyrexia	27	3	<1	22	2	-
Musculoskeletal and connective tissue disorders						
Bone pain	19	<1	-	10	<1	-
Back pain	13	<1	-	7	-	-
Skin and subcutaneous tissue disorders						
Rashes, eruptions and exanthems[a]	13	<1	<1	8	<1	-
Respiratory, thoracic and mediastinal disorders						
Dyspnea	12	1	-	19	2	-
Investigations						
Decreased weight	22	<1	-	6	<1	-
Increased alanine aminotransferase	10	3	-	4	<1	-
Metabolism and nutrition disorders						
Decreased appetite	18	<1	-	12	<1	-
Psychiatric disorders						
Insomnia	19	<1	-	12	<1	-

* Derived from laboratory values and adverse reaction data; data are included for clinical relevance irrespective of rate between arms

[a] Grouped term includes rash maculo-papular, rash macular, rash, rash papular, rash generalized, and rash vesicular.

AVD = doxorubicin, vinblastine, and dacarbazine

ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine

Events were graded using the NCI CTCAE Version 4.03

Events listed are those having a ≥5% difference in rate between treatment arms

Previously Untreated High Risk Classical Hodgkin Lymphoma (cHL)

Study 7: AHOD1331

The safety of ADCETRIS was evaluated in Study 7: AHOD1331 *[see Clinical Studies (14.1)]*. The study included pediatric patients with previously untreated high risk cHL. Patients received ADCETRIS plus AVEPC chemotherapy at 1.8 mg/kg intravenously over 30 minutes prior to other chemotherapy in 21-day cycles (n = 296) or ABVE-PC in 21-day cycles (n = 297). Among patients who received ADCETRIS in combination with AVEPC chemotherapy, the median number of treatment cycles was 5 (range, 1-5).

Serious adverse reactions occurred in 22% of patients who received ADCETRIS plus AVEPC chemotherapy. Serious adverse reactions in >2% of patients included hypotension (3%) and febrile neutropenia (3%).

Table 5: Grade 3 or 4 Adverse Reactions Reported in ≥2% of ADCETRIS + AVEPC Treated Pediatric Patients with Previously Untreated High Risk Classical Hodgkin Lymphoma in Study 7: AHOD1331

	ADCETRIS + AVEPC Total N = 296 % of patients		**ABVE-PC Total N = 297 % of patients**	
System Organ Class Preferred Term	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Blood and lymphatic system disorders				
Anemia	35	1.7	28	2
Febrile neutropenia	28	3.4	31	1.7
Lymphopenia	13	11	8	18
Thrombocytopenia[a]	10	22	11	16
Neutropenia	8	43	4.4	36
Gastrointestinal disorders				
Stomatitis	10	-	7	-
Nausea	3.7	-	2	-
Vomiting	3.7	-	1.3	-
Diarrhea	2.4	-	0.3	-
Colitis	2	0.3	1	-
Infections and infestations				
Infections[b]	9	2.7	7	3.4
Nervous system disorders				
Peripheral sensory neuropathy	6	-	4.4	-
Metabolism and nutrition disorders				
Hypokalemia	5	0.7	6	1
Hyponatremia	3.4	-	3	-
Decreased appetite	2.7	-	1.7	-
Dehydration	2.7	-	1	-

	ADCETRIS + AVEPC Total N = 296 % of patients		ABVE-PC Total N = 297 % of patients	
System Organ Class Preferred Term	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Hepatobiliary disorders				
Alanine aminotransferase increased	3.7	0.3	2.7	0.3
General disorders and administration site conditions				
Infusion-related reactions[c]	3	1	5	1

[a] Includes thrombocytopenia and platelet count decreased
[b] Includes sepsis, device related infection, skin infection, enterocolitis infectious, pneumonia, appendicitis, cellulitis, urinary tract infection, candida infection, mucosal infection, vaginal infection, wound infection, anorectal infection, arteritis infective, bacteremia, catheter site infection, clostridium difficile colitis, gastroenteritis norovirus, gingivitis, H1N1 influenza, herpes simplex reactivation, infective myositis, klebsiella bacteremia, klebsiella sepsis, meningitis, esophageal infection, oral candidiasis, osteomyelitis, otitis media, septic shock, serratia infection, sinusitis, soft tissue infection, staphylococcal infection, vulvitis
[c] Includes anaphylactic reaction, hypersensitivity, drug hypersensitivity, infusion-related reaction, and bronchospasm

Classical Hodgkin Lymphoma Post-Auto-HSCT Consolidation (Study 3: AETHERA)

ADCETRIS was studied in 329 patients with cHL at high risk of relapse or progression post-auto-HSCT in a randomized, double-blind, placebo-controlled clinical trial in which the recommended starting dose and schedule was 1.8 mg/kg of ADCETRIS administered intravenously over 30 minutes every 3 weeks or placebo for up to 16 cycles. Of the 329 enrolled patients, 327 (167 ADCETRIS, 160 placebo) received at least one dose of study treatment. The median number of treatment cycles in each study arm was 15 (range, 1–16) and 80 patients (48%) in the ADCETRIS-treatment arm received 16 cycles *[see Clinical Studies (14.1)]*.

Standard international guidelines were followed for infection prophylaxis for herpes simplex virus (HSV), varicella-zoster virus (VZV), and *Pneumocystis jiroveci* pneumonia (PJP) post-auto-HSCT. Overall, 312 patients (95%) received HSV and VZV prophylaxis with a median duration of 11.1 months (range, 0–20) and 319 patients (98%) received PJP prophylaxis with a median duration of 6.5 months (range, 0–20).

Adverse reactions that led to dose delays in more than 5% of ADCETRIS-treated patients were neutropenia (22%), peripheral sensory neuropathy (16%), upper respiratory tract infection (6%), and peripheral motor neuropathy (6%) *[see Dosage and Administration (2.3)]*. Adverse reactions led to treatment discontinuation in 32% of ADCETRIS-treated patients. Adverse reactions that led to treatment discontinuation in 2 or more patients were peripheral sensory neuropathy (14%), peripheral motor neuropathy (7%), acute respiratory distress syndrome (1%), paresthesia (1%), and vomiting (1%). Serious adverse reactions were reported in 25% of ADCETRIS-treated patients. The most common serious adverse reactions were pneumonia (4%), pyrexia (4%), vomiting (3%), nausea (2%), hepatotoxicity (2%), and peripheral sensory neuropathy (2%).

Table 6: Adverse Reactions Reported in ≥10% in ADCETRIS-Treated Patients with Classical Hodgkin Lymphoma Post-Auto-HSCT Consolidation (Study 3: AETHERA)

	ADCETRIS Total N = 167 % of patients			Placebo Total N = 160 % of patients		
Body System Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Blood and lymphatic system disorders						
Neutropenia*	78	30	9	34	6	4
Thrombocytopenia*	41	2	4	20	3	2
Anemia*	27	4	-	19	2	-
Nervous system disorders						
Peripheral sensory neuropathy	56	10	-	16	1	-
Peripheral motor neuropathy	23	6	-	2	1	-
Headache	11	2	-	8	1	-
Infections and infestations						
Upper respiratory tract infection	26	-	-	23	1	-
General disorders and administration site conditions						
Fatigue	24	2	-	18	3	-
Pyrexia	19	2	-	16	-	-
Chills	10	-	-	5	-	-
Gastrointestinal disorders						
Nausea	22	3	-	8	-	-
Diarrhea	20	2	-	10	1	-
Vomiting	16	2	-	7	-	-
Abdominal pain	14	2	-	3	-	-
Constipation	13	2	-	3	-	-
Respiratory, thoracic and mediastinal disorders						
Cough	21	-	-	16	-	-
Dyspnea	13	-	-	6	-	1
Investigations						
Weight decreased	19	1	-	6	-	-
Musculoskeletal and connective tissue disorders						
Arthralgia	18	1	-	9	-	-
Muscle spasms	11	-	-	6	-	-
Myalgia	11	1	-	4	-	-
Skin and subcutaneous tissue disorders						
Pruritus	12	1	-	8	-	-
Metabolism and nutrition disorders						
Decreased appetite	12	1	-	6	-	-

*Derived from laboratory values and adverse reaction data
Events were graded using the NCI CTCAE Version 4

Relapsed Classical Hodgkin Lymphoma (Study 1)

ADCETRIS was studied in 102 patients with cHL in a single arm clinical trial in which the recommended starting dose and schedule was 1.8 mg/kg intravenously every 3 weeks. Median duration of treatment was 9 cycles (range, 1–16) *[see Clinical Studies (14.1)]*.

Adverse reactions that led to dose delays in more than 5% of ADCETRIS-treated patients were neutropenia (16%) and peripheral sensory neuropathy (13%) *[see Dosage and Administration (2.3)]*. Adverse reactions led to treatment discontinuation in 20% of ADCETRIS-treated patients. Adverse reactions that led to treatment discontinuation in 2 or more patients were peripheral sensory neuropathy (6%) and peripheral motor neuropathy (3%). Serious adverse reactions were reported in 25% of ADCETRIS-treated patients. The most common serious adverse reactions were peripheral motor neuropathy (4%), abdominal pain (3%), pulmonary embolism (2%), pneumonitis (2%), pneumothorax (2%), pyelonephritis (2%), and pyrexia (2%).

Table 7: Adverse Reactions Reported in ≥10% of Patients with Relapsed Classical Hodgkin Lymphoma (Study 1)

	cHL Total N = 102 % of patients		
Body System Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**
Blood and lymphatic system disorders			
Neutropenia*	54	15	6
Anemia*	33	8	2
Thrombocytopenia*	28	7	2
Lymphadenopathy	11	-	-
Nervous system disorders			
Peripheral sensory neuropathy	52	8	-
Peripheral motor neuropathy	16	4	-
Headache	19	-	-
Dizziness	11	-	-
General disorders and administration site conditions			
Fatigue	49	3	-
Pyrexia	29	2	-
Chills	13	-	-
Infections and infestations			
Upper respiratory tract infection	47	-	-
Gastrointestinal disorders			
Nausea	42	-	-
Diarrhea	36	1	-
Abdominal pain	25	2	1
Vomiting	22	-	-
Constipation	16	-	-

	cHL Total N = 102 % of patients		
Body System **Adverse Reaction**	**Any Grade**	**Grade 3**	**Grade 4**
Skin and subcutaneous tissue disorders			
Rash	27	-	-
Pruritus	17	-	-
Alopecia	13	-	-
Night sweats	12	-	-
Respiratory, thoracic and mediastinal disorders			
Cough	25	-	-
Dyspnea	13	1	-
Oropharyngeal pain	11	-	-
Musculoskeletal and connective tissue disorders			
Arthralgia	19	-	-
Myalgia	17	-	-
Back pain	14	-	-
Pain in extremity	10	-	-
Psychiatric disorders			
Insomnia	14	-	-
Anxiety	11	2	-
Metabolism and nutrition disorders			
Decreased appetite	11	-	-

*Derived from laboratory values and adverse reaction data
Events were graded using the NCI CTCAE Version 3.0

Previously Untreated Systemic Anaplastic Large Cell Lymphoma or Other CD30-Expressing Peripheral T-Cell Lymphomas (Study 6, ECHELON-2)

ADCETRIS in combination with CHP was evaluated in patients with previously untreated, CD30-expressing PTCL in a multicenter randomized, double-blind, double dummy, actively controlled trial. Patients were randomized to receive ADCETRIS + CHP or CHOP for 6 to 8, 21-day cycles. ADCETRIS was administered on Day 1 of each cycle, with a starting dose of 1.8 mg/kg intravenously over 30 minutes, approximately 1 hour after completion of CHP [*see Clinical Studies (14.2)*]. The trial required hepatic transaminases ≤3 times upper limit of normal (ULN), total bilirubin ≤1.5 times ULN, and serum creatinine ≤2 times ULN and excluded patients with Grade 2 or higher peripheral neuropathy.

A total of 449 patients were treated (223 with ADCETRIS + CHP, 226 with CHOP), with 6 cycles planned in 81%. In the ADCETRIS + CHP arm, 70% of patients received 6 cycles, and 18% received 8 cycles. Primary prophylaxis with G-CSF was administered to 34% of ADCETRIS + CHP-treated patients and 27% of CHOP-treated patients.

Fatal adverse reactions occurred in 3% of patients in the A+CHP arm and in 4% of patients in the CHOP arms, most often from infection. Serious adverse reactions were reported in 38% of ADCETRIS + CHP- treated patients and 35% of CHOP-treated patients. Serious adverse

reactions occurring in >2% of ADCETRIS + CHP-treated patients included febrile neutropenia (14%), pneumonia (5%), pyrexia (4%), and sepsis (3%).

The most common adverse reactions observed ≥2% more in recipients of ADCETRIS + CHP were nausea, diarrhea, fatigue or asthenia, mucositis, pyrexia, vomiting, and anemia. Other common (≥10%) adverse reactions observed ≥2% more with ADCETRIS + CHP were febrile neutropenia, abdominal pain, decreased appetite, dyspnea, edema, cough, dizziness, hypokalemia, decreased weight, and myalgia.

In recipients of ADCETRIS + CHP, adverse reactions led to dose delays of ADCETRIS in 25% of patients, dose reduction in 9% (most often for peripheral neuropathy), and discontinuation of ADCETRIS with or without the other components in 7% (most often from peripheral neuropathy and infection).

Table 8: Adverse Reactions Reported in ≥10% of ADCETRIS + CHP-Treated Patients with Previously Untreated, CD30-Expressing PTCL (Study 6: ECHELON-2)

	ADCETRIS + CHP Total N = 223 % of patients			**CHOP Total N = 226 % of patients**		
Body System Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Blood and lymphatic system disorders						
Anemia*	66	13	<1	59	12	<1
Neutropenia*	59	17	22	58	14	22
Lymphopenia*	51	18	1	57	19	2
Febrile neutropenia	19	17	2	16	12	4
Thrombocytopenia*	17	3	3	13	3	2
Gastrointestinal disorders						
Nausea	46	2	-	39	2	-
Diarrhea	38	6	-	20	<1	-
Mucositis	30	2	<1	27	3	-
Constipation	29	<1	<1	30	1	-
Vomiting	26	<1	-	17	2	-
Abdominal pain	17	1	-	13	<1	-
Nervous system disorders						
Peripheral neuropathy	52	3	<1	55	4	-
Headache	15	<1	-	15	<1	-
Dizziness	13	-	-	9	<1	-
General disorders and administration site conditions						
Fatigue or asthenia	35	2	-	29	2	-
Pyrexia	26	1	<1	19	-	-
Edema	15	<1	-	12	<1	-
Infections and infestations						
Upper respiratory tract infection	14	<1	-	15	<1	-

	ADCETRIS + CHP Total N = 223 % of patients			CHOP Total N = 226 % of patients		
Body System Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Skin and subcutaneous disorders						
Alopecia	26	-	-	25	1	-
Rash	16	1	<1	14	1	-
Musculoskeletal and connective tissue disorders						
Myalgia	11	-	-	8	-	-
Respiratory, thoracic and mediastinal disorders						
Dyspnea	15	2	-	11	2	-
Cough	13	<1	-	10	-	-
Metabolism and nutrition disorders						
Decreased appetite	17	1	-	12	1	-
Hypokalemia	12	4	-	8	<1	<1
Investigations						
Weight decreased	12	<1	-	8	<1	-
Psychiatric disorders						
Insomnia	11	-	-	14	-	-

* Derived from laboratory values and adverse reaction data. Laboratory values were obtained at the start of each cycle and end of treatment.
The table includes a combination of grouped and ungrouped terms. CHP = cyclophosphamide, doxorubicin, and prednisone; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone
Events were graded using the NCI CTCAE Version 4.03

Relapsed Systemic Anaplastic Large Cell Lymphoma (Study 2)

ADCETRIS was studied in 58 patients with sALCL in a single arm clinical trial in which the recommended starting dose and schedule was 1.8 mg/kg intravenously every 3 weeks. Median duration of treatment was 7 cycles (range, 1–16) *[see Clinical Studies (14.2)]*.

Adverse reactions that led to dose delays in more than 5% of ADCETRIS-treated patients were neutropenia (12%) and peripheral sensory neuropathy (7%) *[see Dosage and Administration (2.3)]*. Adverse reactions led to treatment discontinuation in 19% of ADCETRIS-treated patients. The adverse reaction that led to treatment discontinuation in 2 or more patients was peripheral sensory neuropathy (5%). Serious adverse reactions were reported in 41% of ADCETRIS-treated patients. The most common serious adverse reactions were septic shock (3%), supraventricular arrhythmia (3%), pain in extremity (3%), and urinary tract infection (3%).

Table 9: Adverse Reactions Reported in ≥10% of Patients with Relapsed Systemic Anaplastic Large Cell Lymphoma (Study 2)

	sALCL Total N = 58 % of patients		
Body System Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**
Blood and lymphatic system disorders			
Neutropenia*	55	12	9
Anemia*	52	2	-
Thrombocytopenia*	16	5	5
Lymphadenopathy	10	-	-
Nervous system disorders			
Peripheral sensory neuropathy	53	10	-
Headache	16	2	-
Dizziness	16	-	-
General disorders and administration site conditions			
Fatigue	41	2	2
Pyrexia	38	2	-
Chills	12	-	-
Pain	28	-	5
Edema peripheral	16	-	-
Infections and infestations			
Upper respiratory tract infection	12	-	-
Gastrointestinal disorders			
Nausea	38	2	-
Diarrhea	29	3	-
Vomiting	17	3	-
Constipation	19	2	-
Skin and subcutaneous tissue disorders			
Rash	31	-	-
Pruritus	19	-	-
Alopecia	14	-	-
Dry skin	10	-	-
Respiratory, thoracic and mediastinal disorders			
Cough	17	-	-
Dyspnea	19	2	-
Musculoskeletal and connective tissue disorders			
Myalgia	16	2	-
Back pain	10	2	-
Pain in extremity	10	2	2
Muscle spasms	10	2	-

	sALCL Total N = 58 % of patients		
Body System Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**
Psychiatric disorders			
Insomnia	16	-	-
Metabolism and nutrition disorders			
Decreased appetite	16	2	-
Investigations			
Weight decreased	12	3	-

*Derived from laboratory values and adverse reaction data
Events were graded using the NCI CTCAE Version 3.0

Primary Cutaneous Anaplastic Large Cell Lymphoma and CD30-Expressing Mycosis Fungoides (Study 4: ALCANZA)

ADCETRIS was studied in 131 patients with pcALCL or CD30-expressing MF requiring systemic therapy in a randomized, open-label, multicenter clinical trial in which the recommended starting dose and schedule was ADCETRIS 1.8 mg/kg intravenously over 30 minutes every 3 weeks or physician's choice of either methotrexate 5 to 50 mg orally weekly or bexarotene 300 mg/m^2 orally daily.

Of the 131 enrolled patients, 128 (66 brentuximab vedotin, 62 physician's choice) received at least one dose of study treatment. The median number of treatment cycles in the ADCETRIS treatment arm was 12 (range, 1–16) compared to 3 (range, 1–16) and 6 (range, 1–16) in the methotrexate and bexarotene arms, respectively. Twenty-four (24) patients (36%) in the ADCETRIS-treatment arm received 16 cycles compared to 5 patients (8%) in the physician's choice arm *[see Clinical Studies (14.2)]*.

Adverse reactions that led to dose delays in more than 5% of ADCETRIS-treated patients were peripheral sensory neuropathy (15%) and neutropenia (6%) *[see Dosage and Administration (2.3)]*. Adverse reactions led to treatment discontinuation in 24% of ADCETRIS-treated patients. The most common adverse reaction that led to treatment discontinuation was peripheral neuropathy (12%). Serious adverse reactions were reported in 29% of ADCETRIS-treated patients. The most common serious adverse reactions were cellulitis (3%) and pyrexia (3%).

Table 10: Adverse Reactions Reported in ≥10% ADCETRIS-Treated Patients with pcALCL or CD30-Expressing MF (Study 4: ALCANZA)

	ADCETRIS Total N = 66 % of patients			Physician's Choice[a] Total N = 62 % of patients		
Body System Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Blood and lymphatic system disorders						
Anemia*	62	-	-	65	5	-
Neutropenia*	21	3	2	24	5	-
Thrombocytopenia*	15	2	2	2	-	-

	ADCETRIS Total N = 66 % of patients			Physician's Choice[a] Total N = 62 % of patients		
Body System Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Nervous system disorders						
Peripheral sensory neuropathy	45	5	-	2	-	-
Gastrointestinal disorders						
Nausea	36	2	-	13	-	-
Diarrhea	29	3	-	6	-	-
Vomiting	17	2	-	5	-	-
General disorders and administration site conditions						
Fatigue	29	5	-	27	2	-
Pyrexia	17	-	-	18	2	-
Edema peripheral	11	-	-	10	-	-
Asthenia	11	2	-	8	-	2
Skin and subcutaneous tissue disorders						
Pruritus	17	2	-	13	3	-
Alopecia	15	-	-	3	-	-
Rash maculo-papular	11	2	-	5	-	-
Pruritus generalized	11	2	-	2	-	-
Metabolism and nutrition disorders						
Decreased appetite	15	-	-	5	-	-
Musculoskeletal and connective tissue disorders						
Arthralgia	12	-	-	6	-	-
Myalgia	12	-	-	3	-	-
Respiratory, thoracic and mediastinal disorders						
Dyspnea	11	-	-	-	-	-

*Derived from laboratory values and adverse reaction data
[a] Physician's choice of either methotrexate or bexarotene
Events were graded using the NCI CTCAE Version 4.03

Relapsed or Refractory Large B-Cell Lymphoma (Study 8: ECHELON-3)

The safety of ADCETRIS in combination with lenalidomide and a rituximab product was evaluated in ECHELON-3, a randomized, multicenter, double-blind, placebo-controlled trial in patients with relapsed or refractory LBCL who had received at least 2 prior lines of systemic therapy and who were not eligible for HSCT or CAR T-cell therapy *[see Clinical Studies (14.5)]*.

Patients in the treatment arm (n = 112) received ADCETRIS, 1.2 mg/kg via intravenous infusion every 3 weeks, lenalidomide, and a rituximab product. Placebo replaced ADCETRIS in the placebo plus lenalidomide and rituximab arm (n = 116).

The trial required an absolute neutrophil count ≥1,000/μL, platelet count ≥50,000/μL, creatinine clearance (CrCL) ≥45 mL/min, hepatic transaminases ≤3 times the upper limit of normal (ULN), and bilirubin <1.5 times ULN. The trial excluded patients having Eastern Cooperative Oncology Group (ECOG) performance status above 2, active central nervous system (CNS)

lymphoma, and Grade 2 or higher peripheral neuropathy. Granulocyte colony-stimulating factor (G-CSF) primary prophylaxis was required and administered to 98% of patients in the ADCETRIS plus lenalidomide and rituximab arm and 91% of patients in the lenalidomide and rituximab arm.

The median age was 71 years (range: 21 to 89 years); 44% of patients were female; 53% were White, 26% were Asian, and 4% were Hispanic or Latino. There were no Black or African American patients enrolled in ECHELON-3. Among patients who received ADCETRIS, the median number of treatment cycles was 5 (range, 1-34).

Serious adverse reactions occurred in 60% of patients who received ADCETRIS in combination with lenalidomide and a rituximab product. Serious adverse reactions that occurred in >2% of patients included pneumonia (21%), COVID-19 (13%, includes COVID-19 pneumonia), sepsis (9%), febrile neutropenia (7%), hemorrhage (3.6%), urinary tract infection (3.6%), thrombocytopenia (2.7%) and upper respiratory tract infection (2.7%). Fatal adverse reactions occurred in 12% of patients who received ADCETRIS in combination with lenalidomide and a rituximab product, including COVID-19 (4.5%, includes COVID-19 pneumonia), pneumonia (3.6%), and sepsis (1.8%).

Adverse reactions led to dose reduction of ADCETRIS in 6% of patients, all due to peripheral neuropathy. Adverse reactions leading to dose delay of ADCETRIS in more than 5% of patients included neutropenia (23%), COVID-19 (13%), pneumonia (8%), and thrombocytopenia (8%).

Adverse reactions led to discontinuation of ADCETRIS in 20% of patients. Adverse reactions that led to treatment discontinuation in 3 or more patients included peripheral neuropathy (4.5%) and pneumonia (2.7%).

Table 11: Adverse Reactions Reported in ≥10% of ADCETRIS in Combination with Lenalidomide and a Rituximab Product-Treated Patients in Relapsed or Refractory LBCL (Study 8: ECHELON-3)

	ADCETRIS + Lenalidomide + Rituximab N = 112		**Placebo + Lenalidomide + Rituximab N = 116**	
Body System Adverse Reaction	**All Grades %**	**Grade 3-4 %**	**All Grades %**	**Grade 3-4 %**
General disorders and Administration Site Conditions				
Fatigue[a]	46	10	29	5
Pyrexia	15	1.8	15	0.9
Gastrointestinal disorders				
Diarrhea[a]	31	4.5	23	1.7
Constipation	17	1.8	18	0
Nausea	15	0.9	16	0.9
Abdominal pain[a]	12	1.8	12	1.7
Stomatitis[a]	11	0	7	0
Nervous system disorders				
Peripheral neuropathy[b]	27	5	21	0

Body System Adverse Reaction	ADCETRIS + Lenalidomide + Rituximab N = 112		Placebo + Lenalidomide + Rituximab N = 116	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Infections and Infestations[a]				
COVID-19[c]	27	13	16	8
Pneumonia[d]	27	21	10	9
Upper respiratory tract infection[a]	12	2.7	5	0
Skin and subcutaneous tissue disorders				
Rash[a]	27	2.7	16	0.9
Pruritus[a]	17	0	6	0
Renal and urinary disorders				
Renal insufficiency	20	3.6	14	4.3
Respiratory, thoracic and mediastinal disorders				
Cough	17	0	9	0
Dyspnea[a]	12	0.9	14	2.6
Metabolism and nutrition disorders				
Decreased appetite	17	0.9	9	0
Investigations				
Weight decreased	13	0.9	5	0.9

[a] Includes other related terms.
[b] Includes peripheral sensory neuropathy, peripheral motor neuropathy, paresthesia, hypoesthesia, neuropathy peripheral, hypoesthesia oral, oral dysesthesia, neuralgia, paresthesia oral.
[c] Includes COVID-19 and COVID-19 pneumonia.
[d] Includes pneumonia, COVID-19 pneumonia, atypical pneumonia, bronchopulmonary aspergillosis, lung infiltration, organizing pneumonia, pneumocystis jirovecii pneumonia, pneumonia bacterial, pneumonia fungal, pneumonia streptococcal, pneumonia viral.

Clinically relevant adverse reactions in <10% of patients who received ADCETRIS in combination with lenalidomide and a rituximab product include febrile neutropenia, edema, hypotension, urinary tract infection, sepsis, respiratory tract infection, vomiting, back pain, dizziness, arthralgia, herpes virus infection, bone pain, atrial fibrillation or flutter, lower respiratory tract infection, and cardiac failure.

Table 12: Select Laboratory Abnormalities (≥20%) that Worsened from Baseline in Patients Who Received ADCETRIS + Lenalidomide + Rituximab-Treated Patients in Relapsed or Refractory LBCL (Study 8: ECHELON-3)

Laboratory Abnormality[a]	ADCETRIS + Lenalidomide + Rituximab N = 112[a]		Placebo + Lenalidomide + Rituximab N = 116[a]	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Hematology				
Neutrophils decreased	77	49	63	42
Lymphocytes decreased	65	38	53	30
Platelets decreased	65	29	54	18
Hemoglobin decreased	54	19	49	14

Laboratory Abnormality[a]	ADCETRIS + Lenalidomide + Rituximab N = 112[a]		Placebo + Lenalidomide + Rituximab N = 116[a]	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Chemistry				
Alanine aminotransferase increased	31	0.9	17	0
Potassium decreased	31	7	29	2.9
Albumin decreased	29	0.9	25	1
Creatinine increased	26	2.8	23	0
Calcium decreased	21	0.9	7	0

[a] The denominator used to calculate the rate varied from 105 to 107 in the ADCETRIS + lenalidomide + rituximab arm, and from 97 to 103 in the placebo + lenalidomide + rituximab arm based on the number of patients with a baseline value and at least one post-treatment value.

Additional Important Adverse Reactions

Infusion reactions

In studies of ADCETRIS as monotherapy (Studies 1–4), 13% of ADCETRIS-treated patients experienced infusion-related reactions. The most common adverse reactions in Studies 1-4 (≥3% in any study) associated with infusion-related reactions were chills (4%), nausea (3–4%), dyspnea (2–3%), pruritus (2–5%), pyrexia (2%), and cough (2%). Grade 3 events were reported in 5 of the 51 ADCETRIS-treated patients who experienced infusion-related reactions.

In a study of ADCETRIS in combination with AVD (Study 5, ECHELON-1), infusion-related reactions were reported in 57 patients (9%) in the ADCETRIS + AVD-treated arm. Grade 3 events were reported in 3 of the 57 patients treated with ADCETRIS + AVD who experienced infusion-related reactions. The most common adverse reaction (≥2%) associated with infusion-related reactions was nausea (2%).

In a study of ADCETRIS in combination with CHP (Study 6, ECHELON-2), infusion-related reactions were reported in 10 patients (4%) in the ADCETRIS + CHP-treated arm: 2 (1%) patients with events that were Grade 3 or higher events, and 8 (4%) patients with events that were less than Grade 3.

In a study of ADCETRIS in combination with lenalidomide and rituximab (Study 8, ECHELON-3), Grade 1 or 2 infusion-related reactions were reported in 6 patients (5%) in the ADCETRIS + lenalidomide + rituximab arm.

Pulmonary toxicity

In a trial in patients with cHL that studied ADCETRIS with bleomycin as part of a combination regimen, the rate of non-infectious pulmonary toxicity was higher than the historical incidence reported with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine). Patients typically reported cough and dyspnea. Interstitial infiltration and/or inflammation were observed on radiographs and computed tomographic imaging of the chest. Most patients responded to corticosteroids. The concomitant use of ADCETRIS with bleomycin is contraindicated *[see Contraindications (4)]*.

In a study of ADCETRIS in combination with AVD (Study 5, ECHELON-1), non-infectious pulmonary toxicity events were reported in 12 patients (2%) in the ADCETRIS + AVD arm. These events included lung infiltration (6 patients) and pneumonitis (6 patients), or interstitial lung disease (1 patient).

In a study of ADCETRIS in combination with CHP (Study 6, ECHELON-2), non-infectious pulmonary toxicity events were reported in 5 patients (2%) in the ADCETRIS + CHP arm; all 5 events were pneumonitis. Cases of pulmonary toxicity have also been reported in patients receiving ADCETRIS monotherapy. In Study 3 (AETHERA), pulmonary toxicity was reported in 8 patients (5%) in the ADCETRIS-treated arm and 5 patients (3%) in the placebo arm.

Immunogenicity: Anti-Drug Antibody-Associated Adverse Reactions

During treatment in patients with relapsed or refractory cHL and relapsed or refractory systemic ALCL in Studies 1 and 2, two of the patients (1%) with persistently positive antibodies experienced adverse reactions consistent with infusion reactions that led to discontinuation of treatment *[see Warnings and Precautions (5.2)].* Overall, a higher incidence of infusion-related reactions was observed in patients who developed persistently positive antibodies *[see Clinical Pharmacology (12.6)]*.

6.2 Post Marketing Experience

The following adverse reactions have been identified during post-approval use of ADCETRIS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: febrile neutropenia *[see Warnings and Precautions (5.3)]*.

Gastrointestinal disorders: acute pancreatitis and gastrointestinal complications (including fatal outcomes) *[see Warnings and Precautions (5.12)]*.

Hepatobiliary disorders: hepatotoxicity *[see Warnings and Precautions (5.8)]*.

Infections: PML *[see Boxed Warning, Warnings and Precautions (5.9)]*, serious infections and opportunistic infections *[see Warnings and Precautions (5.4)]*.

Metabolism and nutrition disorders: hyperglycemia *[see Warnings and Precautions (5.13)]*.

Respiratory, thoracic and mediastinal disorders: noninfectious pulmonary toxicity including pneumonitis, interstitial lung disease, and ARDS (some with fatal outcomes) *[see Warnings and Precautions (5.10) and Adverse Reactions (6.1)]*.

Skin and subcutaneous tissue disorders: Toxic epidermal necrolysis, including fatal outcomes *[see Warnings and Precautions (5.11)]*.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on ADCETRIS

CYP3A4 Inhibitors: Co-administration of ADCETRIS with ketoconazole, a potent CYP3A4 inhibitor, increased exposure to MMAE *[see Clinical Pharmacology (12.3)],* which may increase

the risk of adverse reaction. Closely monitor adverse reactions when ADCETRIS is given concomitantly with strong CYP3A4 inhibitors.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

ADCETRIS can cause fetal harm based on the findings from animal studies and the drug's mechanism of action *[see Clinical Pharmacology (12.1)]*. In animal reproduction studies, administration of brentuximab vedotin to pregnant rats during organogenesis at doses similar to the clinical dose of 1.8 mg/kg every three weeks caused embryo-fetal toxicities, including congenital malformations *(see Data).* The available data from case reports on ADCETRIS use in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. Advise a pregnant woman of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Data

Animal Data

In an embryo-fetal developmental study, pregnant rats received 2 intravenous doses of 0.3, 1, 3, or 10 mg/kg brentuximab vedotin during the period of organogenesis (once each on Pregnancy Days 6 and 13). Drug-induced embryo-fetal toxicities were seen mainly in animals treated with 3 and 10 mg/kg of the drug and included increased early resorption (≥99%), post-implantation loss (≥99%), decreased numbers of live fetuses, and external malformations (i.e., umbilical hernias and malrotated hindlimbs). Systemic exposure in animals at the brentuximab vedotin dose of 3 mg/kg is approximately the same exposure in patients with cHL or sALCL who received the recommended dose of 1.8 mg/kg every three weeks.

8.2 Lactation

Risk Summary

There is no information regarding the presence of brentuximab vedotin in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child from ADCETRIS, including cytopenias and neurologic or gastrointestinal toxicities, advise patients that breastfeeding is not recommended during ADCETRIS treatment.

8.3 Females and Males of Reproductive Potential

ADCETRIS can cause fetal harm based on the findings from animal studies and the drug's mechanism of action *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating ADCETRIS therapy.

Contraception

Females

Advise females of reproductive potential to use effective contraception during ADCETRIS treatment and for 2 months after the last dose of ADCETRIS. Advise females to immediately report pregnancy *[see Use in Specific Populations (8.1)].*

Males

ADCETRIS may damage spermatozoa and testicular tissue, resulting in possible genetic abnormalities. Males with female sexual partners of reproductive potential should use effective contraception during ADCETRIS treatment and for 4 months after the last dose of ADCETRIS *[see Nonclinical Toxicology (13.1)].*

Infertility

Females

Based on findings in animal studies with MMAE-containing antibody-drug conjugates (ADCs), ADCETRIS may impair female fertility. The effect on fertility is reversible *[see Nonclinical Toxicology (13.1)].*

Males

Based on findings in rats, male fertility may be compromised by treatment with ADCETRIS *[see Nonclinical Toxicology (13.1)].*

8.4 Pediatric Use

The safety and effectiveness of ADCETRIS have been established in pediatric patients age 2 years and older with previously untreated high risk classical Hodgkin lymphoma in combination with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide. The safety and effectiveness of ADCETRIS have not been established for all other indications *[see Indications and Usage (1)]*.

Previously Untreated, High Risk Classical Hodgkin Lymphoma (cHL) in Combination with Doxorubicin, Vincristine, Etoposide, Prednisone, and Cyclophosphamide

The safety and effectiveness of ADCETRIS have been established in pediatric patients 2 years and older with previously untreated high risk cHL in combination with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide chemotherapy.

Use of ADCETRIS for this indication is supported by evidence from Study 7: AHOD1331, a randomized study which included pediatric patients with previously untreated high risk cHL, including patients in the following age groups: 9 patients 3 to less than 6 years of age, 81

patients 6 to less than 12 years of age, and 345 patients 12 to less than 17 years of age *[see Adverse Reactions (6.1) and Clinical Studies (14.1)]*.

The safety and efficacy of ADCETRIS have not been established for this indication in patients younger than 2 years.

Previously Untreated High Risk Classical Hodgkin Lymphoma (cHL) in Combination with Etoposide, Prednisone, Doxorubicin, Cyclophosphamide, Prednisone, and Dacarbazine

The safety and effectiveness of ADCETRIS in combination with etoposide (E), prednisone (P), and doxorubicin (A)/cyclophosphamide (C), prednisone (P), and dacarbazine (Dac) (AEPA/CAPDac) were assessed but have not been established based on a single arm, open-label trial (NCT01920932) in 77 patients, which included 48 pediatric patients age 6 to less than 17 with previously untreated high risk (IIB, IIIB, IVA, or IVB) cHL. No new safety signals were identified in this study.

Relapsed or Refractory Classical HL (cHL)

ADCETRIS in Combination with Gemcitabine

The safety and effectiveness of ADCETRIS in combination with gemcitabine were assessed but have not been established based on a study (NCT01780662) in 45 patients, which included 18 pediatric patients age 5 to less than 17 with relapsed or refractory cHL. No new safety signals were identified in this study.

ADCETRIS Monotherapy

The safety and effectiveness of ADCETRIS monotherapy was assessed but have not been established based on a study (NCT01492088) in 36 patients, which included 15 pediatric patients age 8 to less than 17 with relapsed or refractory cHL. No new safety signals were identified in this study.

Relapsed or Refractory Systemic ALCL (sALCL)

ADCETRIS monotherapy

The safety and effectiveness of ADCETRIS monotherapy was assessed but have not been established based on a study (NCT01492088) in 36 patients, which included 16 pediatric patients age 7 to less than 17 with sALCL. No new safety signals were identified in this study.

Newly Diagnosed ALK+ ALCL

The safety and effectiveness of ADCETRIS in combination with alternating chemotherapy Courses A (dexamethasone, ifosfamide, methotrexate, etoposide, cytarabine) and B (dexamethasone, methotrexate, cyclophosphamide, doxorubicin) administered every 21 days for a total of 6 cycles was assessed but have not been established based on a study (NCT01979536) in 67 patients, which included 61 pediatric patients age 2 to less than 17 years with newly diagnosed ALK+ ALCL. No new safety signals were identified in this study.

8.5 Geriatric Use

In the clinical trial of ADCETRIS in combination with AVD for patients with previously untreated Stage III or IV cHL (Study 5: ECHELON-1), 9% of ADCETRIS + AVD-treated patients were age 65 and older. Older age was a risk factor for febrile neutropenia, occurring in 39% of patients who were age 65 and older versus 17% of patients less than age 65, who received ADCETRIS + AVD *[see Dosage and Administration (2.3)].* The ECHELON-1 trial did not contain sufficient information on patients age 65 and older to determine whether they respond differently from younger patients *[see Clinical Studies (14.1)]*.

In the clinical trial of ADCETRIS in combination with CHP for patients with previously untreated, CD30-expressing PTCL (Study 6: ECHELON-2), 31% of ADCETRIS + CHP-treated patients were age 65 and older *[see Clinical Studies (14.2)]*. Among older patients, 74% had adverse reactions ≥ Grade 3 and 49% had serious adverse reactions. Among patients younger than age 65, 62% had adverse reactions ≥ Grade 3 and 33% had serious adverse reactions. Older age was a risk factor for febrile neutropenia, occurring in 29% of patients who were age 65 and older versus 14% of patients less than age 65.

Other clinical trials of ADCETRIS in cHL (Study 1; Study 3: AETHERA) and sALCL (Study 2) did not include sufficient numbers of patients who were age 65 and older to determine whether they respond differently from younger patients *[see Clinical Studies (14.1, 14.3)]*.

In the clinical trial of ADCETRIS in pcALCL or CD30-expressing MF (Study 4: ALCANZA), 42% of ADCETRIS-treated patients were age 65 and older *[see Clinical Studies (14.4)].* No meaningful differences in safety or efficacy were observed between these patients and younger patients.

In the clinical trial of ADCETRIS in relapsed or refractory LBCL (Study 8: ECHELON-3) *[see Clinical Studies (14.5)]*, 79 (71%) of ADCETRIS-treated patients were age 65 and older. No meaningful differences in safety or efficacy were observed between these patients and younger patients.

8.6 Renal Impairment

Avoid the use of ADCETRIS in patients with severe renal impairment (CrCL <30 mL/min) *[see Warnings and Precautions (5.6) and Clinical Pharmacology (12.3)].* No dosage adjustment is required for mild (CrCL >50–80 mL/min) or moderate (CrCL 30–50 mL/min) renal impairment.

8.7 Hepatic Impairment

Avoid the use of ADCETRIS in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment *[see Warnings and Precautions (5.7) and Clinical Pharmacology (12.3)]*. Dosage reduction is required in patients with mild (Child-Pugh A) hepatic impairment *[see Dosage and Administration (2.3)]*.

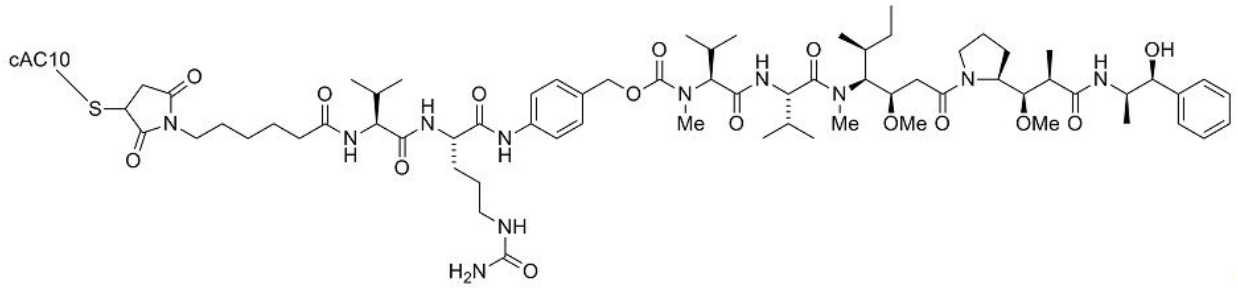
Hepatic impairment for patients with relapsed or refractory large B-cell lymphoma is defined per the National Cancer Institute Organ Dysfunction Working Group.

10 OVERDOSAGE

There is no known antidote for overdosage of ADCETRIS. In case of overdosage, the patient should be closely monitored for adverse reactions, particularly neutropenia, and supportive treatment should be administered.

11 DESCRIPTION

ADCETRIS (brentuximab vedotin) is a CD30-directed antibody and microtubule inhibitor conjugate consisting of three components: 1) the chimeric IgG1 antibody cAC10, specific for human CD30, 2) the microtubule disrupting agent MMAE, and 3) a protease-cleavable linker that covalently attaches MMAE to cAC10.



Brentuximab vedotin has an approximate molecular weight of 153 kDa. Approximately 4 molecules of MMAE are attached to each antibody molecule. Brentuximab vedotin is produced by chemical conjugation of the antibody and small molecule components. The antibody is produced by mammalian (Chinese hamster ovary) cells, and the small molecule components are produced by chemical synthesis.

ADCETRIS (brentuximab vedotin) for injection is supplied as a sterile, white to off-white, preservative-free lyophilized cake or powder in single-dose vials. Following reconstitution with 10.5 mL Sterile Water for Injection, USP, a solution containing 5 mg/mL brentuximab vedotin is produced. The reconstituted product contains 70 mg/mL trehalose dihydrate, 5.6 mg/mL sodium citrate dihydrate, 0.21 mg/mL citric acid monohydrate, and 0.20 mg/mL polysorbate 80 and water for injection. The pH is approximately 6.6.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

CD30 is a member of the tumor necrosis factor receptor family and is expressed on the surface of sALCL cells and on Hodgkin Reed-Sternberg (HRS) cells in cHL. CD30 is variably expressed in other T-cell lymphomas. Expression of CD30 on healthy tissue and cells is limited. In vitro data suggest that signaling through CD30-CD30L binding may affect cell survival and proliferation.

Brentuximab vedotin is an antibody-drug conjugate (ADC). The antibody is a chimeric IgG1 directed against CD30. The small molecule, MMAE, is a microtubule-disrupting agent. MMAE is covalently attached to the antibody via a linker. Nonclinical data suggest that the anticancer activity of ADCETRIS is due to the binding of the ADC to CD30-expressing cells, followed by internalization of the ADC-CD30 complex, and the release of MMAE via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network within the cell, subsequently

inducing cell cycle arrest and apoptotic death of the cells. Additionally, in vitro data provide evidence for antibody-dependent cellular phagocytosis (ADCP).

12.2 Pharmacodynamics

Cardiac Electrophysiology

At the recommended dose of 1.8 mg/kg, brentuximab vedotin had no large QTc prolongation (>10ms).

12.3 Pharmacokinetics

The pharmacokinetics of brentuximab vedotin were evaluated in monotherapy and combination chemotherapy in patients with hematological malignancies. The pharmacokinetics of brentuximab vedotin in combination therapy were similar to those in monotherapy. Total antibody and ADC had similar pharmacokinetic profiles. The pharmacokinetics of the ADC and MMAE are presented.

ADC

Maximum concentrations of ADC were observed near the end of infusion. Exposures were approximately dose proportional from 1.2 to 2.7 mg/kg (1.5 times the highest approved recommended dosage).

- 1.8 mg/kg Q3W: Steady state was achieved within 21 days, and minimal to no accumulation of ADC was observed.
- 1.2 mg/kg Q2W: Steady state was achieved within 56 days, 1.27-fold accumulation (14-day AUC) was observed.
- 1.2 mg/kg Q3W: Steady state was achieved within 21 days, and minimal to no accumulation of ADC was observed.

MMAE

Maximum concentrations of MMAE were observed approximately 1 to 3 days after end of infusion. Exposures decreased with continued administration of ADCETRIS with approximately 50% to 80% of the exposure of the first dose observed at subsequent doses.

- 1.8 mg/kg Q3W: Steady state was achieved within 21 days.
- 1.2 mg/kg Q2W: Steady state was achieved within 56 days.
- 1.2 mg/kg Q3W: Steady state was achieved within 21 days.

Distribution

In humans, the mean steady state volume of distribution was approximately 6–10 L for ADC.

In vitro, the binding of MMAE to human plasma proteins ranged from 68–82%. MMAE is not likely to displace or to be displaced by highly protein-bound drugs.

Elimination

ADC elimination exhibited a multi-exponential decline with a t1/2 of approximately 4 to 6 days.

MMAE elimination exhibited a mono-exponential decline with a t1/2 of approximately 3 to 4 days. Elimination of MMAE appeared to be limited by its rate of release from ADC.

Metabolism

A small fraction of MMAE released from brentuximab vedotin is metabolized. In vitro data indicate that the MMAE metabolism that occurs is primarily via oxidation by CYP3A4/5.

Excretion

After a single dose of 1.8 mg/kg of ADCETRIS in patients, approximately 24% of the total MMAE administered was recovered in both urine and feces over a 1-week period, approximately 72% of which was recovered in the feces, and the majority was excreted unchanged.

Specific Populations

Sex and race do not have a meaningful effect on the pharmacokinetics of brentuximab vedotin.

Pediatric Patients

The pharmacokinetics of brentuximab vedotin and MMAE were evaluated in 65 pediatric patients aged 3 to <6 years (N=3), 6 to <12 years (N=30) and 12 to <17 years (N=32). Following the recommended dosage of brentuximab vedotin 1.8 mg/kg Q3W, the dose-normalized steady state C_{avg} of brentuximab vedotin in patients 12 to <17 years of age were generally consistent with those in adult patients administered brentuximab vedotin 1.2 mg/kg Q2W. The median AUC of ADC was 22% lower in patients 6 to <12 years of age (median [range] body weight = 28.8 kg [16.2, 80.8 kg]), and 37% lower in patients 3 to <6 years of age (median [range] body weight = 17.0 kg [10.7, 31.1 kg]), respectively, compared to that in patients 12 to <17 years of age (median [range] body weight = 52.7 kg [28.5, 123.9 kg]). The AUC of MMAE was 25% lower in patients 6 to <12 years of age, and 41% lower in patients 3 to <6 years of age, respectively, compared to that in patients 12 to <17 years of age. After accounting for body weight, other factors such as age, sex, race, and baseline albumin had no clinically significant effect on the PK of ADC and MMAE in pediatric patients 3 to <17 years of age.

Renal Impairment

The pharmacokinetics of brentuximab vedotin and MMAE were evaluated after the administration of 1.2 mg/kg of ADCETRIS to patients with mild (CrCL >50–80 mL/min; n=4), moderate (CrCL 30–50 mL/min; n=3) and severe (CrCL <30 mL/min; n=3) renal impairment. The AUC of MMAE was approximately 2-fold higher in patients with severe renal impairment compared to patients with normal renal function and not meaningfully altered in patients with mild or moderate renal impairment.

Hepatic Impairment

The pharmacokinetics of brentuximab vedotin and MMAE were evaluated after the administration of 1.2 mg/kg of ADCETRIS to patients with mild (Child-Pugh A; n=1), moderate (Child-Pugh B; n=5) and severe (Child-Pugh C; n=1) hepatic impairment. The AUC of MMAE was approximately 2.3-fold higher in patients with hepatic impairment compared to patients with normal hepatic function.

Drug Interaction Studies

Effects of Other Drugs on ADCETRIS

Co-administration of ADCETRIS with ketoconazole, a potent CYP3A4 inhibitor, increased exposure to MMAE by approximately 34%.

Co-administration of ADCETRIS with rifampin, a potent CYP3A4 inducer, reduced exposure to MMAE by approximately 46%.

Effects of ADCETRIS on Other Drugs

Co-administration of ADCETRIS did not affect exposure to midazolam, a CYP3A4 substrate.

In vitro studies using human liver microsomes indicate that MMAE inhibits CYP3A4/5 but not other CYP450 isoforms. MMAE did not induce any major CYP450 enzymes in human hepatocytes.

In vitro studies indicate that MMAE is a substrate and not an inhibitor of the efflux transporter P-glycoprotein (P-gp).

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies (ADA) in the studies described below with incidence of ADA in other studies, including those of ADCETRIS or of other brentuximab vedotin products.

Among adult patients with relapsed or refractory cHL and relapsed or refractory systemic ALCL in Studies 1 and 2 *[see Clinical Studies (14.1) and (14.3)]*, treatment-emergent ADA (or anti-brentuximab vedotin antibodies) developed in 37% (58/156) of patients who were tested for anti-brentuximab vedotin antibodies. Approximately 7% of patients in these trials developed persistently positive antibodies (positive test at more than 2 time points) and 30% developed transiently positive antibodies (positive at 1 or 2 post-baseline time points). Two of the patients (1%) with persistently positive antibodies experienced adverse reactions consistent with infusion reactions that led to discontinuation of treatment. Overall, a higher incidence of infusion-related reactions was observed in patients who developed persistently positive antibodies. The incidence of treatment-emergent neutralizing antibodies against brentuximab vedotin was 62% (36/58). The effect of anti-brentuximab vedotin antibodies on efficacy is not known.

Among pediatric patients with previously untreated high risk cHL in Study 7 *[see Clinical Studies (14.1)]*, of the 26 patients tested, none of the patients tested positive for anti-brentuximab vedotin antibodies.

Among adult patients with LBCL in Study 8 *[see Clinical Studies 14.5]*, treatment -emergent anti--brentuximab vedotin antibodies developed in 8% (8/97) of patients who were tested. The effect of anti-brentuximab vedotin antibodies on efficacy is not known.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with brentuximab vedotin or the small molecule (MMAE) have not been conducted.

MMAE was genotoxic in the rat bone marrow micronucleus study through an aneugenic mechanism. This effect is consistent with the pharmacological effect of MMAE as a microtubule-disrupting agent. MMAE was not mutagenic in the bacterial reverse mutation assay (Ames test) or the L5178Y mouse lymphoma forward mutation assay.

Fertility studies with brentuximab vedotin or MMAE have not been conducted. However, results of repeat-dose toxicity studies indicate the potential for brentuximab vedotin to impair female and male reproductive function and fertility. In a 4-week repeat-dose toxicity study in rats with weekly dosing at 0.5, 5, or 10 mg/kg brentuximab vedotin, seminiferous tubule degeneration, Sertoli cell vacuolation, reduced spermatogenesis, and aspermia were observed. Effects in animals were seen mainly at 5 and 10 mg/kg of brentuximab vedotin. These doses are approximately 3 and 6-fold the human recommended dose of 1.8 mg/kg, respectively, based on body weight.

MMAE-containing ADCs have been associated with adverse ovarian effects when administered to sexually immature animals. Adverse effects included decrease in, or absence of, secondary and tertiary ovarian follicles after weekly administration to cynomolgus monkeys in studies of 4-week duration. These effects showed a trend towards recovery 6 weeks after the end of dosing; no changes were observed in primordial follicles.

14 CLINICAL STUDIES

14.1 Classical Hodgkin Lymphoma

Randomized Clinical Trial in Previously Untreated Stage III or IV Classical Hodgkin Lymphoma (Study 5: ECHELON-1, NCT01712490)

The efficacy of ADCETRIS in combination with chemotherapy for the treatment of patients with previously untreated Stage III or IV cHL was evaluated in a randomized, open-label, 2-arm, multicenter trial. Of the 1334 total patients, 664 patients were randomized to the ADCETRIS + doxorubicin [A], vinblastine [V] and dacarbazine [D] (ADCETRIS + AVD) arm and 670 patients were randomized to the A+ bleomycin [B] + V + D (ABVD) arm. Patients in both treatment arms were treated intravenously on Days 1 and 15 of each 28-day cycle for up to 6 cycles. Dosing in each treatment arm was administered according to the following:

- ADCETRIS + AVD arm: ADCETRIS 1.2 mg/kg over 30 minutes, doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2
- ABVD arm: doxorubicin 25 mg/m^2, bleomycin 10 units/m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2

Efficacy was established based on modified progression-free survival (modified PFS) per independent review facility (IRF). A modified PFS event is defined as progression, death, or receipt of additional anticancer therapy for patients who are not in a complete response (CR) after completion of frontline therapy.

Patients had Stage III (36%) or IV disease (64%), and 62% had extranodal involvement at diagnosis. Most patients were male (58%) and white (84%). The median age was 36 years (range, 18-83); 186 patients (14%) were 60 years or older.

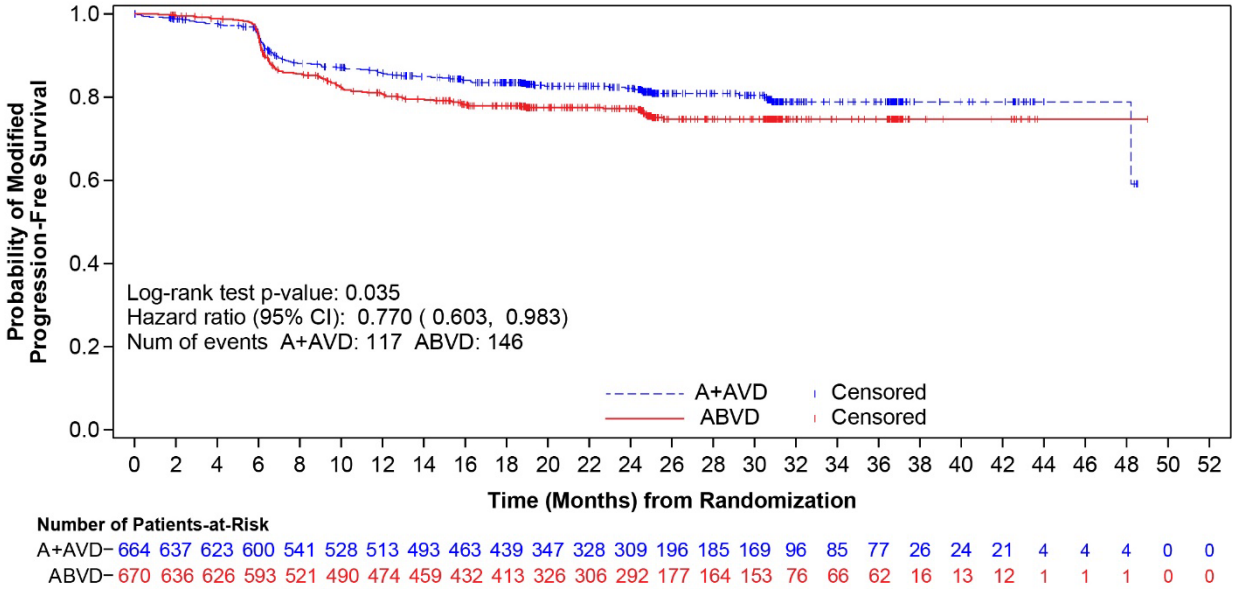
The efficacy results are summarized in Table 13 and Figure 1.

Table 12: Efficacy Results in Patients with Previously Untreated Stage III or IV Classical Hodgkin Lymphoma (Study 5: ECHELON-1)

Modified Progression-Free Survival per IRF+	**ADCETRIS + AVD N=664**	**ABVD N=670**
Number of events (%)	117 (18%)	146 (22%)
Median months (95% CI)	NE*	NE*
Hazard ratio (95% CI)[a]	0.77 (0.60, 0.98)	
P-value[b]	0.035	
Reason leading to a modified PFS event		
Progressive disease	90 (14)	102 (15)
Death due to any cause	18 (3)	22 (3)
Receipt of additional anticancer therapy for patients not in CR after frontline therapy	9 (1)	22 (3)

* Not estimable.
+ At the time of analysis, the median follow-up time for both arms was 24.6 months.
[a] Hazard ratio (A+AVD/ABVD) and 95% confidence intervals are based on a stratified Cox's proportional hazard regression model with stratification factors region and number of International Prognostic Factor Project (IPFP) risk factors at baseline with treatment as the explanatory variable in the model.
[b] P-value is from a stratified log-rank test with stratification factors baseline IPFP group and region; alpha = 0.05.

Figure 1: Kaplan-Meier Curve of IRF-Assessed Modified Progression-Free Survival (Study 5: ECHELON-1)

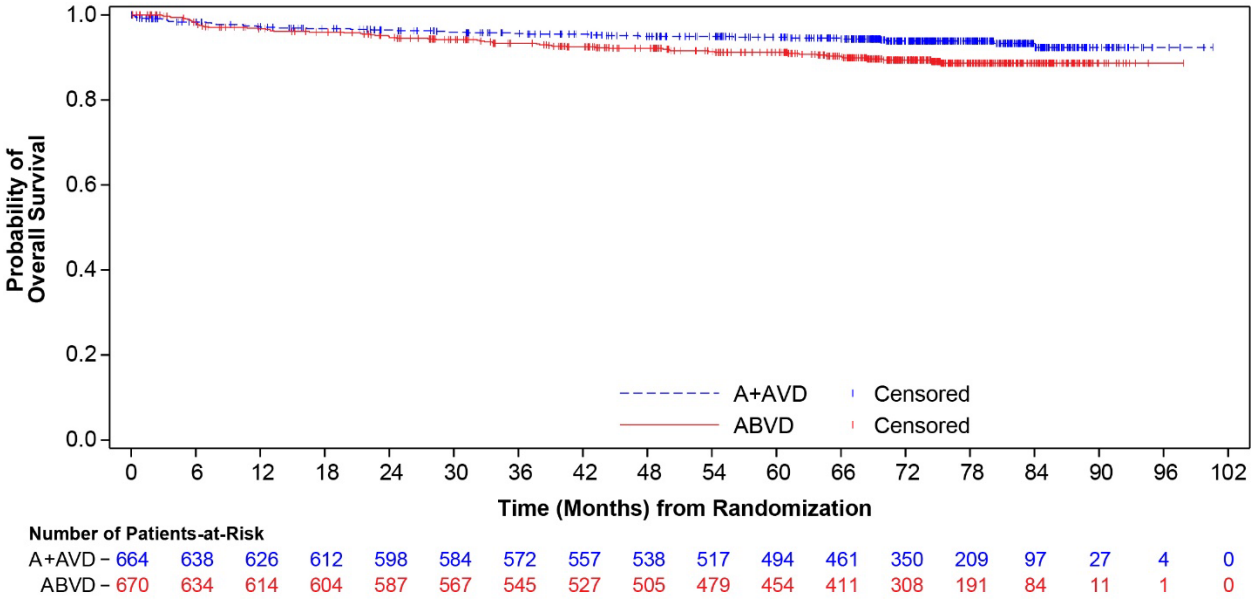


A+AVD = ADCETRIS plus AVD (doxorubicin, vinblastine, and dacarbazine)
ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine
The first post-treatment response assessment (CT and PET scan) was performed 3-7 weeks after the last dose of frontline therapy, which corresponds to about 6-7 months after the first dose of study drug.

At the time of the modified PFS analysis, the prespecified interim OS analysis did not demonstrate a significant difference. The CR rate per IRF assessment at the end of the randomized regimen was 73% on the ADCETRIS + AVD arm and 70% on the ABVD arm.

A prespecified second interim analysis showed a statistically significant improvement in OS in the ADCETRIS + AVD arm (39 deaths) compared to the ABVD arm (64 deaths). With an estimated median follow-up of 6.1 years, the stratified hazard ratio was 0.59 (95% CI, 0.396; 0.879), with a 2-sided p-value of 0.009 (significance level, 0.0365). Median OS was not reached in either treatment arm (Figure 2).

Figure 2: Kaplan-Meier Curve of Overall Survival (Study 5: ECHELON 1)



Randomized Clinical Trial in Previously Untreated High Risk Classical Hodgkin Lymphoma (Study 7, AHOD1331, NCT02166463)

The efficacy of ADCETRIS in combination with chemotherapy for the treatment of pediatric patients (2 to <22 years of age) with previously untreated, high risk cHL was evaluated in a randomized, open-label, actively controlled trial. High risk was defined as Ann Arbor Stage IIB with bulk disease, Stage IIIB, Stage IVA, and Stage IVB. Of the 600 total patients randomized, 300 were randomized to ADCETRIS + Doxorubicin [A], Vincristine [V], Etoposide [E], Prednisone [P], Cyclophosphamide [C] (ADCETRIS + AVEPC) arm and 300 patients were randomized to A+ Bleomycin [B]+V+E+P+C (ABVE-PC) arm. Patients in each treatment arm received up to 5 cycles of the following:

- ADCETRIS + AVEPC arm: ADCETRIS 1.8 mg/kg over 30 minutes (day 1), doxorubicin 25 mg/m^2 (days 1 and 2), vincristine 1.4 mg/m^2 (day 8), etoposide 125 mg/m^2 (days 1-3), prednisone 20 mg/m^2 BID (days 1-7), cyclophosphamide 600 mg/m^2 (days 1 and 2)
- ABVE-PC arm: doxorubicin 25 mg/m^2 (days 1 and 2), bleomycin 5 units/m^2 (day1) and 10 units/m^2 (day 8), vincristine 1.4 mg/m^2 (days 1 and 8), etoposide 125 mg/m^2 (days 1-3), prednisone 20 mg/m^2 BID (days 1-7), cyclophosphamide 600 mg/m^2 (days 1 and 2)

The median age was 15 years (range: 3-21 years); 53% were male, 74% were White, 11% Black, and 3% Asian. Nine patients were <6 years, 81 patients were 6 to <12 years, 448 patients were 12 to <18 years, and 62 patients were ≥18 years. Of the 600 enrolled patients, 20% had disease stage of IIB with bulk disease, 19% had IIIB, 29% had IVA, and 31% had IVB.

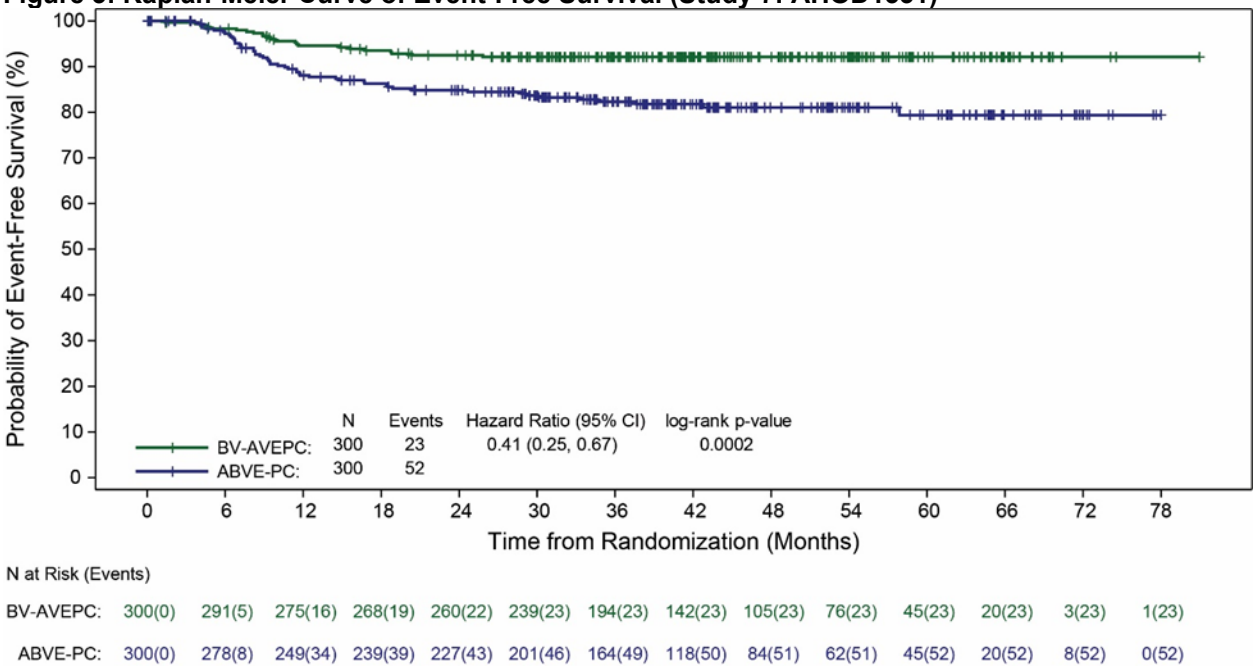
Efficacy was established based on event-free-survival (EFS), defined as the time from randomization to the earliest of disease progression or relapse, second malignancy, or death due to any cause. Efficacy results are summarized in Table 14.

Table 13: Efficacy Results in Pediatric Patients with Previously Untreated High Risk Classical Hodgkin Lymphoma (Study 7: AHOD1331)

Event-Free Survival	ADCETRIS + AVEPC N = 300	ABVE-PC N = 300
Number of Events (%)	23 (8)	52 (17)
Median (95% CI)	NR	NR
Hazard Ratio (95% CI)[a]	0.41 (0.25, 0.67)	
P-value (log-rank test)[b]	0.0002	

NR = Not reached.
[a] Hazard ratio (BV-AVEPC/ABVE-PC) and 95% confidence intervals are based on a Cox proportional hazard regression model stratified by clinical characteristics (Stage IIB with bulk vs. Stage IIIB vs. Stage IVA vs. Stage IVB) as recorded at randomization.
[b] Two-sided p-value from log-rank test stratified by clinical characteristic (disease stage).

Figure 3: Kaplan-Meier Curve of Event-Free Survival (Study 7: AHOD1331)



Randomized Placebo-Controlled Clinical Trial in Classical Hodgkin Lymphoma Post-Auto-HSCT Consolidation (Study 3: AETHERA, NCT01100502)

The efficacy of ADCETRIS in patients with cHL at high risk of relapse or disease progression post-auto-HSCT was studied in a randomized, double-blind, placebo-controlled clinical trial. Three hundred twenty-nine (329) patients were randomized 1:1 to receive placebo or ADCETRIS 1.8 mg/kg intravenously over 30 minutes every 3 weeks for up to 16 cycles, beginning 30–45 days post-auto-HSCT. Patients in the placebo arm with progressive disease per investigator could receive ADCETRIS as part of a separate trial. The primary endpoint was progression-free survival (PFS) determined by independent review facility (IRF). Standard international guidelines were followed for infection prophylaxis for HSV, VZV, and PJP post-auto-HSCT *[see Clinical Trial Experience (6.1)]*.

High risk of post-auto-HSCT relapse or progression was defined according to status following frontline therapy: refractory, relapse within 12 months, or relapse ≥12 months with extranodal disease. Patients were required to have obtained a complete response (CR), partial response (PR), or stable disease (SD) to most recent pre-auto-HSCT salvage therapy.

A total of 329 patients were enrolled and randomized (165 ADCETRIS, 164 placebo); 327 patients received study treatment. Patient demographics and baseline characteristics were generally balanced between treatment arms. The 329 patients ranged in age from 18–76 years (median, 32 years) and most were male (53%) and white (94%). Patients had received a median of 2 prior systemic therapies (range, 2–8) excluding autologous hematopoietic stem cell transplantation.

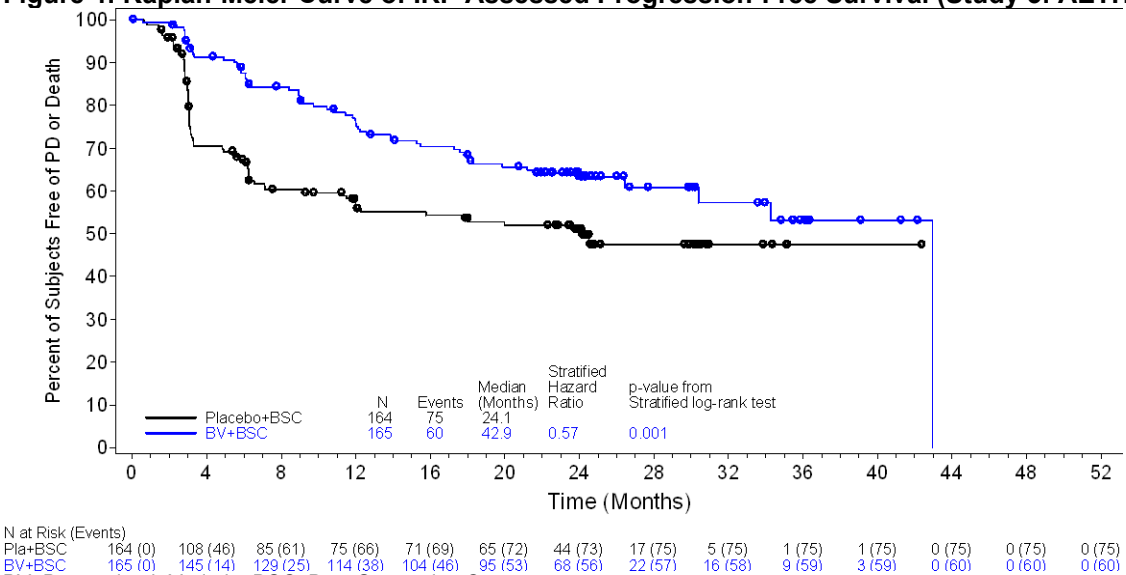
The efficacy results are summarized in Table 15. PFS is calculated from randomization to date of disease progression or death (due to any cause). The median PFS follow-up time from randomization was 22 months (range, 0–49). Study 3 (AETHERA) demonstrated a statistically significant improvement in IRF-assessed PFS and increase in median PFS in the ADCETRIS arm compared with the placebo arm. At the time of the PFS analysis, an interim overall survival analysis demonstrated no difference.

Table 14: Efficacy Results in Patients with Classical Hodgkin Lymphoma Post-Auto-HSCT Consolidation (Study 3: AETHERA)

Progression-Free Survival per IRF	**ADCETRIS N = 165**	**Placebo N = 164**
Number of events (%)	60 (36)	75 (46)
Median months (95% CI)	42.9+ (30.4, 42.9+)	24.1 (11.5, NE*)
Stratified Hazard Ratio (95% CI)	0.57 (0.40, 0.81)	
Stratified Log-Rank Test P-value	0.001	

* Not estimable
\+ Estimates are unreliable

Figure 4: Kaplan-Meier Curve of IRF-Assessed Progression-Free Survival (Study 3: AETHERA)



BV: Brentuximab Vedotin; BSC: Best Supportive Care

Clinical Trial in Relapsed Classical Hodgkin Lymphoma (Study 1, NCT00848926)

The efficacy of ADCETRIS in patients with cHL who relapsed after autologous hematopoietic stem cell transplantation was evaluated in one open-label, single-arm, multicenter trial. One hundred two (102) patients were treated with 1.8 mg/kg of ADCETRIS intravenously over 30 minutes every 3 weeks. An independent review facility (IRF) performed efficacy evaluations which included overall response rate (ORR = complete response [CR] + partial response [PR]) and duration of response as defined by clinical and radiographic measures including computed tomography (CT) and positron-emission tomography (PET) as defined in the 2007 Revised Response Criteria for Malignant Lymphoma (modified).

The 102 patients ranged in age from 15–77 years (median, 31 years) and most were female (53%) and white (87%). Patients had received a median of 5 prior therapies including autologous hematopoietic stem cell transplantation.

The efficacy results are summarized in Table 16. Duration of response is calculated from date of first response to date of progression or data cutoff date.

Table 15: Efficacy Results in Patients with Classical Hodgkin Lymphoma (Study 1)

	N = 102		
		Duration of Response, in months	
	Percent (95% CI)	**Median (95% CI)**	**Range**
CR	32 (23, 42)	20.5 (12.0, NE*)	1.4 to 21.9+
PR	40 (32, 49)	3.5 (2.2, 4.1)	1.3 to 18.7
ORR	73 (65, 83)	6.7 (4.0, 14.8)	1.3 to 21.9+

*Not estimable
+Follow up was ongoing at the time of data submission

14.2 Systemic Anaplastic Large Cell Lymphoma and Other CD30-Expressing Peripheral T-Cell Lymphomas

Randomized Clinical Trial in Previously Untreated Systemic Anaplastic Large Cell Lymphoma or Other CD30-Expressing Peripheral T-Cell Lymphomas (Study 6: ECHELON-2, NCT01777152)

The efficacy of ADCETRIS in combination with chemotherapy for the treatment of adult patients with previously untreated, CD30-expressing PTCL was evaluated in a multicenter, randomized, double-blind, double-dummy, actively controlled trial. For enrollment, the trial required CD30 expression ≥10% per immunohistochemistry. The trial excluded patients with primary cutaneous CD30-positive T-cell lymphoproliferative disorders and lymphomas. The trial required hepatic transaminases ≤3 times ULN, total bilirubin ≤1.5 times ULN, and serum creatinine ≤2 times ULN.

Of the 452 total patients, 226 patients were randomized to the ADCETRIS + CHP arm and 226 patients were randomized to the CHOP arm. Patients in both treatment arms were treated intravenously on Day 1 of each 21-day cycle for 6 to 8 cycles; prednisone was administered orally on Days 1-5. Dosing in each treatment arm was administered according to the following:

- ADCETRIS + CHP arm: ADCETRIS 1.8 mg/kg over 30 minutes, cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, and prednisone 100 mg orally
- CHOP arm: cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2, and prednisone 100 mg orally

The median age was 58 years (range: 18 to 85), 63% were male, 62% were White, 22% were Asian, and 78% had an ECOG performance status of 0-1. Of the 452 patients enrolled, the disease subtypes included patients with systemic ALCL [70%; 48% anaplastic lymphoma kinase (ALK) negative and 22% ALK positive], PTCL NOS (16%), angioimmunoblastic T-cell lymphoma (12%), adult T-cell leukemia/lymphoma (2%), and enteropathy-associated T-cell lymphoma (<1%). Most patients had Stage III or IV disease (81%) and a baseline international prognostic index of 2 or 3 (63%).

During randomized treatment, on the ADCETRIS + CHP arm, 70% of patients received 6 cycles and 18% of patients received 8 cycles. On the CHOP arm, 62% of patients received 6 cycles and 19% received 8 cycles.

Efficacy was based on IRF-assessed PFS, which was defined as time from randomization to progression, death due to any cause, or receipt of subsequent anticancer chemotherapy to treat residual or progressive disease. Other efficacy endpoints included PFS in patients with systemic ALCL, overall survival, complete response rate, and overall response rate. Efficacy results are summarized in Table 17. Kaplan-Meier curves for PFS and overall survival are presented in Figure 5 and Figure 6, respectively.

Table 16: Efficacy Results in Patients with Previously Untreated, CD30-Expressing PTCL (Study 6: ECHELON-2)

Outcomes per IRF[a]	**ADCETRIS + CHP N=226**	**CHOP N=226**
PFS		
Number of events, n (%)	95 (42)	124 (55)
Median PFS, months (95% CI)	48.2 (35.2, NE)	20.8 (12.7, 47.6)
Hazard ratio (95% CI)[b]	0.71 (0.54, 0.93)	
P-value[c]	0.011	
Reason leading to a PFS event, n (%)		
Progressive disease	71 (31)	86 (38)
Death	13 (6)	17 (8)
Receipt of subsequent anticancer chemotherapy to treat residual or progressive disease	11 (5)	21 (9)
PFS for patients with sALCL		
N	163	151
Number of patients with a PFS event, n (%)	56 (34)	73 (48)
Median PFS, months (95% CI)	55.7 (48.2, NE)	54.2 (13.4, NE)
Hazard ratio (95% CI)[b]	0.59 (0.42, 0.84)	
P-value[c]	0.003	

Outcomes per IRF[a]	ADCETRIS + CHP N=226	CHOP N=226
OS[d]		
Number of deaths	51 (23)	73 (32)
Median OS, months (95% CI)	NE (NE, NE)	NE (54.2, NE)
Hazard ratio (95% CI)[b]	0.66 (0.46, 0.95)	
P-value[c]	0.024	
CR Rate[e]		
% (95% CI)	68 (61, 74)	56 (49, 62)
P-value[f]	0.007	
ORR[e]		
% (95% CI)	83 (78, 88)	72 (66, 78)
P-value[f]	0.003	

NE = Not estimable

a Efficacy endpoints were tested at a two-sided alpha level 0.05 in the following order: PFS in ITT, PFS in the sALCL subgroup, complete remission rate, overall survival, and objective response rate in ITT.

b Hazard ratio (A+CHP/CHOP) and 95% confidence intervals are based on a stratified Cox's proportional hazard regression model with the following stratification factors (ALK-positive sALCL and International Prognostic Index [IPI] score at baseline).

c P-value is calculated using a stratified log-rank test.

d Median OS follow-up in the ADCETRIS+CHP arm was 41.9 months; in the CHOP arm was 42.2 months.

e Best response per 2007 International Working Group Criteria at end of treatment.

f P-value is calculated using a stratified Cochran-Mantel-Haenszel test

Figure 5: Kaplan-Meier Curve of IRF-Assessed Progression-Free Survival (Study 6: ECHELON-2)

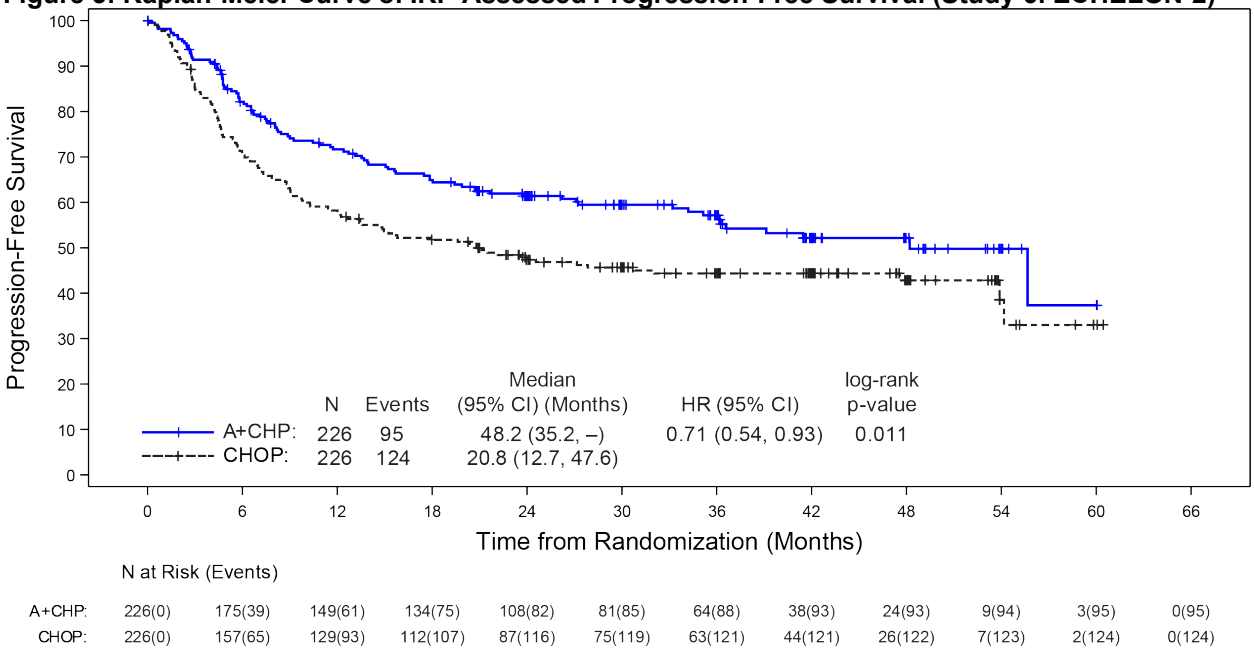
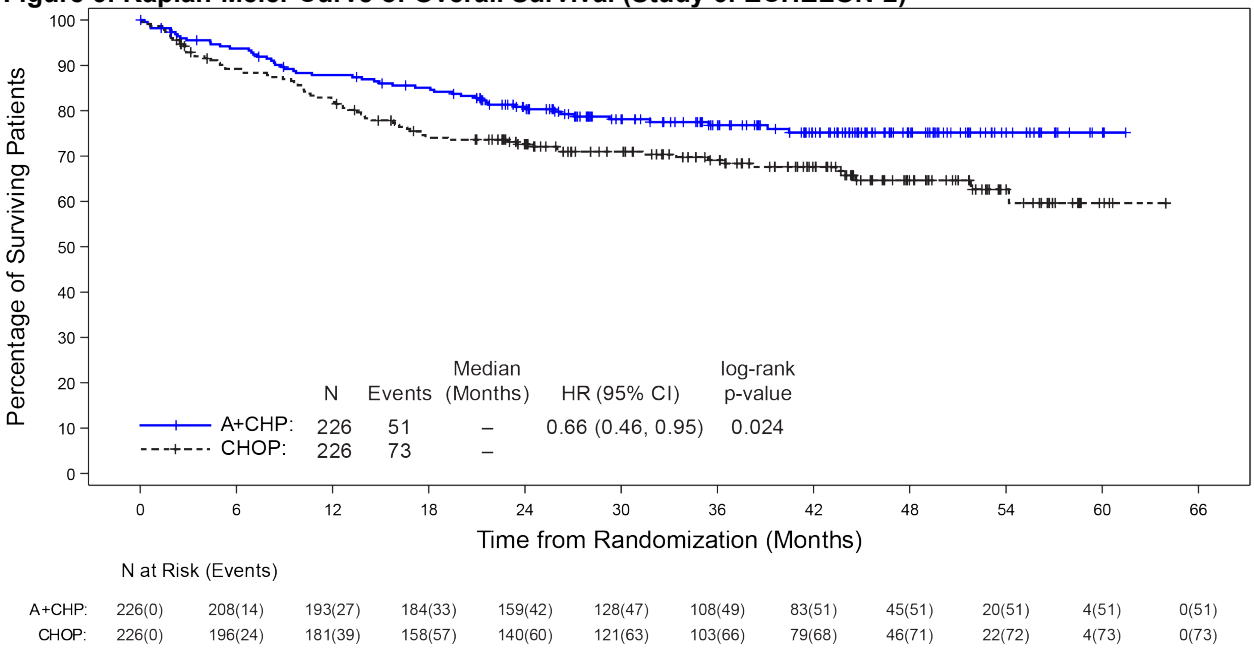


Figure 6: Kaplan-Meier Curve of Overall Survival (Study 6: ECHELON-2)



Median overall survival was not reached in either treatment arm.

14.3 Systemic Anaplastic Large Cell Lymphoma

Clinical Trial in Relapsed sALCL (Study 2, NCT00866047)

The efficacy of ADCETRIS in patients with relapsed sALCL was evaluated in one open-label, single-arm, multicenter trial. This trial included patients who had sALCL that was relapsed after prior therapy. Fifty-eight (58) patients were treated with 1.8 mg/kg of ADCETRIS administered intravenously over 30 minutes every 3 weeks. An IRF performed efficacy evaluations which included overall response rate (ORR = complete response [CR] + partial response [PR]) and duration of response as defined by clinical and radiographic measures including computed tomography (CT) and positron-emission tomography (PET) as defined in the 2007 Revised Response Criteria for Malignant Lymphoma (modified).

The 58 patients ranged in age from 14–76 years (median, 52 years) and most were male (57%) and white (83%). Patients had received a median of 2 prior therapies; 26% of patients had received prior autologous hematopoietic stem cell transplantation. Fifty percent (50%) of patients were relapsed, and 50% of patients were refractory to their most recent prior therapy. Seventy-two percent (72%) were anaplastic lymphoma kinase (ALK)-negative.

The efficacy results are summarized in Table 18. Duration of response is calculated from date of first response to date of progression or data cutoff date.

Table 17: Efficacy Results in Patients with Systemic Anaplastic Large Cell Lymphoma (Study 2)

	N = 58		
		Duration of Response, in months	
	Percent (95% CI)	Median (95% CI)	Range
CR	57 (44, 70)	13.2 (10.8, NE*)	0.7 to 15.9+
PR	29 (18, 41)	2.1 (1.3, 5.7)	0.1 to 15.8+
ORR	86 (77, 95)	12.6 (5.7, NE*)	0.1 to 15.9+

* Not estimable
+ Follow up was ongoing at the time of data submission

14.4 Primary Cutaneous Anaplastic Large Cell Lymphoma and CD30-Expressing Mycosis Fungoides

Randomized Clinical Trial in Primary Cutaneous Anaplastic Large Cell Lymphoma and CD30-expressing Mycosis Fungoides (Study 4: ALCANZA, NCT01578499)

The efficacy of ADCETRIS in patients with primary cutaneous anaplastic large cell lymphoma (pcALCL) or mycosis fungoides (MF) requiring systemic therapy was studied in ALCANZA, a randomized, open-label, multicenter clinical trial. In ALCANZA, one hundred thirty-one (131) patients were randomized 1:1 to receive ADCETRIS 1.8 mg/kg intravenously over 30 minutes every 3 weeks or physician's choice of methotrexate (5 to 50 mg orally weekly) or bexarotene (300 mg/m^2 orally daily). The randomization was stratified by baseline disease diagnosis (MF or pcALCL). Patients could receive a maximum of 16 cycles (21-day cycle) of therapy every 3 weeks for those receiving brentuximab vedotin or 48 weeks of therapy for those in the control arm.

Patients with pcALCL must have received prior radiation or systemic therapy, and must have at least 1 biopsy with CD30-expression of ≥10%. Patients with MF must have received prior systemic therapy and have had skin biopsies from at least 2 separate lesions, with CD30-expression of ≥10% in at least 1 biopsy.

A total of 131 patients were randomized (66 ADCETRIS, 65 physician's choice). The efficacy results were based on 128 patients (64 patients in each arm with CD30-expression of ≥10% in at least one biopsy). Among 128 patients, the patients' age ranged from 22–83 years (median, 60 years), and 55% of them were male and 85% of them were white. Patients had received a median of 4 prior therapies (range, 0–15), including a median of 1 prior skin-directed therapy (range, 0–9) and 2 systemic therapies (range, 0–11). At study entry, patients were diagnosed as Stage 1 (25%), Stage 2 (38%), Stage 3 (5%), or Stage 4 (13%).

Efficacy was established based on the proportion of patients achieving an objective response (CR+PR) that lasts at least 4 months (ORR4). ORR4 was determined by independent review facility (IRF) using the global response score (GRS), consisting of skin evaluations per modified severity-weighted assessment tool (mSWAT), nodal and visceral radiographic assessment, and detection of circulating Sézary cells (MF patients only). Additional efficacy outcome measures included proportion of patients achieving a complete response (CR) per IRF, and progression-free survival (PFS) per IRF.

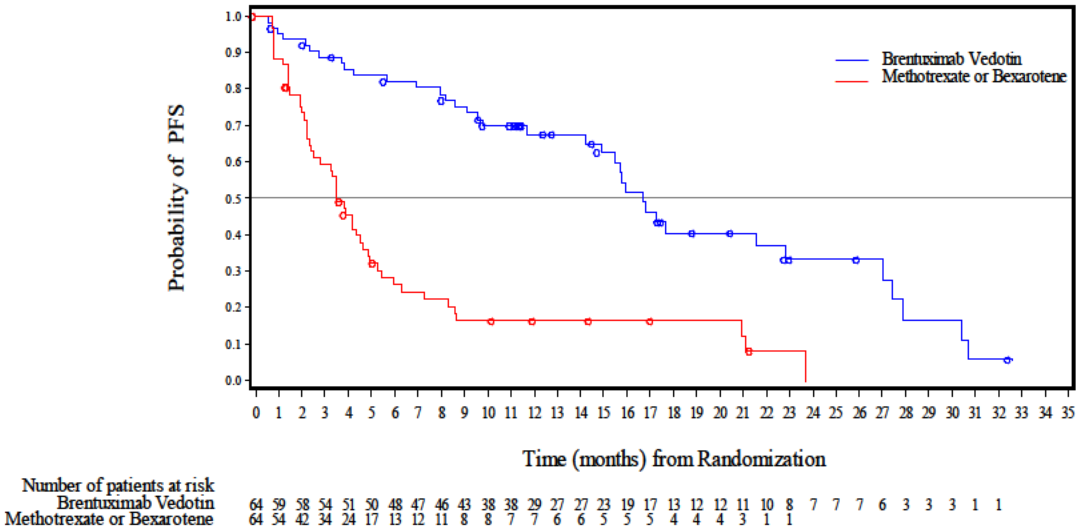
The efficacy results are summarized in Table 19 below and the Kaplan-Meier curves of IRF-assessed PFS are shown in Figure 7.

Table 18: Efficacy Results in Patients with Relapsed pcALCL or CD30-Expressing MF (Study 4: ALCANZA)

	ADCETRIS N = 64	Physician's Choice[a] N = 64
ORR4[b]		
Percent (95% CI[c])	56.3 (44.1, 68.4)	12.5 (4.4, 20.6)
P-value[d]	<0.001	
ORR	67.2 (55.7, 78.7)	20.3 (10.5, 30.2)
CR		
Percent (95% CI[c])	15.6 (7.8, 26.9)	1.6 (0, 8.4)
P-value[d,e]	0.0066	
PR	51.6 (39.3, 63.8)	18.8 (9.2, 28.3)
PFS		
Number of events (%)	36 (56.3)	50 (78.1)
Median months (95% CI[c])	16.7 (14.9, 22.8)	3.5 (2.4, 4.6)
Hazard Ratio (95% CI[c])	0.27 (0.17, 0.43)	
Log-Rank Test P-value[d,e]	<0.001	

[a] Physician's choice of either methotrexate or bexarotene
[b] ORR4 is defined as proportion of patients achieving an objective response (CR+PR) that lasts at least 4 months
[c] CI=Confidence Interval
[d] Test of the treatment difference was stratified by baseline disease diagnosis (MF or pcALCL)
[e] Adjusted for multiplicity

Figure 7: Kaplan-Meier Curve of Progression-free Survival (Study 4: ALCANZA)



Supportive trials include 2 single-arm trials, which enrolled patients with MF who were treated with ADCETRIS 1.8 mg/kg intravenously over 30 minutes every 3 weeks. Out of 73 patients with MF from the 2 pooled supportive trials, 34% (25/73) achieved ORR4. Among these 73 patients, 35 had 1% to 9% CD30-expression and 31% (11/35) achieved ORR4.

14.5 Relapsed or Refractory Large B-Cell Lymphoma (LBCL)

Randomized Clinical Trial in Relapsed or Refractory Large B-Cell Lymphoma (Study 8: ECHELON-3)

The efficacy of ADCETRIS in combination with lenalidomide and a rituximab product for the treatment of adult patients with relapsed or refractory LBCL after two or more lines of systemic therapy was evaluated in ECHELON-3 (NCT04404283), a randomized, multicenter, double-blind, placebo-controlled trial. Eligible patients were 18 years of age and older with relapsed or refractory LBCL, including DLBCL NOS, DLBCL arising from indolent lymphoma, or HGBL, an ECOG performance status of 0–2, and were not eligible to receive an auto-HSCT or CAR T-cell therapy. The study excluded patients with active CNS lymphoma or Grade 2 or higher peripheral neuropathy.

Patients were randomized 1:1 to receive ADCETRIS plus lenalidomide and a rituximab product or to receive placebo plus lenalidomide and a rituximab product until disease progression or unacceptable toxicity. Randomization was stratified by CD30 expression (≥1% versus <1%), prior allogenic or autologous HSCT therapy, prior CAR T-cell therapy and cell of origin (germinal-center B-cell like [GCB] or non-GCB). Dosing in each treatment arms as follows:

- ADCETRIS plus lenalidomide and rituximab arm: ADCETRIS 1.2 mg/kg via intravenous infusion every 3 weeks, lenalidomide 20 mg orally daily, and rituximab 375 mg/m^2 via intravenous infusion every 3 weeks. Starting with Cycle 2, rituximab intravenous treatment could be substituted with rituximab 1,400 mg and hyaluronidase human 23,400 Units via subcutaneous injection every 3 weeks.

- Placebo plus lenalidomide and rituximab arm: lenalidomide 20 mg orally daily, and rituximab 375 mg/m^2 via intravenous infusion every 3 weeks. Starting with Cycle 2, rituximab intravenous treatment could be substituted with rituximab 1,400 mg and hyaluronidase human 23,400 Units via subcutaneous injection every 3 weeks.

Prophylaxis with granulocyte-colony stimulating factor (G-CSF) was mandated for both arms.

Of the 230 patients randomized (112 to ADCETRIS plus lenalidomide and rituximab, 118 to placebo plus lenalidomide and rituximab), the median age was 71 years (range 21 to 89 years); 57% were male, 53% were White, 26% were Asian and 4% were Hispanic or Latino. Race and ethnicity was not reported in 46 (20%) patients. There were no Black or African American patients enrolled. Of the total 230 patients, 71% had DLBCL NOS, 26% had transformed disease from prior indolent lymphoma, 16% had HGBL with MYC and BCL2 and/or BCL6 rearrangements or HGBL NOS. Of the patients with DLBCL NOS, 73 (45%) and 91 (55%) had GCB and non-GCB subtypes, respectively. Twenty-nine percent of patients had received prior CAR T-cell therapy and 12% had received prior HSCT. The median number of prior systemic therapies was 3 (range 2-8) with 41% receiving 2 prior therapies and 50% receiving 3 or more prior therapies. Eighty four percent had refractory disease to last therapy.

The major efficacy outcome was overall survival (OS). Additional efficacy outcome measures included progression free survival (PFS) and Objective Response Rate (ORR) according to investigator assessment per the Lugano Criteria for Response Assessment 2014. The results are presented in Table 20 and Figures 8 and 9.

Table 20: Efficacy Results in Relapsed or Refractory LBCL (Study 8: ECHELON-3)

	ADCETRIS + Lenalidomide + Rituximab (N=112)	Placebo + Lenalidomide + Rituximab (N=118)
Overall Survival		
Deaths, n (%)	58 (51.8)	76 (64.4)
Median, months (95% CI)	13.8 (10.3, 18.8)	8.5 (5.4, 11.7)
HR (95% CI)[a]	0.63 (0.45, 0.89)	
p-value[b,c]	0.0085	
PFS per Investigator		
Number (%) of patients with event	71 (63.4)	85 (72.0)
Progressive disease, n (%)	56 (50.0)	71 (60.2)
Death, n (%)	15 (13.4)	14 (11.9)
Median, months (95% CI)	4.2 (2.9, 7.1)	2.6 (1.4, 3.1)
HR (95% CI)[a]	0.53 (0.38, 0.73)	
p-value[b]	<0.0001	
Objective Response Rate per Investigator		
Objective response rate (CR or PR), n (%)	72 (64.3)	49 (41.5)
95% CI for ORR[d]	(54.7, 73.1)	(32.5, 51.0)
p-value[e]	0.0006	
Complete response (CR), n (%)	45 (40.2)	22 (18.6)

CI = confidence interval; CR = complete response; HR = hazard ratio; PFS = progression free survival; OS = overall survival. Stratified analyses were based on the stratification factors of cell of origin (GCB, non-GCB) and CD30 status (≥1%, <1%) at randomization.

[a] Hazard ratio and 95% CI based on a stratified Cox regression model.

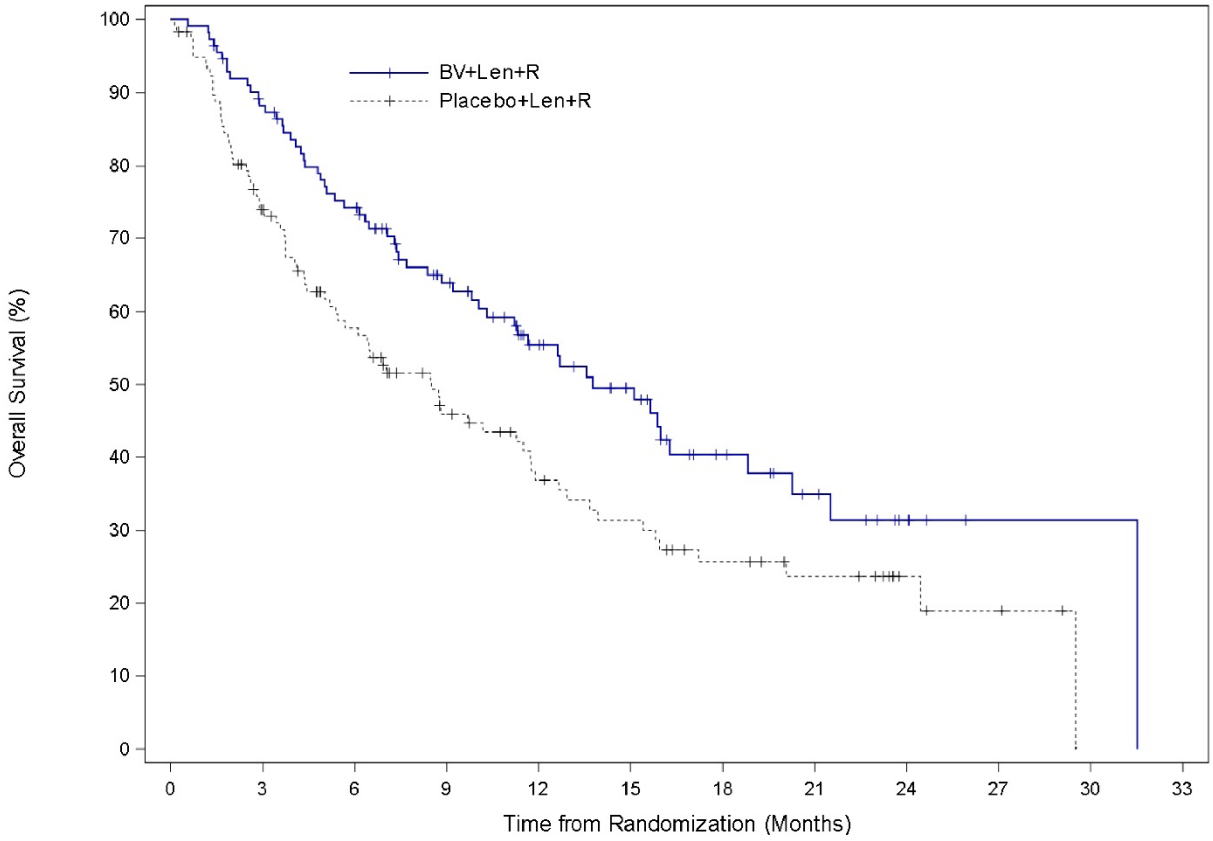
[b] Two-sided p-value from a stratified log-rank test.

[c] O'Brien Flemming efficacy boundary 2-sided p-value=0.0232.

[d] Exact 95% CI computed using the Clopper-Pearson method (Clopper 1934).

[e] Two-sided p-value based on stratified Cochran-Mantel-Haenszel test (CMH).

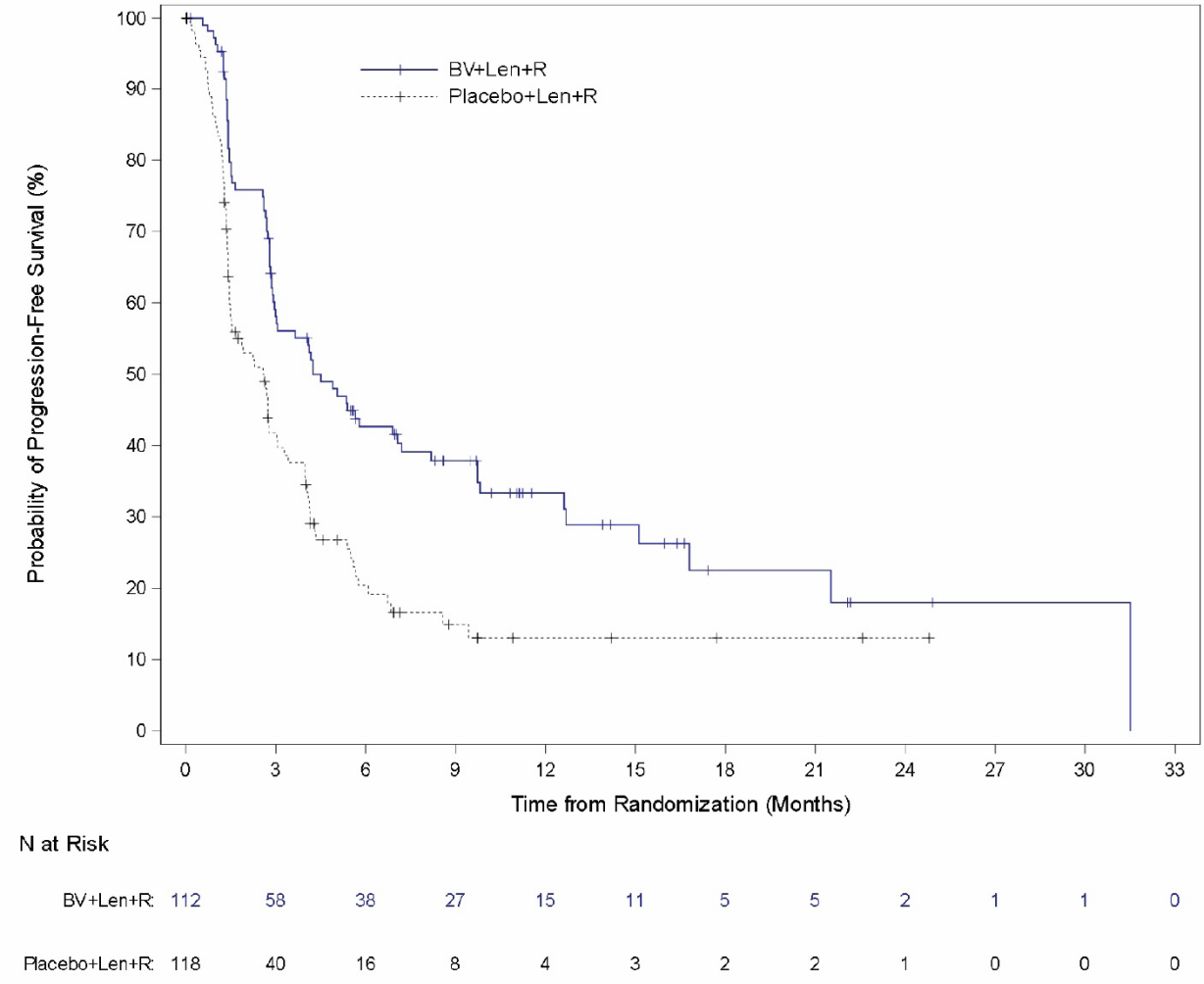
Figure 8: Kaplan-Meier Curve of Overall Survival (Study 8: ECHELON-3)



N at Risk

BV+Len+R:	112	96	79	57	40	30	17	11	5	1	1	0
Placebo+Len+R:	118	81	58	39	28	23	16	12	5	3	0	0

Figure 9: Kaplan-Meier Curve of Progression-Free Survival (Study 8: ECHELON-3)



15 REFERENCES

1. OSHA Hazardous Drugs. *OSHA*. [Accessed on 30 July 2013, from http://www.osha.gov/SLTC/hazardousdrugs/index.html]

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ADCETRIS (brentuximab vedotin) for Injection is supplied as a sterile, white to off-white preservative-free lyophilized cake or powder in individually-boxed single-dose vials:

- NDC (51144-050-01), 50 mg brentuximab vedotin

Storage

Store vial refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light.

Special Handling

ADCETRIS is a hazardous product. Follow special handling and disposal procedures[1].

17 PATIENT COUNSELING INFORMATION

Peripheral Neuropathy

Advise patients that ADCETRIS can cause a peripheral neuropathy. They should be advised to report to their health care provider any numbness or tingling of the hands or feet or any muscle weakness *[see Warnings and Precautions (5.1)]*.

Fever/Neutropenia

Advise patients to contact their health care provider if a fever of 100.5°F or greater or other evidence of potential infection such as chills, cough, or pain on urination develops *[see Warnings and Precautions (5.3)]*.

Infusion Reactions

Advise patients to contact their health care provider if they experience signs and symptoms of infusion reactions including fever, chills, rash, or breathing problems within 24 hours of infusion *[see Warnings and Precautions (5.2)]*.

Hepatotoxicity

Advise patients to report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice *[see Warnings and Precautions (5.8)]*.

Progressive Multifocal Leukoencephalopathy

Instruct patients receiving ADCETRIS to immediately report if they have any of the following neurological, cognitive, or behavioral signs and symptoms or if anyone close to them notices these signs and symptoms *[see Boxed Warning, Warnings and Precautions (5.9)]*:

- changes in mood or usual behavior
- confusion, thinking problems, loss of memory
- changes in vision, speech, or walking
- decreased strength or weakness on one side of the body

Pulmonary Toxicity

Instruct patients to report symptoms that may indicate pulmonary toxicity, including cough or shortness of breath *[see Warnings and Precautions (5.10)]*.

Acute Pancreatitis

Advise patients to contact their health care provider if they develop severe abdominal pain *[see Warnings and Precautions (5.12)]*.

Gastrointestinal Complications

Advise patients to contact their health care provider if they develop severe abdominal pain, chills, fever, nausea, vomiting, or diarrhea *[see Warnings and Precautions (5.12)]*.

Hyperglycemia

Educate patients about the risk of hyperglycemia and how to recognize associated symptoms *[see Warnings and Precautions (5.13)]*.

Females and Males of Reproductive Potential

ADCETRIS can cause fetal harm. Advise women receiving ADCETRIS to use effective contraception during ADCETRIS treatment and for 2 months after the last dose of ADCETRIS.

Advise males with female sexual partners of reproductive potential to use effective contraception during ADCETRIS treatment and for 4 months after the last dose of ADCETRIS *[see Use in Specific Populations (8.3)]*.

Advise patients to report pregnancy immediately *[see Warnings and Precautions (5.14)]*.

Lactation

Advise patients to avoid breastfeeding while receiving ADCETRIS *[see Use in Specific Populations (8.2)]*.

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LAB-1598-0.3

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125388Orig1s108

MULTI-DISCIPLINE REVIEW

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

NDA/BLA Multi-disciplinary Review and Evaluation

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

Application Type	sBLA – efficacy supplement for new indication
Application Number(s)	125388/S-108
Priority or Standard	Standard
Submit Date(s)	May 21, 2024
Received Date(s)	May 21, 2024
PDUFA Goal Date	March 21, 2025
Division/Office	Division of Hematologic Malignancies II/OOD
Review Completion Date	February 11, 2025
Established Name	Brentuximab vedotin
(Proposed) Trade Name	Adcetris
Pharmacologic Class	CD30-directed antibody-drug conjugate
Applicant	Seagen Inc.
Formulation(s)	For injection: 50 mg lyophilized powder in a single-use vial
Dosing Regimen	1.2 mg/kg up to a maximum of 120 mg every 3 weeks in combination with lenalidomide and rituximab
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Traditional Approval
Recommended Indication(s)/Population(s) (if applicable)	Adult patients with relapsed or refractory large B-cell lymphoma (LBCL), including diffuse large B-cell lymphoma (DLBCL) NOS, DLBCL arising from indolent lymphoma, or high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy who are not eligible for auto-HSCT or CAR T-cell therapy, in combination with lenalidomide and a rituximab product

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

Glossary

ABVD	doxorubicin, bleomycin, vinblastine, and dacarbazine
ABC	non-GCB activated B-cell-like
ADA	anti-drug antibody
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AESI	adverse events of special interest
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
ATA	antitherapeutic antibodies
AVD	doxorubicin, vinblastine, and dacarbazine
BCL	B-cell lymphoma
BICR	blinded independent central review
BLA	biologics license application
BR	bendamustine and rituximab
BV	brentuximab vedotin
cAC10	chimeric monoclonal antibody directed against CD30
CAR-T	chimeric antigen receptor T-cell
CCOD	clinical cutoff date
C_{eoi}	end-of-infusion concentrations
C_{trough}	trough concentrations
cHL	classical Hodgkin lymphoma
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CHP	cyclophosphamide, doxorubicin, and prednisone
CR	complete response
CRF	case report form
CSR	clinical study report
CT	computed tomography
DFS	disease-free survival
DLBCL	diffuse large B-cell lymphoma
DMC	data monitoring committee
DOR	duration of response
eCRF	electronic case report form
E/PY	number of events/person-year
EBV	Epstein-Barr virus
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EOT	end of treatment
EQ-5D-5L	EuroQol-5 dimension-5 level
E-R	exposure-response
FACT-Lym	Functional Assessment of Cancer Therapy-Lymphoma
FDA	Food and Drug Administration
FL	first line
GCB	germinal center B-cell-like
GCP	good clinical practice

G-CSF	granulocyte-colony stimulating factor
HGBCL/HGBL	high grade B-cell lymphoma
HR	hazard ratio
HSCT	autologous hematopoietic stem cell transplant
IEC	independent ethics committee
IHC	Immunohistochemistry
IND	Investigational New Drug
IPD	important protocol deviation
IPI	International Prognostic Index
IRB	institutional review board
ISE	integrated summary of effectiveness
IRF	independent review facility
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
KM	Kaplan-Meier
LBCL	Large B-cell lymphoma
Max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	minimum
MMAE	monomethyl auristatin E
MRU	medical resource utilization
MYC	myelocytomatosis oncogene
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse
NE	not evaluable, not estimable
nHL	non-Hodgkin lymphoma
NME	new molecular entity
NOS	not otherwise specified
OPQ	Office of Pharmaceutical Quality
ORR	overall response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
Pbo	placebo
PBRER	periodic benefit-risk evaluation report
PD	pharmacodynamics
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PMC	post-marketing commitment
PMR	post-marketing requirement
PR	partial response
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PTCL	peripheral T-cell lymphoma
Q3W	once every 3 weeks
QD	once daily
QoL	quality of life

RCHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
RCHP	rituximab, cyclophosphamide, doxorubicin, and prednisone
RDI	relative dose intensity
REMS	risk evaluation and mitigation strategy
R+Len or R2	rituximab+lenalidomide
R/R	relapsed/refractory
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ classification
SPM	second primary malignancy
TEAE	treatment emergent adverse event
TLS	tumor lysis syndrome
ULN	upper limit of normal
USPI	United States prescribing information

1 Executive Summary

1.1. Product Introduction

The review team recommends traditional approval of brentuximab vedotin (Adcetris) in combination with lenalidomide and a rituximab product (R2) for the treatment of adult patients with relapsed or refractory (R/R) large B-cell lymphoma (LBCL), including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS), DLBCL arising from indolent lymphoma, or high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy who are not eligible for autologous hematopoietic stem cell transplant (auto-HSCT) or chimeric antigen receptor (CAR) T-cell therapy.

Brentuximab vedotin (BV) is a CD30-directed antibody-drug conjugate (ADC) consisting of 3 components: 1) the chimeric IgG1 antibody cAC10, specific for human CD30; 2) the microtubule-disrupting agent monomethyl auristatin E (MMAE); and 3) a protease-cleavable linker that covalently attaches MMAE to cAC10. Targeted delivery of MMAE to CD30-expressing tumor cells is the primary mechanism of action of brentuximab vedotin. Binding of MMAE to tubulin disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptotic death of the cell.

Brentuximab vedotin received initial approval in 2011 and is approved either as monotherapy or in combination with chemotherapy for patients with classical Hodgkin lymphoma (cHL), systemic anaplastic large cell lymphoma (sALCL), and other CD30 expressing peripheral T-cell lymphomas (PTCL) as listed below:

- Adult patients with previously untreated Stage III or IV classical Hodgkin lymphoma (cHL), in combination with doxorubicin, vinblastine, and dacarbazine
- Pediatric patients 2 years and older with previously untreated high risk classical Hodgkin lymphoma (cHL), in combination with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide
- Adult patients with classical Hodgkin lymphoma (cHL) at high risk of relapse or progression as post-autologous hematopoietic stem cell transplantation (auto-HSCT) consolidation
- Adult patients with classical Hodgkin lymphoma (cHL) after failure of auto-HSCT or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates
- Adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL) or other CD30-expressing peripheral T-cell lymphomas (PTCL), including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified (NOS), in combination with cyclophosphamide, doxorubicin, and prednisone

- Adult patients with systemic anaplastic large cell lymphoma (sALCL) after failure of at least one prior multi-agent chemotherapy regimen
- Adult patients with primary cutaneous anaplastic large cell lymphoma (pcALCL) or CD30-expressing mycosis fungoides (MF) who have received prior systemic therapy

This application provides for expansion of the indications for brentuximab vedotin to include a new indication for brentuximab vedotin in combination with lenalidomide and a rituximab product for adult patients with relapsed or refractory large B-cell lymphoma (LBCL), including diffuse large B-cell lymphoma (DLBCL) NOS, DLBCL arising from indolent lymphoma, or high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy who are not eligible for auto-HSCT or CAR T-cell therapy.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial Evidence of Effectiveness (SEE) was established with one adequate and well-controlled clinical investigation and confirmatory evidence.

Substantial evidence of effectiveness of BV in combination with R2 in patients with R/R LBCL is based on overall survival in ECHELON-3 (Study SGN35-031), an adequate and well-controlled, multicenter, randomized, double-blinded, placebo-controlled trial. The study evaluated BV in combination with R2 (BV+R2) versus placebo in combination with R2 (Pbo+R2) in patients with R/R LBCL who were not eligible for auto-HSCT or CAR-T cell therapy. In ECHELON-3, 230 patients were randomized (1:1) to receive BV+R2 (n=112) or Pbo+R2 (n=118) until disease progression or unacceptable toxicity. The median number of prior systemic therapies was 3 (range 2-8) with 41% receiving 2 prior therapies and 50% receiving 3 or more prior therapies.

ECHELON-3 met its primary endpoint with statistically significant and clinically meaningful improvement in overall survival (OS) in the intention-to-treat (ITT) population. On a prespecified interim analysis, the median OS for patients who were randomized to the BV+R2 arm was 13.8 months (95% CI: 10.3, 18.8) compared to 8.5 months (95% CI: 5.4, 11.7) for those randomized to the Pbo+R2 arm. The OS hazard ratio (HR) was 0.63 (95% CI: 0.45, 0.89), with a stratified log-rank p-value of 0.0085 (two-sided α=0.0232).

The key secondary endpoints of progression free survival (PFS) per investigator and overall response rate (ORR) per investigator were also met. The median PFS was 4.2 months (95% CI: 2.9, 7.1) in the BV+R2 arm vs. 2.6 months (95% CI: 1.4, 3.1) in the Pbo+R2 arm. The PFS HR was 0.53 (95% CI: 0.38, 0.73; P <0.0001). Treatment with BV+R2 also resulted in a significantly higher ORR of 64.3% (95% CI: 54.7, 73.1) compared to the Pbo+R2 arm of 41.5% (95% CI: 32.5, 51.0); 2-sided P = 0.0006.

The statistically significant OS difference between arms, supported by PFS and ORR, provides substantial evidence of effectiveness and demonstrates clinical benefit. The ECHELON-3 trial utilized a control arm of R2, which is not an FDA-approved regimen for patients with R/R LBCL and usage in the U.S. is limited, this is a notable limitation of the trial. Additionally, in the ECHELON-3 trial there were low numbers of some histologic subtypes of LBCL, a lack of

central review of CD30 expression for some patients, and limitations in the representativeness of the enrolled trial population to that of a U.S. population with R/R LBCL. The safety data was consistent with the safety profile described previously for BV in other similar disease settings.

Overall, based on the totality of data, the review team concluded that BV+R2 has a favorable benefit-risk determination and supports the recommendation for traditional approval for BV in combination with R2 for the treatment of adult patients R/R LBCL, including DLBCL NOS, DLBCL arising from indolent lymphoma, or HGBL, after two or more lines of systemic therapy who are not eligible for auto-HSCT or CAR T-cell therapy. Of note, the Applicant's proposed indication did not include ineligibility for auto-HSCT or CAR T-cell therapy, however, this was included in the revised indication statement to be consistent with the patient population enrolled in ECHELON-3.

Additionally, the efficacy data of response rate and durability from the SGN35-012 trial, an adequate and well-controlled trial, in patients with relapsed or refractory large B-cell lymphoma treated with brentuximab vedotin provides confirmatory evidence in support of the new indication.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Efficacy: The efficacy of brentuximab vedotin (BV) in combination the lenalidomide and rituximab (R2) in adult patients with relapsed or refractory (R/R) large B-cell lymphoma (LBCL) who are not eligible for autologous stem cell transplant (ASCT) or chimeric antigen receptor (CAR) T-cell therapy is based on overall survival (OS) in addition to progression-free survival (PFS) and objective response rate (ORR) as assessed by investigator (INV) per Lugano criteria in the ECHELON-3 trial. ECHELON-3 is a multicenter, randomized, double-blinded, placebo-controlled trial that enrolled 230 adult patients with R/R LBCL after two or more lines of systemic therapy who were not eligible for auto-HSCT or CAR T-cell therapy. The study randomized 230 patients in a 1:1 ratio to receive BV+R2 (n=112) or Pbo+R2 (n=118) until disease progression or unacceptable toxicity. The median number of prior systemic therapies was 3 (range 2-8) with 41% receiving 2 prior therapies and 50% receiving 3 or more prior therapies. ECHELON-3 met its primary endpoint with significant improvement in overall survival (OS) in the intention-to-treat (ITT) population. The median OS for patients who were randomized to the BV+R2 arm was 13.8 months (95% CI: 10.3, 18.8) compared to 8.5 months (95% CI: 5.4, 11.7) for those randomized to the R2 arm. The OS hazard ratio (HR) was 0.63 (95% CI: 0.45, 0.89; P = 0.0085). The key secondary endpoints of PFS per INV and ORR were also met. The median PFS was 4.2 months (95% CI: 2.9, 7.1) with BV+R2 vs 2.6 months (95% CI: 1.4, 3.1) with R2. The PFS HR was 0.53 (95% CI: 0.38, 0.73; P < 0.0001). Treatment with BV+R2 resulted in significantly higher investigator-assessed ORR (64.3%; 95% CI: 54.7, 73.1) compared to the R2 arm (41.5%; 95% CI: 32.5, 51.0; 2-sided P = 0.0006).

Several concerns were raised during the review process including the relevance and applicability of the R2 control arm (R2 is not an approved regimen for patients with R/R LBCL), limited number of some LBCL subtypes, variability in the assessment of CD30 expression status, and limitations in the representativeness of the enrolled population to a U.S. population with R/R LBCL.

Safety: The safety profile of BV+R2 was generally consistent with that described previously with BV in patients with other lymphoid malignancies. In 112 patients treated with BV+R2, fatal adverse reactions (AR) occurred in 12% of patients and serious adverse reactions occurred in 60%. Adverse reactions resulting in discontinuation of BV occurred in 20% of patients receiving BV+R2, most commonly due to peripheral neuropathy peripheral neuropathy (4.5%) and pneumonia (2.7%). Adverse reactions resulting in dose reduction of BV occurred in 6% of patients, all due to peripheral neuropathy. The most common ARs including laboratory abnormalities ≥ 20% were decreased neutrophil, decreased lymphocytes, decreased platelets, decreased hemoglobin, fatigue, diarrhea, decreased potassium, increased ALT, peripheral neuropathy, rash, pneumonia, COVID-19, and increased creatinine.

Benefit/Risk: In patients with R/R LBCL, including DLBCL NOS, DLBCL arising from indolent lymphoma, or HGBL, after 2 or more lines of systemic therapy who were not eligible for auto-HSCT or CAR T-cell therapy, BV+R2 has a favorable benefit-risk balance. Overall survival is a clinically meaningful endpoint that measures both efficacy and safety. The statistically significant OS difference between arms, supported by PFS and ORR, provides substantial evidence of effectiveness and demonstrates clinical benefit.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• LBCL is an aggressive lymphoma with typically rapidly progressive, symptomatic disease and is fatal if not treated. • The median age of diagnosis of LBCL in the U.S. is 65 years, with many patients having comorbidities that may preclude intensive chemotherapy or autologous stem cell transplant.	• Relapsed and refractory LBCL is a serious and life-threatening condition.
Current Treatment Options	• Therapy options for patients with R/R LBCL differ based on eligibility for intensive chemotherapy and autologous stem cell transplant. • Systemic treatment options for R/R LBCL include chemoimmunotherapy such as polatuzumab in combination with bendamustine and rituximab and CAR-T cell therapies. Agents under accelerated approval are tafasitamab plus lenalidomide, loncastuximab tesirine, selinexor, epcoritamab and glofitamab. • CAR-T therapies are not readily available for all patients with R/R LBLC due to a variety of factors to include the need for processing, manufacturing issues, and patient location/site availability. • Numerous patients with R/R LBCL are not eligible for intensive therapy due to age or comorbidities.	• Patients with R/R LBCL, specifically those who are not eligible for intensive therapy have limited treatments available. • New therapeutic options are needed to improve outcomes in patients with R/R LBCL who are not candidates for intensive therapy or CAR-T cell therapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• ECHELON-3 met its primary endpoint with significant improvement in overall survival (OS) in the intention-to-treat (ITT) population. The median OS for patients who were randomized to the BV+R2 arm was 13.8 months (95% CI: 10.3, 18.8) compared to 8.5 months (95% CI: 5.4, 11.7) for those randomized to the R2 arm (HR 0.63; 95% CI: 0.45, 0.89; log-rank p-value = 0.0085, two-sided α=0.05). • The key secondary endpoints of PFS per INV and ORR were also met. Median PFS was 4.2 months (95% CI: 2.9, 7.1) with BV+R2 vs 2.6 months (95% CI: 1.4, 3.1) with R2 (HR 0.53; 95% CI: 0.38, 0.73; P <0.0001). Treatment with BV+R2 resulted in significantly higher investigator-assessed ORR (64.3%; 95% CI: 54.7, 73.1) compared to the R2 arm (41.5%; 95% CI: 32.5, 51.0; 2-sided P = 0.0006).	• Based on the OS superiority, supported by PFS and ORR in a randomized phase 3 study, BV+R2 has clinically meaningful efficacy in patients with R/R LBCL, including DLBCL NOS, DLBCL arising from indolent lymphoma, or HGBL after 2 or more lines of systemic therapy who were not eligible for auto-HSCT or CAR T-cell therapy • There is adequate evidence of a positive treatment effect with the addition of BV to R2, compared to R2, in the intended population.
Risk and Risk Management	• In 112 patients treated with BV+R2, fatal adverse reactions (AR) occurred in 12% of patients and serious adverse reactions occurred in 60%. Most common ARs including laboratory abnormalities ≥ 20% were decreased neutrophil, decreased lymphocytes, decreased platelets, decreased hemoglobin, fatigue, diarrhea, decreased potassium, increased ALT, peripheral neuropathy, rash, pneumonia, COVID-19, and increased creatinine. • Adverse events of special interest included:	• No new safety signals were identified for brentuximab vedotin in combination with R2. • BV+R2 has an acceptable safety profile in the intended population. • Peripheral neuropathy, infusion-related

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- Peripheral neuropathy (all grades): 27% in the BV arm vs. 21% in the control arm - Infections (all grades): 62% in the BV arm vs. 49% in the control arm - Peripheral neuropathy: 27% in the BV arm vs. 21% in the control arm - Grade 3-4 neutropenia: 39% in the BV arm vs. 23% in the control arm - Grade 3-4 thrombocytopenia: 29% in the BV arm vs. 18% in the control arm • Adverse reactions led to discontinuation of BV in 20% of patients. Adverse reactions that led to treatment discontinuation in 3 or more patients included peripheral neuropathy (4.5%) and pneumonia (2.7%). Adverse reactions led to dose reduction of BV in 6% of patients, all due to peripheral neuropathy. Adverse reactions leading to dose delay of BV in more than 5% of patients included neutropenia (23%), COVID-19 (13%), pneumonia (8%), and thrombocytopenia (8%). • Adverse events including laboratory abnormalities occurring at a rate of 10% or higher in the BV+R2 compared to the control arm were: neutrophils decreased (77% vs 63%), platelets decreased (65% vs 54%), fatigue (46% vs 29%), neutropenia (46% vs 32%), peripheral sensory neuropathy (20% vs 8%), pruritis (17% vs 6%).	reaction, hematologic toxicities, serious or opportunistic infections, tumor lysis syndrome, hepatotoxicity, pulmonary toxicity, serious dermatologic reactions, gastrointestinal complications, hyperglycemia are included in the Warnings and Precautions. • Primary prophylaxis with GCSF should be mandated to mitigate complications from neutropenia.

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

X

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

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

The updated 5th edition of the World Health Organization (WHO) classification has refined the categorization of large B-cell lymphomas, a collection of clinicopathological entities of which diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS), is the most frequently occurring, representing >80% of all cases (Sehn 2021; Kurz 2023). Other types of large B-cell lymphomas, such as T-cell/histiocyte-rich large B-cell lymphoma or high-grade B-cell lymphoma with MYC and BCL2 rearrangements, occur rarely and the approach to treatment is similar amongst the subtypes. The discussion here within will be focused on the most common subtype, DLBCL NOS, which will be referred to simply as DLBCL going forward.

In the US, the rate of new cases of DLBCL is 5.5 per 100,000 men and women per year based on 2017-2021 cases, age adjusted . With the average age at diagnosis being approximately 65 years, the prevalence and incidence of DLBCL are expected to increase in the coming years due to the underlying aging of the population in the US (Kanas 2022). In the US, the incidence of DLBCL is generally higher in males with new cases occurring in 6.6/100,000, compared to 4.6/100,000 in females. Among men, incidence was highest in Hispanics (7.2/100,000), non-Hispanic Whites (6.7/100,000) and non-Hispanic Asian/Pacific Islanders (6.3/100,000) with a similar trend in females.

DLBCL is usually aggressive, marked by rapidly growing tumors in lymph nodes, spleen, liver, bone marrow, or other organs (Martelli 2013; Li 2018). Clinical presentation, tumor behavior, and prognosis are variable, depending mainly on the extranodal site from which it arises. The majority of patients are diagnosed with advanced, stage III-IV disease, meaning disease has spread to both sides of the diaphragm or diffuse involvement of disease and require therapy. The 5-year relative survival for DLBCL overall is 64.7%, with stage IV associated with the lowest survival rate (55.2%) .

Advances in understanding the molecular landscape have revealed distinct genomic subtypes of DLBCL arising from cell of origin (germinal center B-cell-like [GCB] and non-GCB activated B-cell-like [ACB]). GCB subtype accounts for approximately 60% of DLBCL and may be a positive prognostic factor in terms of outcomes (Li 2018). There are other biologic factors, such as rearrangements involving MYC, BCL2, and/or BCL6, that are associated with poor prognosis (Sehn 2021).

Outcomes for patients with R/R DLBCL after ≥2 prior lines of systemic therapy is poor: approximately 75% of patients will either be refractory or have disease recurrence within 5 years of therapy in the third-line in the US . Per the SCHOLAR-1 retrospective pooled analysis of studies in DLBCL, the 2-year survival rate is 17% with a median overall survival (OS) of 6.1 months (95% CI: 5.2, 7.0) in these patients (Crump 2017). This finding is consistent with a recent analysis of real-world data that showed for patients with ≥2 prior lines the median OS was

6.2 months (95% CI: 5.2, 10.9) and worse for patients ≥3 prior lines at 5.1 months (95% CI: 3.2, 7.3) (Ip 2024).

The FDA's Assessment:

FDA agrees with the Applicant's position on diffuse large B-cell lymphoma (DLBCL) but notes that the Applicant's use of the term "DLBCL" throughout the Applicant's sections in this document refers to large B-cell lymphoma (LBCL) and encompasses histologies distinct from DLBCL, including high grade B-cell lymphoma (HGBL) with *MYC* and *BCL2* and/or *BCL6* rearrangements (also referred to as double hit or triple hit lymphoma), HGBL NOS, T-cell/histiocyte-rich LBCL, anaplastic lymphoma kinase (ALK) positive LBCL and others (refer to section 8.1.1. eligibility criteria for the full list). These other histologies have a similar or worse prognosis than DLBCL NOS and in general, treatment approaches in the relapsed/refractory setting are similar across these histologic subtypes. The FDA considers LBCL as the most appropriate overarching term to describe the population included in this application.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

More than 60% of newly diagnosed patients can be cured with R-CHOP, a chemoimmunotherapy regimen combining rituximab (R) with cyclophosphamide (C), doxorubicin (H), vincristine (O), and prednisolone (P). Approximately 10% to 15% of patients treated with R-CHOP have primary refractory disease (i.e., an incomplete response or a relapse within 6 months after treatment), and an additional 20% to 25% will have a relapse after an initial response, typically within the first 2 years. Additionally, approximately 20% to 25% of patients are not candidates for initial treatment with R-CHOP due to pre-existing conditions or age . The CD79b targeted antibody-drug conjugate, polatuzumab vedotin (Polivy), was recently approved by the FDA for the treatment of newly diagnosed high-risk DLBCL in combination with R-CHP (pola-R-CHP). While this regimen demonstrated a significant improvement in PFS as compared to R-CHOP, it failed to show a difference in survival (Tilly 2022).

For patients whose disease does not respond to frontline therapy, the outlook for relapsed or refractory (R/R) DLBCL has historically been poor. High-dose chemotherapy with autologous hematopoietic stem cell transplant (HSCT) has been a historical mainstay in the second-line setting for chemo-sensitive R/R DLBCL. However, approximately 50% of patients will ultimately relapse post-HSCT. Additionally, HSCT comes with significant toxicities and only a minority of patients are eligible for transplant . Chimeric antigen receptor T-cell (CAR T-cell) therapies (CD19-directed) and bispecific antibodies recently emerged as treatment options for R/R DLBCL. While these therapies have demonstrated impressive antitumor activity, not all patients will respond to treatment and given the seriousness of the associated adverse events, and therefore are not appropriate for or available to all patients. Beyond front-line, the survival rates for patients drop significantly with each subsequent treatment resulting in a high unmet need for well tolerated and effective treatments in this patient population (Tilly 2022).

The treatment landscape for R/R DLBCL has evolved in recent years with multiple treatments receiving either full or accelerated approval for patients after 2 lines of prior therapy (Table 1).

Results from an open-label randomized study of 80 patients with R/R DLBCL after ≥2 prior lines treated with polatuzumab in combination with bendamustine and rituximab (pola-BR) vs BR alone led to an accelerated approval for polatuzumab in 2019. In the final results of this study, data from an additional 106 patients enrolled in a single arm extension treated with pola-BR demonstrated consistent response rates and median overall survival (12.5 months, 95% CI: 8.3, 23.1) compared to that observed with the randomized cohort of pola-BR (Sehn 2022). Pola-BR received full approval in April 2023. Tafasitamab, loncastuximab teserine, and selinexor were granted accelerated approval based on open-label single arm studies demonstrating overall response rates between 29% and 55%. Full approval for these agents pending results from confirmatory trials.

Recently, T-cell engager therapies such as CAR T-cell therapy and bispecific antibodies were granted full and accelerated approvals, respectively, based on notable response rates and disease-free outcomes in R/R DLBCL patients with difficult to treat disease. However, the complexity of CAR T-cell administration limits widespread use and the long-term safety and efficacy of T-cell engager therapies are still emerging. Relapse following CAR T-cell therapy occurs in about 60% of patients and approximately 40% to 50% of patients do not respond to treatment with bispecific antibodies (Byrne 2019; Chow 2019; Trabolsi 2024). Treatment options are very limited for this group of patients.

Despite these recent advances in treatment there is currently no standard of care treatment for patients with R/R DLBCL after ≥2 prior lines of systemic therapy. Survival rates dramatically decline after each line of therapy for R/R DLBCL owing to the aggressiveness of the disease. As newer therapies such as CAR T-cell therapies and bispecific antibodies become more widely used in the US, there is a significant unmet need for patients who fail these therapies or as an alternative treatment for patients who cannot receive these treatments due to pre-existing conditions or due to lack of access.

Table 1: Applicant- Summary of Treatment Armamentarium Relevant to R/R DLBCL After Two or More Prior Lines

Product(s) Name	Relevant Indication	Year of Approval and Type of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
CAR-T-Cell Therapy						
Axicabtagene ciloleucel (Yescarta)	Adult patients with R/R LBCL after ≥2 lines of systemic therapy, including DLBCL NOS, trFL, HGBCL and PMBCL	2017 – full approval	IV infusion of 2×10^6 anti-CD19 CAR-T cells/kg	ORR 72% CR 51% mDoR (months): 9.2 (95% CI: 5.4, NE) mDoCR (months): not reached (95% CI: 8.1, NE)	Gr 3 - 4 cytopenias: neutropenia 92%, thrombocytopenia 56% febrile neutropenia: 34% Any grade CRS: 94% Gr 3+ CRS: 13% Any grade neurological AE: 87% Gr 3+ Neurological AE: 31%	Only available at specialized centers and through YESCARTA REMS
Tisagenlecleucel (Kymriah)	Adult patients with R/R large B- cell lymphoma after ≥2 lines of systemic therapy, including DLBCL NOS, HGBCL, trFL	2018 – full approval	IV infusion of 0.6 to 6×10^8 CAR-T cells	ORR 50% CR rate 32% mDoR (months): not reached (95% CI: 5.1, NE) mDoCR (months): not reached (95% CI: 10, NE)	Gr 3 - 4 cytopenias: neutropenia 82% thrombocytopenia 56% Febrile neutropenia: 17% Any grade CRS: 74% Gr 3+ CRS: 23% Any grade neurological AE: 60% Gr 3+ Neurological AE: 19%	Only available at specialized centers and through KYMRIAH REMS
CAR-T-Cell Therapy						

Product(s) Name	Relevant Indication	Year of Approval and Type of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Lisocabtagene maraleucel (Breyanzi)	Adult patients with R/R large B-cell lymphoma after ≥2 lines of systemic therapy, including DLBCL NOS, trFL, HGBCL, PMBCL, and follicular lymphoma grade 3B	2021 – full approval	IV infusion of 50 to 110 × 10^6 CAR-T cells	ORR 73% CR 54% mDoR (months): 16.7 (95% CI: 5.3, NE) mDoCR (months): not reached (95% CI: 16.7, NE)	Gr 3 - 4 cytopenias: neutropenia 88% thrombocytopenia 41% Febrile neutropenia: 9% Any grade CRS: 46% Gr 3+ CRS: 4.1% Any grade Neurological AE: 35% Gr 3+Neurological AE: 12%	Only available at specialized centers and through BREYANZI REMS.
Anti-CD79b Antibody-Drug Conjugate						
Polatuzumab vedotin (Polivy)	In combination with bendamustine and a rituximab for adult patients with R/R DLBCL NOS, after ≥2 prior therapies.	2019 – accelerated approval 2023- full approval	1.8 mg/kg IV q 21 days for 6 cycles in combination with bendamustine and rituximab	ORR at EOT: 45% (as assessed by independent review) CR at EOT: 40% Best ORR at any point: 63% Best response of CR at any point 50%	Gr 3-4 cytopenias: neutropenia 42% thrombocytopenia 40% Febrile neutropenia: 11% Any grade peripheral neuropathy: 40%	Eligible patients were not candidates for autologous HSCT at study entry.
CD19 Cytolytic Antibody						
Tafasitamab (Monjuvi)	In combination with lenalidomide for adult patients with R/R DLBCL NOS, ineligible for (b) (4) Includes trFL	2020 – accelerated approval	IV 12 mg/kg in 28-day cycles on days 1, 4, 8, 15 and 22 during cycle 1; once weekly during cycles 2-3, then every 2 weeks during cycles 4-12. In combination with Lenalidomide (25 mg PO) for cycles 1-12.	ORR 55% CR 37% mDoR (months): 21.7 (range: 0, 24)	Gr 3-4 cytopenias: neutropenia 49%, thrombocytopenia 17% Febrile neutropenia: 12% Gr 3+ infections: 30%	Study included DLBCL patients who received 1 to 3 prior systemic therapies

Product(s) Name	Relevant Indication	Year of Approval and Type of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Loncastuximab tesirine (Zynlonta)	Adult patients with R/R LBCL after ≥2 lines of systemic therapy, including DLBCL NOS, (b) (4) and HGBCL.	2021 – accelerated approval	IV on Day 1 of each cycle (Q3W): 0.15 mg/kg Q3W for 2 cycles; 0.075 mg/kg Q3W for subsequent cycles.	ORR 48.3% CR 24.1% mDoR (months): 10.3 (95% CI: 6.9, NE)	Gr 3-4 cytopenias: neutropenia 30%, thrombocytopenia 17%, Gr 3+ infection: 10% Gr 3 cutaneous reactions: 4%	Eligible patients were not candidates for HSCT.
XPO1 Inhibitor						
Selinexor (Xpovio)	Adult patients with R/R DLBCL NOS, including trFL, after ≥2 lines of systemic therapy	2020 – accelerated approval	60 mg PO qd days 1 and 3 weekly	ORR 29% CR 13%	Gr 3-4 cytopenias: neutropenia 31%, thrombocytopenia 49%, Gr 3-4 GI toxicity: 13% Gr 3+ infections: 25% Any grade neurological AE: 25% Gr 3+ Neurological AE: 6%	Included DLBCL patients who received 2 to 5 prior systemic regimens. Eligible patients were not candidates for HSCT
Glofitamab (Columvi)	R/R DLBCL NOS or LBCL arising from follicular lymphoma, after ≥2 lines of systemic therapy	2023 – accelerated approval	IV, weekly step-up dosing starting on Day 8 (2.5 mg), Day 15 (10 mg) of C1, followed by a dose of 30 mg on Day 1 of C2–12	ORR 51.1% (80/155) CR 39% (60/155) DOR 18.4 m	Any Gr 56%, AEs leading to termination 9%, CRS 3.9%, ICANS 3%, TLS 1%, FN 3%	Included DLBCL patients who received ≥2 prior systemic therapies. Included transformed DLBCL
Epcoritamab (Epkinly)	R/R DLBCL NOS including diffuse LBCL arising from indolent lymphoma, and high-grade B-cell lymphoma after ≥2 lines of systemic therapy.	2023 – accelerated approval	Subcutaneous, weekly (C1-C3), every 2 weeks (C4–C9), every 4 weeks (C10 and beyond)	ORR 63.1% (99/157) CR 38.9% (61/157) DOR 12 m	Any 61.1%, AEs leading to termination 7%, CRS 2.5%, ICANS 0.6%, TLS 1.3%	Included patients who received ≥2 prior systemic therapies. Included transformed DLBCL.

Product(s) Name	Relevant Indication	Year of Approval and Type of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
						Eligible patients were not candidates for HSCT.

C=cycle; CR=complete response; CRS=Cytokine release syndrome; DLBCL=diffuse large B-cell lymphoma; DoR=duration of response; DoCR=duration of complete response; FN=febrile neutropenia; Gr=grade; HSCT=autologous hematopoietic stem cell transplantation; ICANS=immune effector cell-associated neurotoxicity syndrome; LBCL=large B-cell lymphoma; NOS=not otherwise specified; ORR=objective response rate; PO=oral; qd=once a day; R/R=relapsed/refractory; TLS=tumor lysis syndrome; trFL=transformed follicular lymphoma

The FDA's Assessment:
The FDA generally agrees with the Applicant's position. Of note, the populations for the trials that supported the approvals of loncastuximab tesirine and epcoritamab included patients who may have been eligible for HSCT as ineligibility for HSCT was not a requirement for study enrollment. Additional treatment options for patients with R/R LBCL based on clinical guidelines include auto-HSCT for patients that are eligible and the following regimens:

- CEOP (cyclophosphamide, etoposide, vincristine, prednisone) ± rituximab
- DA-EPOCH ± rituximab
- GDP ± rituximab or (gemcitabine, dexamethasone, carboplatin) ± rituximab
- GemOx ± rituximab
- Rituximab
- Brentuximab vedotin for CD30+ disease
- Ibrutinib (non-GCB DLBCL)
- Lenalidomide ± rituximab (non-GCB DLBCL)

There is no standard accepted preferred therapy for patients with relapsed LBCL who are not eligible for intensive therapy and autologous HSCT or CAR-T cell therapy.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Brentuximab vedotin (BV; ADCETRIS®) initial marketing approval was granted by the FDA in August 2011, and since then the product has been approved in 81 countries/regions. Authorized indications in the US include the following:

1.1 Previously untreated stage III or IV classical Hodgkin lymphoma (cHL), in combination with chemotherapy

1.2 Previously untreated high risk cHL in pediatric patients 2 years and older, in combination with chemotherapy

1.3 cHL consolidation

1.4 Relapsed cHL

1.5 Previously untreated systemic anaplastic large cell lymphoma (sALCL) or other CD30-expressing peripheral T-cell lymphomas (PTCL), in combination with chemotherapy

1.6 Relapsed sALCL

1.7 Relapsed primary cutaneous anaplastic large cell lymphoma or CD30-expressing mycosis fungoides who have received prior systemic therapy

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

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

In the development and conduct of pivotal ECHELON-3 trial (SGN35-031), the Applicant sought the FDA's guidance for the initial trial design and subsequent major protocol amendment of ECHELON-3 (protocol amendment 05). On 20-May-2024, the Applicant had a pre-sBLA meeting with the FDA to discuss the adequacy of ECHELON-3 interim analysis results to support a sBLA filing. The outcomes of these interactions are summarized in Table 2.

Table 2: Applicant- FDA Interactions for ECHELON-3 Study

Date	Description of Correspondence and Cross-Referenced Document	IND Serial Number (SN) or Reference ID
19-Dec-2019	**Type B Pre-Phase 3 Meeting** to discuss the design of registrational study ECHELON-3 for R/R DLBCL.	IND 071634 Reference ID 4536879
02-May-2023	**Type D Meeting** to discuss major changes to the design of ECHELON-3 in protocol amendment 05. Agreement reached on several changes. The FDA also noted that Len+ R comparator is not approved for patients with R/R DLBCL and the study is an add-on design. The sponsor should provide evidence to support the applicability of the trial results to a U.S. population of patients with R/R DLBCL.	IND 071634 Reference ID 5167609
26-Apr-2024	**Response to FDA non-hold comments:** The sponsor submitted a response to the FDA's 17 October 2023 non-hold comments on ECHELON-3 protocol amendment 05 and the statistical analysis plan (SAP).	IND 071634, SN2306
20-May-2024	**Pre-sBLA meeting:** The sponsor sought FDA's alignment that the benefit-risk profile of BV+Len+R based on the results of ECHELON-3 supports an sBLA submission for the intended indication.	NA

BV=brentuximab vedotin; CAR T-cell=chimeric antigen receptor T-cell; DLBCL=diffuse large B-cell lymphoma; HSCT=hematopoietic stem cell transplantation; ITT=intent-to-treat; L=lenalidomide; NA=not applicable; R=rituximab; R/R=relapsed/refractory; sBLA=supplemental Biologics License Application

The FDA's Assessment:

The Agency agrees with the Applicant's position on the types and dates of the pre-submission interactions. Several issues were discussed at the Type D meeting and at the pre-sBLA meeting to include the following:

- Concerns regarding the use of R2 as a control arm and the applicability of this control arm to a US population.
- Enrolling a representative R/R LBCL population consistent with a U.S. population.
- Heterogeneity of the population with regards to LBCL subtypes with limited numbers for some histologic subtypes. Refer to Table 9 for additional details on the prior meetings with the Applicant.

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

4.1. Office of Scientific Investigations (OSI)

OSI was consulted to perform an audit of the Applicant's U.S. office. This inspection covered the Sponsor's study conduct related to ECHELON-3 (Study SGN35-031).

Records reviewed during the inspection included:

Sponsor electronic Trial Master File (eTMF)

• Investigator agreements or 1572s

• Financial disclosures

- Training records
- Protocol compliance
- Adverse events and serious adverse events including reporting
- Electronic systems used
- Transfer of regulatory obligations and oversight
- Monitoring of clinical study sites
- Written procedures relevant to the conduct of the trial
- Drug safety reporting
- Overall record(s) maintenance, adequacy, and retention:

The Sponsor's criteria for selection of clinical investigator sites included a feasibility assessment, a completed investigator qualification questionnaire, and a successful Pre-Study Visit (PSV). There were 98 clinical sites that screened and/or randomized subjects in 14 countries, and 83 sites did not conduct the study under the IND. While there were no clinical investigators whose participation was terminated, Site 82011 in the Republic of Korea was placed on an enrollment pause on 10/18/2023 for inability to resolve open queries and issues in a timely fashion due to high enrollment. Enrollment was not reinstated at this site, as global enrollment was completed shortly thereafter on 11/23/2023.

The Clinical Research Organization (CRO), (b) (4) was responsible for monitor selection and training. Monitors' qualifications for the selected sites were reviewed. No issues with qualifications were identified. For the sites reviewed, there were no instances in which unblinded personnel engaged in or conducted any of the blinded monitoring activities. The Sponsor's written business and operational procedures related to monitoring activities were reviewed. The Sponsor's most recent version (v05 dated 4/17/2024) of the clinical monitoring plan (CMP) for

the SGN35-031 study was reviewed. The CRO's most current CMPs for blinded and unblinded monitoring activities were reviewed. Pre-trial, site initiation, and interim monitoring visits within the eTMF for selected sites were reviewed. During the inspection, it was noted, per the Sponsor's CMP (v02 dated 4/2/2021), the first interim monitoring visit should be completed "approximately 2 weeks after the first subject receives that first dose of study drug." At Sites 33018 and 42001, the first monitoring visit was conducted 22 days and 24 days, respectively, after the first subject was dosed with the investigational drug. For site 33018, it was noted that the first monitoring visit was delayed for the first subject due to COVID-19. No other deviations or concerns with monitoring activities were noted. The delays in conducting the first monitoring visit due to COVID-19 at sites 33018 and 42001 did not follow the clinical monitoring plan which did not appear to impact study efficacy or safety results.

Information in the safety database, receipt of product safety-related information, and notification to Global Safety Risk Management and safety signal management were reviewed. There was no underreporting of adverse events identified. The written procedures and work instructions relating to clinical data management, data flow and integrity, and the implementation process for clinical studies in support of ongoing data review and cleaning were reviewed; no deficiencies or deviations were noted. Electronic systems including Medidata Rave for eCRF and ARGUS for safety, electronic signatures, and related audit trails were reviewed; no issues were identified.

Overall, based on the OSI inspection report, study SGN35-031 appears to have been conducted adequately. No issues were identified that impact the benefit-risk assessment for this application.

4.2. Product Quality

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

4.3. Clinical Microbiology

The FDA's Assessment:
Not applicable

4.4. Devices and Companion Diagnostic Issues

The FDA's Assessment:
The primary mechanism of action of brentuximab vedotin is due to binding of brentuximab vedotin to CD30-positive tumor cells. Although, in LBLC, there are uncertainties regarding the correlation with tumor CD30 expression and activity of BV in combination with R2 as there are alternative mechanisms of action not related to CD30 expression (bystander immunostimulatory effects) that may facilitate activity even with low or absent CD30 expression.

In LBCL, CD30 expression is variable and reported to be positive in 14-37% of patients (Hu 2013, Slack 2014, Malysz 2016, Santoso 2020). The correlation of CD30 expression with prognosis or response to CD30 targeted therapy in patients with relapsed or refractory large B-

cell lymphoma is unclear and limited by variability of assessment of CD30 expression and threshold for CD30 positivity reported. The activity of BV as monotherapy was evaluated by the Applicant in patients with CD30 positive (≥1% of tumor cells expressing CD30 by immunohistochemistry) and CD30 negative (<1% of tumor cells expressing CD30) in Study SGN35-012. Part A of the study included 49 patients with CD30 positive R/R DLBCL treated with BV monotherapy. Of the 48 efficacy evaluable patients, the ORR was 43.8% (95% CI: 29.5%, 58.8%) and the CR rate was 18.8% (95% CI: 8.95%, 32.6%). In Part C of the study, 52 efficacy evaluable patients with CD30 undetectable R/R DLBCL were treated with BV monotherapy. Of the 52 efficacy evaluable patients, the ORR was 30.8% (95% CI: 18.7%, 45.1%) and the CRR was 11.5% (95% CI: 4.35%, 23.4%). This data was included in the application and supports the activity of BV in patients with R/R DLBCL whose tumors are CD30 positive or have undetectable CD30 expression.

During the design of the ECHELON-3 study, the FDA advised that a CD30 companion diagnostic may be needed to support the approval of the proposed regimen in the intended population. The earlier versions of the ECHELON-3 protocol included dual primary endpoints of PFS in ITT population and PFS in patients with CD30 positive disease. In addition, CD30 expression was determined by a central assay prior to randomization and patients were stratified for CD30 status (<1% or ≥1%). Based on evolving data evaluating BV as monotherapy and in combination in patients with NHL that were both CD30 positive and CD30 negative, in April 2023, the ECHELON-3 trial endpoints were revised to include OS in the ITT population as the primary endpoint and OS in the CD30 positive population as one of the additional secondary endpoints. With this amendment, the assessment of CD30 expression was also changed to allow for local assessment. In the ECHELON-3 study, of the 230 patients enrolled, 32% were CD30 positive (≥1%) and 68% were CD30 negative (<1%). Based on the study results and other supportive clinical data, a correlation between CD30 expression and efficacy was not demonstrated in patients with LBCL and therefore, a companion diagnostic was not warranted for this indication.

5 Nonclinical Pharmacology/Toxicology

The FDA's Assessment:
No new non-clinical pharmacology/toxicology data were provided in this submission.

X X

Primary Reviewer Supervisor

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:
The Applicant submitted an efficacy supplement to support the approval of a new combination of brentuximab vedotin at 1.2 mg/kg Q3W with lenalidomide and rituximab (BV+Len+R) in patients with relapsed or refractory large B-cell lymphoma (LBCL). The proposed dose of 1.2 mg/kg brentuximab vedotin has been previously approved for patients with classical Hodgkin lymphoma in combination with chemotherapy in a Q2W regimen. Additionally, a higher dosage of 1.8 mg/kg Q3W brentuximab vedotin has been previously approved for patients with classical Hodgkin lymphoma and in patients with anaplastic large cell lymphoma in combination with chemotherapy.

The primary efficacy and safety data supporting this proposed indication was obtained from Study SGN35-031 (ECHELON-3), which was a randomized, double-blind, placebo-controlled, active comparator, multicenter Phase 3 trial to compare the effects of brentuximab vedotin (n=112) or placebo (n=118) in combination with Len+R in patients with relapsed or refractory LBCL. The patients in the brentuximab vedotin group received 1.2 mg/kg via IV administration Q3W on day 1 of each 21-day cycle. Patients in both treatment arms received lenalidomide at a dose of 20 mg QD and 375 mg/m^2 rituximab on day 1 of every cycle, then Q3W. The mean overall survival (OS) was 13.8 months (95% CI: 10.3, 18.8) for the BV+Len+R arm compared to 8.5 months (95% CI: 5.4, 11.7) for the placebo+Len+R arm. The rate of progression free survival (PFS) for BV+Len+R was a 47.3% reduction in the risk of disease progression or death (95% CI: 0.38, 0.73).

No clear exposure-response (E-R) associations were identified between observed Cycle 1 antibody-drug conjugate (ADC) maximum concentration (C_{max}) and OS, PFS, or ORR in Study ECHELON-3 patients who received BV+Len+R. The exposure-efficacy analysis generally supports the proposed dosage of BV in combination with Len + R. Higher observed Cycle 1 ADC concentration at the end of infusion (C_{EOI}; i.e., Cycle 1 ADC C_{max}) was associated with higher probability of TEAE leading to any dose modification of one or more treatment drug, TEAE leading to dose delay or interruption of one or more drug, Grade ≥3 infection, any grade peripheral neuropathy, and Grade ≥2 peripheral neuropathy in Study ECHELON-3 patients who received at least one dose of BV+Len+R. Higher Cycle 1 ADC C_{EOI} was also associated with shorter time to onset of first TEAE leading to any dose modification of one or more treatment drug, TEAE leading to dose delay or interruption of one or more drug, and Grade ≥3 infection. Neither monomethyl auristatin E (MMAE) C_{max} nor MMAE C_{avg} were evaluated in ECHELON-3, and so no E-R safety conclusions are available regarding MMAE exposure in ECHELON-3. Overall, the E-R analysis generally supports a positive benefit-risk relationship with the proposed dosage of BV in the general patient population.

Brentuximab vedotin dose individualization is required for subpopulations based on intrinsic factors, specifically hepatic impairment. Based on the tabular comparison of safety, patients with mild hepatic impairment showed higher safety events compared to those with normal hepatic function despite generally comparable PK profile of ADC and MMAE (C_{EOI} and C_{trough})

following 1.2 mg/kg Q3W BV in combination with Len+R in ECHELON-3. Therefore, appropriate dose-reductions should be implemented for patients with mild hepatic impairment. Further, given the known hepatotoxicity concerns with brentuximab vedotin, patients with moderate and severe hepatic impairment should avoid use.

In ECHELON-3, the incidence rate of anti-drug antibodies (ADA) development against brentuximab vedotin in patients with LBCL upon treatment with BV+Len+R (8%) were lower than those reported previously in patients with cHL and relapsed or refractory systemic ALCL (37%). The effect of anti-brentuximab vedotin antibodies on efficacy are not expected to be clinically meaningful.

Recommendations:

The Office of Clinical Pharmacology has reviewed the information contained in the current efficacy supplement and concluded that this supplement is approvable from a clinical pharmacology perspective.

There are no postmarketing requirement (PMR) or postmarketing commitment (PMC) from a clinical pharmacology perspective.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:

The clinical pharmacology data of BV in adults has been previously submitted (BLA125388, SN0218, m2.7.2). The new clinical pharmacology data presented in this current submission includes an assessment of pharmacokinetics (PK) and immunogenicity of BV in adult patients with R/R DLBCL from ECHELON-3 study (Intent-to-treat [ITT] subjects who received at least one dose of BV; n=112). Additionally, exposure-response (ER) relationships were evaluated using clinical data from ECHELON-3. Key findings are as follows:

The PK of BV analytes of ADC and monomethyl auristatin E (MMAE) following 1.2 mg/kg once every 3 weeks (Q3W) intravenous (IV) dose of BV in combination with lenalidomide and rituximab were consistent with those previously characterized in adult populations.

8% of the subjects treated with BV+Len+R were anti-drug antibody (ADA) positive on study. Given the low incidence of ADA, no definitive conclusions can be drawn on its impact on PK, safety, and efficacy in adult R/R DLBCL patients.

No apparent relationship between exposure and efficacy endpoints of OS and PFS were found.

Overall, no exposure-driven safety risks were found for BV. In the BV+Len+R regimen, there were no consistent relationships between exposure and incidence of Grade 3 or higher TEAEs, Grade 3 or higher neutropenia, Grade 4 or higher neutropenia, Grade 3 or higher infections, febrile neutropenia, and Grade 2 or higher peripheral neuropathy (PN).

The Applicant's Position:

The observed PK following IV administration of 1.2 mg/kg Q3W dose of BV in combination with lenalidomide and rituximab were similar to that of monotherapy setting. There was no indication of differential efficacy and overall safety with exposure. Collectively, these PK and ER findings and the positive benefit-risk profile demonstrated in the randomized pivotal ECHELON-3 study support the recommended 1.2 mg/kg Q3W BV dose in combination with lenalidomide and rituximab for the proposed indication.

The FDA's Assessment:
The FDA agrees with the Applicant's position that the observed PK following IV administration of 1.2 mg/kg Q3W dose of BV in combination with Len+R were similar to that in the monotherapy setting. FDA also concurs that the results from PK and E-R findings demonstrate a positive benefit profile to support the clinical benefit of BV+Len+R for the treatment of patients with R/R LBCL (see Section 6.2.2 for details). FDA also agrees with the Applicant that the observed low incidence of ADA positivity (8%, 8/97 patients) among patients treated with BV + Len + R are not expected to be clinically meaningful.

However, FDA disagrees with the Applicant's conclusion that the overall safety is not associated with BV exposure. E-R analysis for safety showed that higher Cycle 1 ADC C_{EOI} (i.e., Cycle 1 ADC C_{max}) was associated with increased incidence of several safety endpoints among patients who received at least one dose of BV+Len+R in ECHELON-3 study. Overall, E-R analysis is supportive of the proposed dosage in the general population; however, the risk of worse toxicity with higher MMAE exposure cannot be ruled out. Refer to Sections 6.3.1 and 6.3.2 for additional information.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:

The PK of BV in adult population has been extensively studied since its initial approval in 2011. In brief, the PK of BV analytes of ADC and MMAE were consistent across indications when BV was given as a single agent or as part of a combination, with body weight being the only clinically meaningful factor. Therefore, only sparse PK was collected in ECHELON-3. Blood samples were drawn at predose in Cycle 1 through Cycle 4 (trough concentrations [C_{trough}]), at end of infusion in Cycle 1 and Cycle 2 (C_{eoi}), and at end of treatment (EOT). A cross-study comparison of the observed C_{trough} and end of infusion concentration (C_{eoi}) was conducted. No population PK analysis was performed.

The objective of this PK comparison was to confirm that the observed PK of ADC and MMAE following 1.2 mg/kg Q3W IV dose of BV in adult R/R DLBCL subjects were consistent with that of monotherapy setting. The monotherapy PK of BV following IV administration of 1.8 mg/kg Q3W was characterized in study SGN35-012 in R/R DLBCL subjects and was included for comparison. Additionally, the observed PK from the most recent combination study SGN35-014 (ECHELON-2) where 1.8 mg/kg Q3W BV was given in combination with CHOP to front line PTCL subjects was also included to confirm the PK of BV was consistent across tumor types. After dose normalization, the observed ranges of geometric means for C_{eoi} and C_{trough} for both ADC and MMAE appear similar among the three studies.

Table 3: Applicant- Comparison of Dose-Normalized ADC and MMAE Concentrations between ECHELON-3, ECHELON-2, and SGN35-012 Studies

	BV ADC Concentration (µg/mL) GM (%CV)			BV MMAE Concentration (ng/mL) GM (%CV)		
	SGN35-031 (ECHELON-3) N=122	SGN35-014 (ECHELON-2) N=223	SGN35-012 (Part C) N=53	SGN35-031 (ECHELON-3) N=122	SGN35-014 (ECHELON-2) N=223	SGN35-012 (Part C) N=53
BV Dose	1.2 mg/kg Q3W +Len+R	1.8 mg/kg Q3W[a] +CHOP	1.8 mg/kg Q3W[a]	1.2 mg/kg Q3W +Len+R	1.8 mg/kg Q3W[a] +CHOP	1.8 mg/kg Q3W[a]
Disease	R/R DLBCL	PTCL	R/R DLBCL	R/R DLBCL	PTCL	R/R DLBCL
Cycle 1 C_{eoi}	26.5 (29.8%)	21.55 (26%)	26.7 (43%)	0.135 (107.3%)	0.18 (170%)	0.09 (69%)
Cycle 1 C_{trough}	0.303 (67.4%)	0.287 (96%)	0.57 (94%)	0.118 (86.5%)	0.06 (120%)	0.14 (65%)
Cycle 2 C_{eoi}	26.118 (29.4%)	20.01 (29%)	25.7 (36%)	0.256 (73.8%)	0.15 (87%)	0.25 (93%)
Cycle 2 C_{trough}	0.408 (112.8%)	0.47 (47%)	0.67 (92%)	0.122 (80.4%)	0.067 (84%)	0.09(71%)
Cycle 3 C_{trough}	0.446 (74.5%)	0.53 (47%)	0.67 (112%)	0.107 (76.9%)	0.067 (78%)	0.08(72%)

ADC=anti-body drug conjugate; C_{eoi}=end of infusion concentration; CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone; C_{trough}=trough concentration; CV=coefficient of variation; DLBCL=diffuse large B-cell lymphoma; GM=geometric mean; Len=lenalidomide; PTCL=peripheral T-cell lymphoma; R=rituximab; R/R=relapsed/refractory

a Concentration data were dose normalized (multiplied by 2/3) to enable comparisons with the exposures following 1.8 mg/kg Q3W administration in SGN35-012 and ECHELON-2.

Source: m5.3.5.1, ECHELON-3 CSR, Table 14.8.1.1and 14.8.2.1, ECHELON-2 m2.7.2, Table 3-1, and SGN35-012 CSR, Table 14.2.20.1 and Table 14.2.21.1

ER analyses focused on the clinical data from 112 subjects randomized to BV+Len+R arm. No relationships between Cycle 1 C_{trough} of ADC and efficacy endpoints were found. Subjects randomized to the BV+Len+R arm showed consistent OS and PFS benefits across all tertiles of BV exposure. The Kaplan-Meier (KM) curves for OS and PFS did not rank by ADC exposure tertiles and were separated from the placebo+Len+R arm (Figure 6 and Figure 7). These results support the consistent treatment benefit of BV across the range of exposures achieved in subjects with R/R DLBCL at the 1.2 mg/kg Q3W dosing regimen used in ECHELON-3.

ER tertile analysis was conducted to evaluate whether higher BV exposure was associated with increased incidence of Grade 3 or higher TEAEs, Grade 3 or higher neutropenia, Grade 4 or higher neutropenia, Grade 3 or higher infections, febrile neutropenia, and Grade 2 or higher PN. Amongst these safety parameters, ADC exposure was found to be a predictor for only Grade 2 or higher PN, consistent with previous ER findings whereas MMAE exposure was not predictive of any of the safety endpoints evaluated (Table 6 and Table 7).

The Applicant's Position:

The recommended dose regimen for adult patients with R/R DLBCL who have received at least 2 prior systemic therapies is 1.2 mg/kg Q3W BV given in combination with lenalidomide and rituximab. The proposed dosing regimen is supported in ECHELON-3 by a statistically

significant and clinically meaningful improvement in the primary efficacy endpoint of OS and key secondary endpoints of PFS and objective response rate (ORR), as well as a manageable and tolerable safety profile with a BV relative dose intensity (RDI) of 94.4%, similar PK and immunogenicity to those previously established, and the totality of ER findings.

The FDA's Assessment:
FDA generally agrees with the Applicant that the proposed recommended dosing regimen of 1.2 mg/kg Q3W BV in combination with Len+R for patients with R/R DLBCL is supported by the observed efficacy data including OS, PFS, and ORR in ECHELON-3 study.

The observed dose-normalized exposures of ADC and MMAE in ECHELON-3 were generally comparable to those reported in SGN35-012. Of note, higher variability (%CV) was reported for MMAE concentrations making it challenging to identify a meaningful difference among the different regimens compared across SGN35-012 and ECHELON-3 studies. Further, PK analysis in ECHELON-3 study did not evaluate C_{max} or C_{avg} for MMAE, which limits the ability to evaluate PK comparability (**Table 3**).

The FDA disagrees with the Applicant's position regarding the totality of E-R findings. E-R analysis for safety showed that higher Cycle 1 ADC C_{EOI} (i.e., Cycle 1 ADC C_{max}) was associated with increased incidence of any grade peripheral neuropathy, Grade ≥ 2 peripheral neuropathy, Grade ≥ 3 infection, TEAE leading to dose modification of one or more treatment drug, and TEAE leading to dose delay, interruption, or elimination of one or more treatment drug in Study ECHELON-3 patients who received at least one dose of BV+Len+R (**Figure 15** in Section 19.4.2.4).

Refer to Sections 6.3.1 and 6.3.2 for additional information.

6.2.2.2. Therapeutic Individualization

Data:

The clinical pharmacology of BV has been well characterized across various indications when given as a single agent or administered in combination with chemotherapy (Li 2017; Suri 2018a). The PK of both ADC and MMAE were approximately dose proportional from 0.1 to 2.7 mg/kg with a maximum tolerated dose of 1.8 mg/kg Q3W given as monotherapy (Younes 2010). Body weight was identified as the only clinically relevant intrinsic factor for the PK of BV in the adult population, consistent with its approved body weight-based dosages.

Due to the sparse PK collection by study design, a cross-study comparison of PK using observed C_{trough} and C_{eoi} concentration ranges for ADC and MMAE were conducted. No additional population PK analysis was performed. The observed BV PK were consistent with previously observed when administered as monotherapy (Study SGN35-012). As shown in Table 3, the observed ranges of geometric means for C_{eoi} and C_{trough} for both ADC and MMAE appear similar between Study SGN35-012 and SGN35-031. Additional details of cross study PK comparisons are provided in Table 3.

Intrinsic/Extrinsic Factors

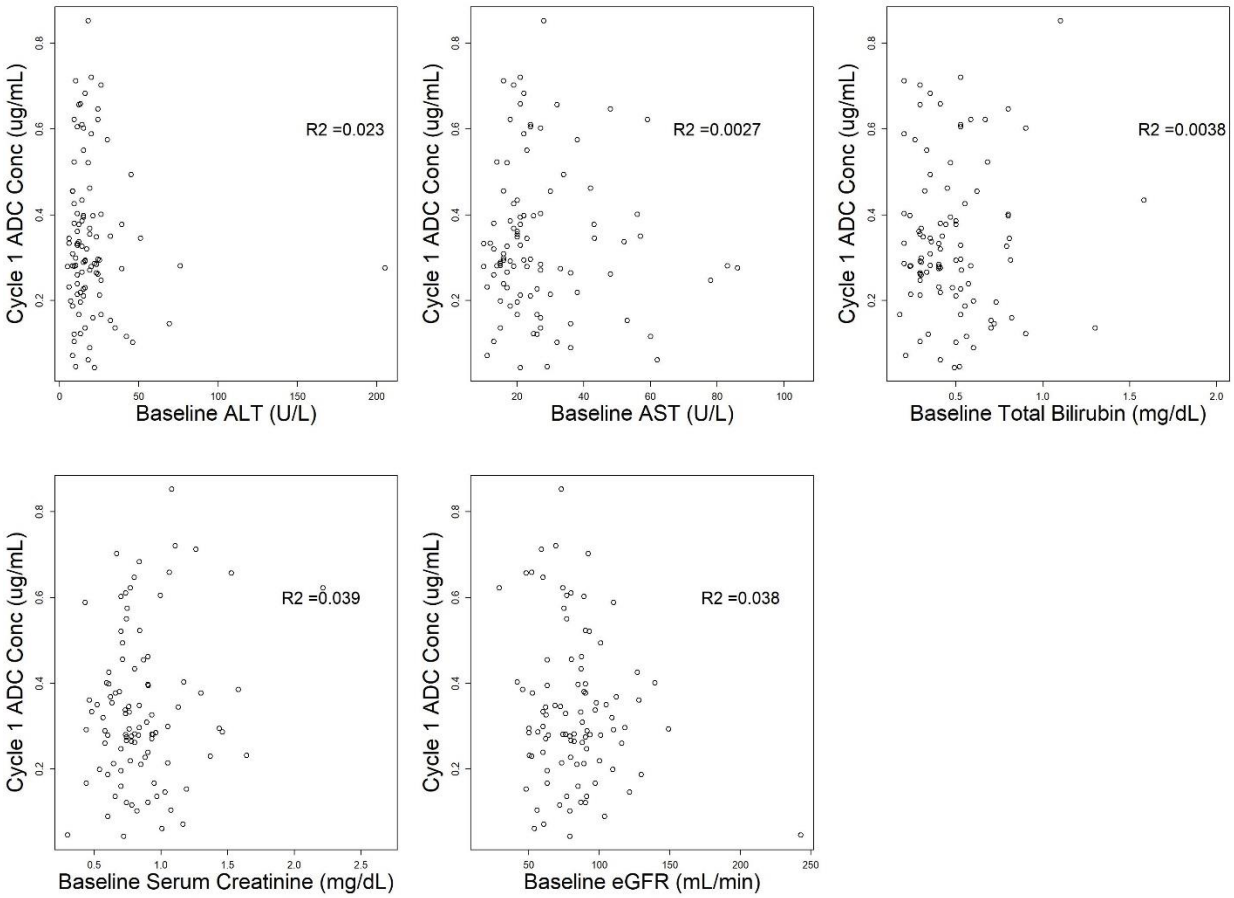
Body weight is the only clinically relevant covariate for the PK of BV and is accounted for by the body weight-based dose employed in ECHELON-3 study.

Special populations:

Renal: The ECHELON-3 study enrolled subjects with estimated glomerular filtration rate ≥45 mL/min. No dose adjustment of BV is required in mild and moderate renal impairment groups ([redacted] (b) (4)

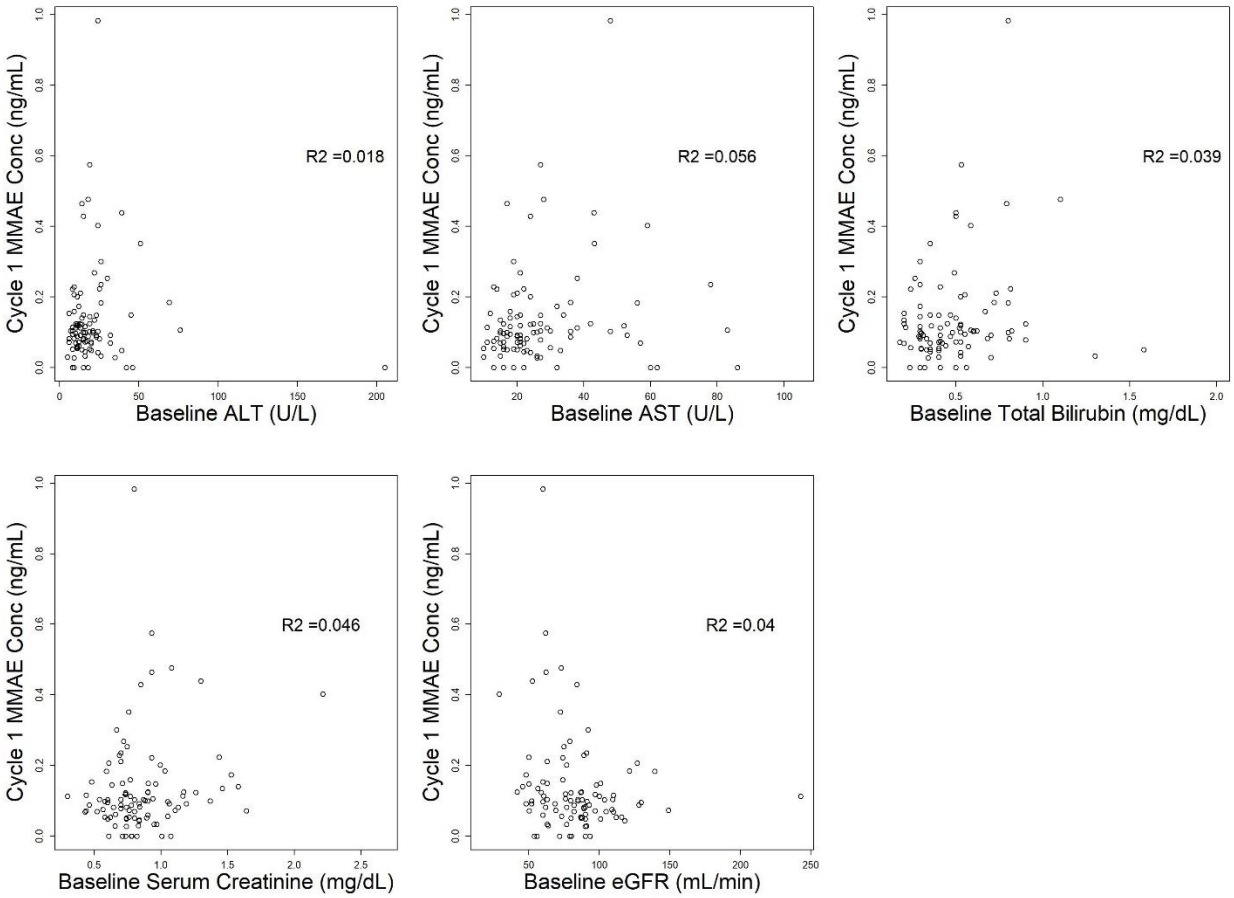
Hepatic: The ECHELON-3 study enrolled subjects with baseline aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≤3.0 x upper limit of normal (ULN) and ≤5.0 x ULN, respectively, for subjects with documented hepatic involvement of lymphoma. No dose reduction from the 1.2 mg/kg Q3W dose of BV is warranted for subjects meeting the above criteria. Of note, amongst the ITT population with reportable PK for BV, no relationships between baseline level of hepatic function biomarkers (ALT, AST, and total bilirubin) and PK exposure of BV were found (Figure 1 and Figure 2).

Figure 1: Applicant- Relationships between Renal and Hepatic Biomarkers and ADC Concentrations



Source: m5.3.3.5, ECHELON-3 Brentuximab Vedotin PK and Exposure-Response Analyses Data Memo, Figure 4.

Figure 2: Applicant- Relationships between Renal and Hepatic Biomarkers and MMAE Concentrations



Source: m5.3.3.5, ECHELON-3 Brentuximab Vedotin PK and Exposure-Response Analyses Data Memo, Figure 5.

The Applicant's Position:

Body weight was identified as the only clinically relevant intrinsic factor for the PK of BV in the adult population, (b) (4) (b) (4) The observed PK of ADC and MMAE following 1.2 mg/kg Q3W BV in ECHELON-3 were similar to those observed in monotherapy setting. No relationships between baseline renal/hepatic function biomarkers and PK exposures of BV (Cycle 1 C_{trough} for ADC and MMAE) were found. Therefore, no dose adjustment is required for intrinsic/extrinsic factors after accounting for body weight.

The FDA's Assessment:

The FDA agrees with the Applicant that the observed PK of BV in ECHELON-3 is generally similar when compared to previously observed PK when BV is administered as monotherapy (Study SGN35-012) as the dose-normalized concentrations of ADC and MMAE were within range of previously reported values. It should be noted that MMAE concentrations showed

higher interindividual variability (% CV). Further, the PK comparisons did not evaluate C_{max} or C_{avg} for MMAE (**Table 3**).

While the FDA acknowledges an absence of clear relationships between baseline renal/hepatic function biomarkers and PK exposures of BV (Cycle 1 C_{trough} for ADC and MMAE), the FDA disagrees with the Applicant's position that dosage adjustment is not required for hepatic impairment. While PK exposure of ADC and MMAE (C_{EOI} and C_{trough}) were comparable between mild hepatic impairment and normal hepatic function subgroups, C_{max} and C_{avg} of MMAE across various hepatic function subgroups were not assessed in ECHELON-3. Tabular comparisons of safety following 1.2 mg/kg Q3W BV in ECHELON-3 study showed that patients with mild hepatic impairment generally reported higher safety events compared to those with normal hepatic function. Therefore, a lower dosage of 0.9 mg/kg Q3W BV in combination with Len+R in patients with mild hepatic impairment is recommended for the proposed indication. Additionally, due to limited information in patients with moderate or severe hepatic impairment, and the known hepatotoxicity concerns with BV, patients with moderate and severe hepatic impairment should avoid use of BV. Refer to Sections 6.3.1 and 6.3.2.3 for detailed information.

Immunogenicity assessments to evaluate antidrug antibodies (ADA) were performed in 97 patients who received at least 1 dose of BV in ECHELON-3. Blood samples were collected before administration of the study drugs at Cycles 1, 2, 3, and 4 Day 1 predose timepoints and at the EOT. Overall, 96 patients (99%) were ADA negative at baseline. Of these 96 patients, 88 patients (91%) were ADA negative post-baseline and 8 patients (8%) were ADA positive post-baseline thus treatment-emergent. 1 patient (1%) was ADA positive at baseline, however this 1 patient (1%) was ADA negative post-baseline. Patients that were ADA positive on treatment tended to become positive on Cycle 2 and all subjects decrease in titer or tested negative in later cycles. Given the decrease in titer, many of the positive responses may not be biologically meaningful. For ECHELON-3, patients that were ADA positive post-baseline (8%) is below what is reported in the package insert (37%). The FDA notes that given the low incidence of anti-BV ADA, the effect of anti-BV ADAs are not expected to be clinically meaningful for the proposed indication.

6.2.2.3. Outstanding Issues

No outstanding issues with regard to clinical pharmacology and dosing.

The FDA's Assessment:
FDA agrees with the Applicant's position that there are no outstanding issues with regards to clinical pharmacology and dosing in this application.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:

General pharmacology and PK characteristics of BV in adults were previously submitted in BLA 125388 and are summarized in ADCETRIS US Prescribing Information. (Li 2017)The population PK of BV has been well characterized across various indications when given as a

single agent or administered in combination with chemotherapy (Li 2017; Suri 2018a) (Suri 2019). Results of these analyses indicate that there is no clinically meaningful difference in BV PK across tumor types given as monotherapy or in combination therapy. Amongst the intrinsic factors evaluated in these analyses, including age, sex, race, tumor type, baseline albumin, immunogenicity etc., body weight is identified as the only significant factor contributing to the PK variability of BV.

While a formal population PK analysis was not conducted due to sparse PK collection by design, a cross-study PK comparison confirmed pharmacokinetic parameter estimates for C_{eoi} and C_{trough} were similar between ECHELON-3 and the monotherapy PK of BV in R/R DLBCL population (Study SGN35-012) (Table 3). Importantly, within the clinical exposures achieved in ITT subjects randomized to receive 1.2 mg/kg Q3W BV+Len+R regimen, no apparent relationship between exposure and efficacy/safety endpoints were found. Consistent OS and PFS benefits were observed across exposure tertiles of the active analyte of ADC (Figure 6 and Figure 7). Amongst the safety endpoints evaluated (Grade 3 or higher TEAE, Grade 3 or higher neutropenia, Grade 4 or higher neutropenia, Grade 3 or higher infections, febrile neutropenia, and Grade 2 or higher PN) only ADC was found to be a predictor for Grade 2 or higher PN, while MMAE was not predictive of any safety endpoints tested (Table 6 and Table 7).

The Applicant's Position:

The observed PK of ADC and MMAE following 1.2 mg/kg Q3W BV+Len+R in R/R DLBCL subjects from ECHELON-3 were consistent with the previously established PK profile of BV. Collectively, the positive benefit-risk profile from ECHELON-3, the observed consistent PK exposure parameter estimates, and the totality of BV exposure-response findings support the recommended regimen of 1.2 mg/kg Q3W BV in combination with lenalidomide and rituximab.

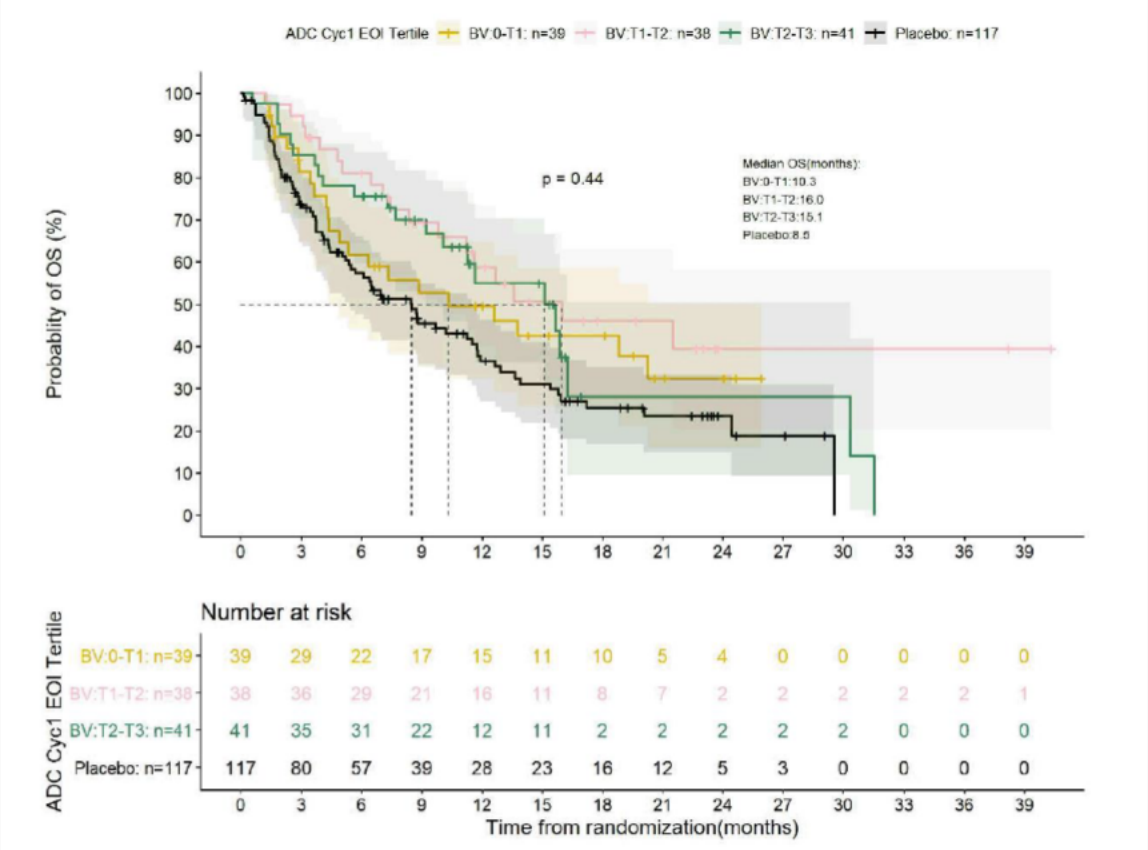
The FDA's Assessment:

FDA generally agrees with the Applicant's position that no clear E-R associations were identified between ADC exposure and efficacy. However, the FDA disagrees with the Applicant's position that no associations were identified between exposure and safety.

FDA requested updated E-R efficacy and safety analyses utilizing Cycle 1 Day 1 ADC C_{EOI} (i.e., ADC Cycle 1 C_{max}), which was available in a greater number of patients and determined to be a more reliable exposure metric for E-R analysis compared to Cycle 1 ADC C_{trough} in ECHELON-3. The updated E-R analyses included data from 118 patients with a PK measurement at the end of Cycle 1 BV infusion, including 9 patients in the safety run-in and 109 patients in the randomized BV+Len+R arm.

No clear exposure-efficacy associations were identified between observed Cycle 1 ADC C_{EOI} and OS or PFS (**Figure 3** and **Figure 4**, respectively). Additionally, no clear association was identified between observed Cycle 1 ADC C_{EOI} and ORR (**Figure 5**). The E-R analysis for efficacy did not identify any concerns regarding efficacy and generally supports the proposed dosage of 1.2 mg/kg Q3W BV in combination with Len + R. Refer to Section 19.4.2.2 for additional details regarding the E-R efficacy assessment.

Figure 3: Kaplan-Meier Plots for Overall Survival by Tertiles of ADC Cycle 1 Day 1 End of Infusion Concentrations in ECHELON-3

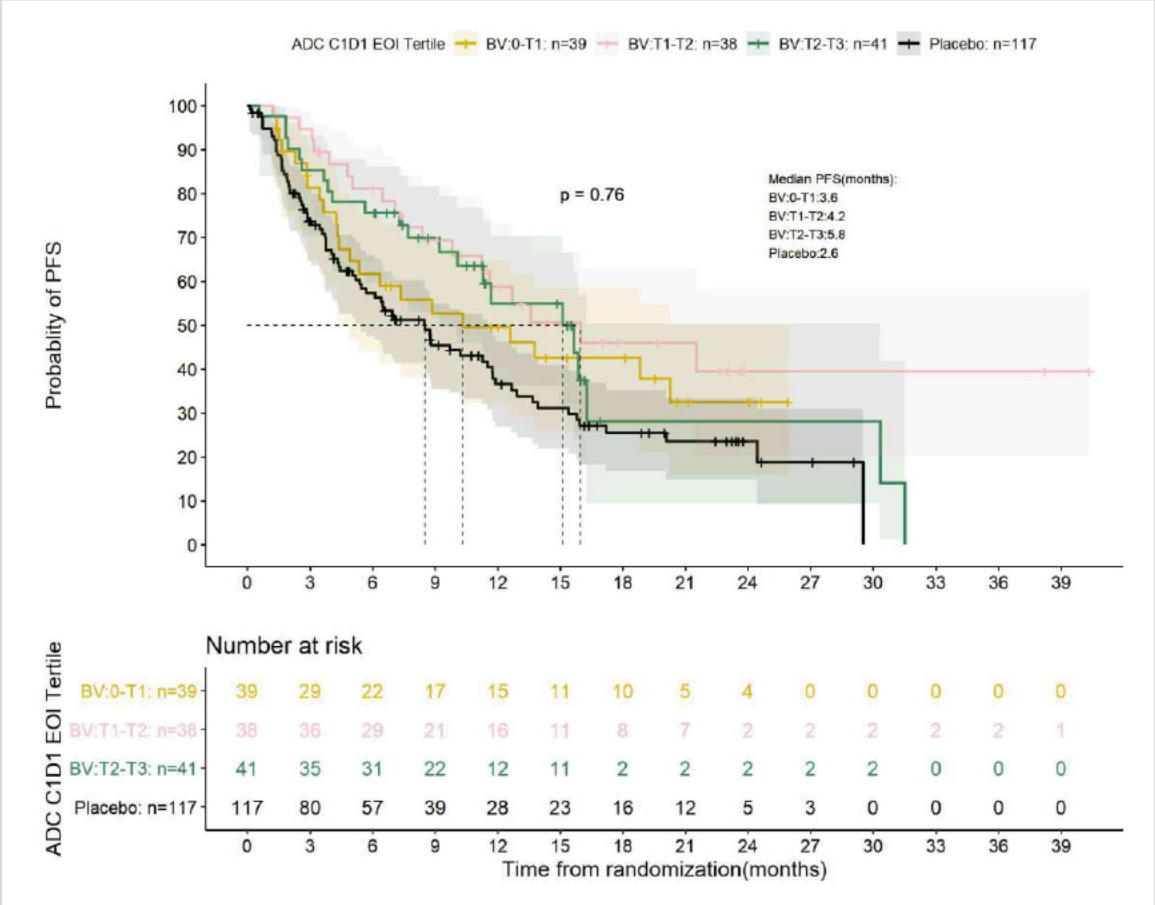


Included all subjects in the ITT population in Placebo+Len+R arm and subjects with reportable PK values at C1D1 EOI in BV+Len+R arm and in safety run-in arm. Subjects who received BV were categorized into 3 groups based on their individual ADC C1D1 EOI concentrations. Subjects with missing concentration values and implausible PK concentrations (i.e., subjects (b) (6) and (b) (6)) are not included. The maximum values of ADC C1D1 EOI concentrations in T1, T2, and T3 were 23.3, 30.0, and 63.4 µg/mL respectively. Shaded bands indicate 95% confidence intervals.

ADC = antibody-drug conjugate; BV = brentuximab vedotin; C1D1 = Cycle 1 Day 1; EOI = end of BV infusion; ITT = intent-to-treat; Len = lenalidomide; OS = overall survival; PK = pharmacokinetic; R = rituximab; T = tertile.

Source: Figure 1 in Applicant's response to 19Sept2024 information request (seqn 0409)

Figure 4: Kaplan-Meier Plots for Progression Free Survival by Tertiles of ADC Cycle 1 Day 1 End of Infusion Concentrations in ECHELON-3

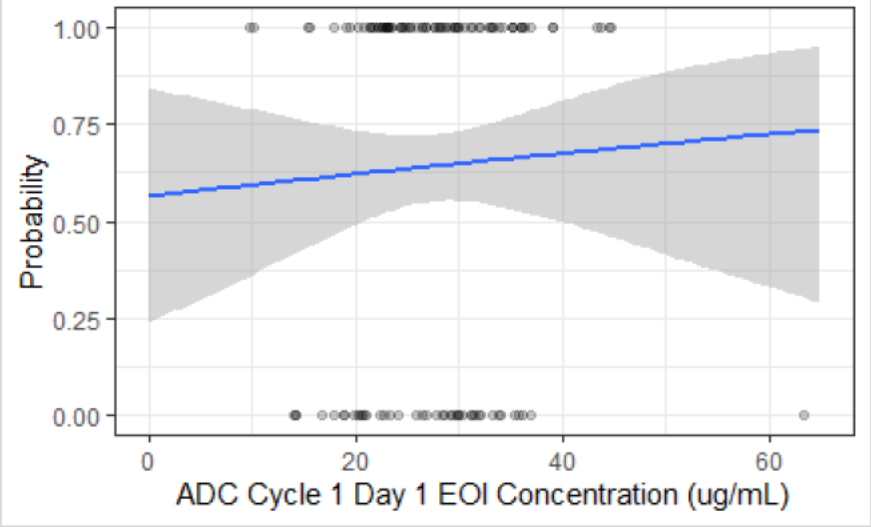


Included all subjects in the ITT population in Placebo+Len+R arm and subjects with reportable PK values at C1D1 EOI in BV+Len+R arm and in safety run-in arm. Subjects who received BV were categorized into 3 groups based on their individual ADC C1D1 EOI concentrations. Subjects with missing concentration values and implausible PK concentrations (i.e., subjects (b) (6) and (b) (6)) are not included. The maximum values of ADC C1D1 EOI concentrations in T1, T2, and T3 were 23.3, 30.0, and 63.4 µg/mL respectively. Shaded bands indicate 95% confidence intervals.

ADC = antibody-drug conjugate; BV = brentuximab vedotin; C1D1 = Cycle 1 Day 1; EOI = end of BV infusion; ITT = intent-to-treat; Len = lenalidomide; PFS = progression free survival; PK = pharmacokinetic; R = rituximab; T = tertile.

Source: Figure 1 in Applicant's response to 19Sept2024 information request (seqn 0409)

Figure 5: Logistic Regression of ORR versus ADC Cycle 1 Day 1 End of Infusion Concentrations in ECHELON-3 Patients who Received BV+Len+R



Analysis included data from 117 patients in ECHELON-3 who received at least one dose of BV and had reportable PK concentrations at C1D1 EOI. Note that the ADC concentration at C1D1 EOI equals the maximum ADC concentration following the first BV dose.
ADC = antibody-drug conjugate; BV = brentuximab vedotin; C1D1 = Cycle 1 Day 1; EOI = end of BV infusion; Len = lenalidomide; ORR = overall response rate; PK = pharmacokinetic; R = rituximab.
Source: Reviewer's analysis of E-R efficacy datasets submitted in Applicant's response to 19Sept2024 information request (seqn 0409)

FDA disagrees with the Applicant's position that no E-R safety associations were identified with observed Cycle 1 exposure. The updated E-R safety analysis found that higher observed Cycle 1 ADC C_{EOI} (i.e., Cycle 1 ADC C_{max}) was associated with increased incidence of peripheral neuropathy (any grade and Grade ≥2); Grade ≥3 infection; TEAE leading to any dose modification of any treatment drug; and TEAE leading to any dose delay, interruption, hold, or skip of any treatment drug (**Figure 15**).

FDA also compared time to first event across exposure quartiles to account for potential differences in TEAE onset and treatment duration. Higher Cycle 1 ADC C_{EOI} was associated with shorter time to first TEAE leading to any dose modification of any treatment drug (**Figure 16**) and shorter time to first TEAE leading to any dose delay, interruption, hold, or skip of any treatment drug (**Figure 17**). The highest two quartiles of ADC C_{EOI} also had higher risk of Grade ≥3 infection and peripheral neuropathy (any grade and Grade ≥2) compared to the lower two quartiles or placebo (**Figure 18**). Refer to Section 19.4.2.4 for the detailed E-R safety assessment.

The FDA also disagrees with the Applicant's position that dosage adjustment is not required for intrinsic factors such as organ impairment. FDA noted comparable PK exposure of ADC and MMAE (C_{EOI} and C_{trough}) among patients with mild hepatic impairment and normal hepatic function (**Table 4**). However, hepatic impairment is expected to have a larger impact on MMAE C_{max} and C_{avg} compared to MMAE C_{EOI} or C_{trough}. Although MMAE concentrations at the end of the Cycle 1 Day 1 BV infusion and prior to the Cycle 2 Day 1 BV infusion were collected, the time to maximum MMAE concentration is 1 to 3 days after BV administration. (b) (4)

(b) (4)

(b) (4) Based on the available safety data, and the known hepatotoxicity concerns with BV, a lower starting dose of 0.9 mg/kg for BV in combination with Len+R should be implemented in patients with mild hepatic impairment for the currently proposed indication.

Table 4: PK in Mild Hepatic Impairment vs Normal Patients in ECHELON-3

	PK Sample Time	Statistic	Normal hepatic function	Mild hepatic impairment	Moderate hepatic impairment
ADC (ug/mL)	Cycle 1 End-of-Infusion	N	92	25	1
		Geometric Mean	**24.2**	**25.8**	63.4
		5th to 95th percentile	15.5 - 39.0	15.2 - 34.9	-
	Cycle 1 Ctrough	N	84	22	0
		Geometric Mean	**0.309**	**0.282**	-
		5th to 95th percentile	0.107 - 0.72	0.091 - 0.646	-
MMAE (ng/mL)	Cycle 1 End-of-Infusion	N	92	25	1
		Geometric Mean	**0.125**	**0.152**	0.138
		5th to 95th percentile	0.045 - 0.825	0.043 - 0.915	-
	Cycle 1 Ctrough	N	84	22	0
		Geometric Mean	**0.095**	**0.119**	-
		5th to 95th percentile	0.015 - 0.415	0.013 - 0.954	-

Concentrations below LLOQ were set to 1/2 * LLOQ value for descriptive statistics of exposure.
ADC LLOQ = 0.0125 ug/mL. MMAE LLOQ=0.025 ng/mL.
ADC = antibody-drug conjugate; Ctrough = trough concentration; CV = coefficient of variation; EOI = end of brentuximab vedotin infusion; LLOQ = lower limit of quantification; MMAE = monomethyl auristatin E.
Source: Reviewer's analysis of Applicant's updated E-R datasets submitted in response to 19Sept2024 information request (seqn 0409)

Tabular comparisons of safety in patients following 1.2 mg/kg Q3W BV in ECHELON-3 showed that higher Grade ≥ 3 treatment-related TEAE (73%), treatment-related TE SAE (38%), pneumonia (27%), tooth infections (8%), rates of dose reductions (12%), and levels of ALT (8%), AST (8%), and blood bilirubin (4%) increased in mild hepatic impairment vs normal patients who received at least one dose of 1.2 mg/kg Q3W BV+Len+R in ECHELON-3 (**Table 5**). Additionally, there is insufficient data on moderate and severe hepatic impairment from ECHELON-3 study. Overall, there is inconclusive evidence to rule out potential safety risk among patients with mild hepatic impairment without an appropriate dosage-modification. The FDA recommends that a lower dosing regimen of 0.9 mg/kg Q3W should be implemented for BV in patients with mild hepatic impairment. Further, given the known hepatotoxicity concerns with BV, patients with moderate and severe hepatic impairment should avoid use.

Table 5: Treatment-Emergency Adverse Events by Baseline Hepatic Function and Preferred Term – ECHELON-3 BV Treated Subjects

Preferred Term	Normal (N=95) n (%)	Mild (N=26) n (%)	Moderate (N=1) n (%)	Total (N=122) n (%)
Grade 3 or higher treatment-related TEAE	65 (68)	19 (73)	1 (100)	85 (70)
Treatment-related TE SAE	27 (28)	10 (38)	1 (100)	38 (31)
Pneumonia	15 (16)	7 (27)	0	22 (18)
Dose reduction	7 (7)	3 (12)	0	10 (8)
Tooth infection	0	2 (8)	0	2 (2)
Alanine aminotransferase increased	2 (2)	2 (8)	0	4 (3)
Aspartate aminotransferase increased	2 (2)	2 (8)	0	4 (3)
Blood bilirubin increased	0	1 (4)	0	1 (1)

Source: Applicant's tabular comparisons of safety in patients with mild, moderate, and severe hepatic impairment vs normal hepatic function patients in ECHELON-3, submitted in response to 01Oct2024 information request (seqn 0419). Hepatic impairment for patients with relapsed or refractory large B-cell lymphoma is defined per the National Cancer Institute Organ Dysfunction Working Group.

6.3.2. Clinical Pharmacology Questions

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

Yes. The clinical pharmacology program provides supportive evidence of BV effectiveness.

Data:

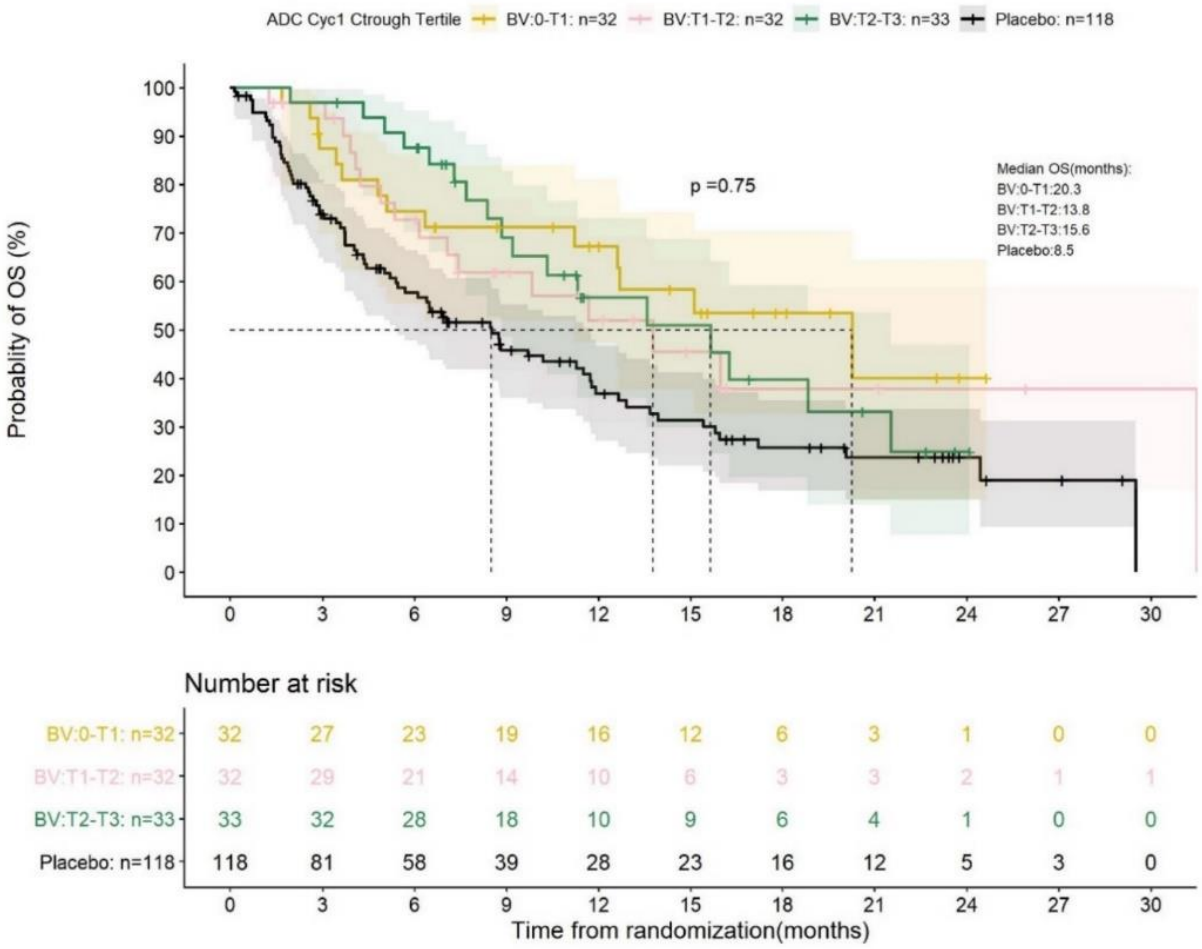
Evidence of effectiveness was obtained from the randomized phase 3 study ECHELON-3. At the data cutoff date of 22-Jan-2024, ITT population consisted of 112 subjects randomized to the BV+Len+R arm and 118 ITT subjects randomized to the comparator arm (Placebo+Len+R). Treatment on the BV+Len+R arm resulted in a statistically significant and clinically meaningful efficacy. The median OS was 13.8 months (95% CI: 10.3, 18.8) for the BV+Len+R arm versus 8.5 months (95% CI: 5.4, 11.7) for the placebo+Len+R arm. The estimated percentage of subjects alive at 12 months was 55.4% (95% CI: 44.9%, 64.7%) for the BV+Len+R arm and 36.8% (95% CI: 27.1%, 46.6%) for the placebo+Len+R arm. PFS was superior for the BV+Len+R arm with a 47.3% reduction in the risk of disease progression or death (stratified hazard ration [HR] 0.527; 95% CI: 0.380, 0.729; 2-sided p=<0.0001).

To support the clinical efficacy observed with the 1.2 mg/kg Q3W dose of BV observed in ECHELON-3, exposure-efficacy relationship was evaluated in subjects who were randomized to and treated with BV+Len+R regimen. No apparent relationships between ADC exposure and survival endpoints of OS and PFS were found in tertile analysis. Consistent survival benefits over the comparator arm were seen across exposure tertiles (Figure 6 and Figure 7).

The Applicant's Position:

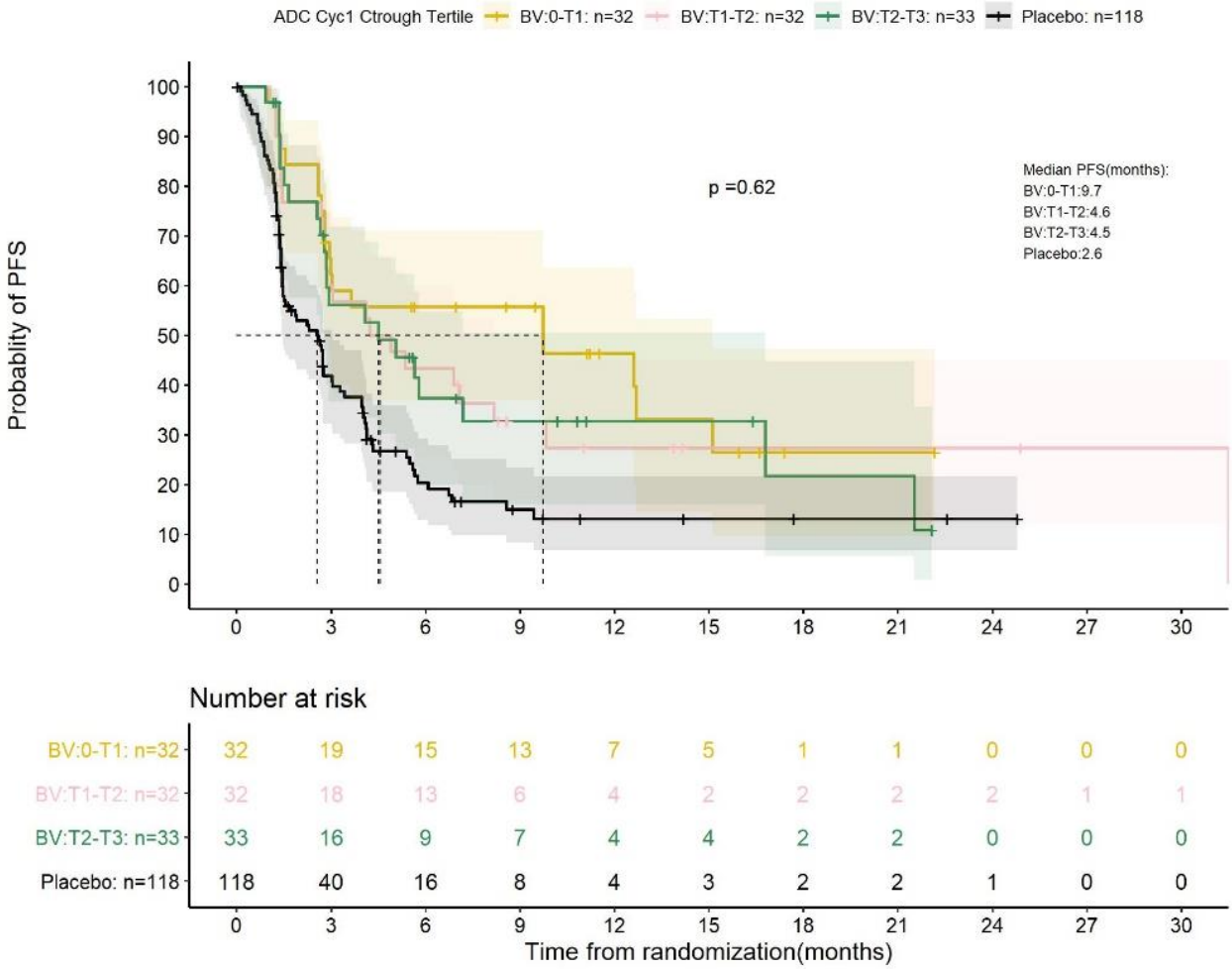
The relationships between BV exposure and efficacy endpoints of OS and PFS showed that treatment with 1.2 mg/kg Q3W BV + Len + R was associated with a clinically meaningful efficacy across the entire range of exposures achieved in the ECHELON-3 study.

Figure 6: Applicant- Kaplan-Meier Plots for Overall Survival (OS) by Tertiles of ADC Cycle 1 Trough Concentrations



Included all subjects in the ITT population in Placebo+Len+R arm and subjects in the ITT population with reportable PK values at C2D1 predose in BV+Len+R arm. Subjects in the BV+Len+R arm were categorized into 3 groups based on their ADC Cycle 1 C_{trough} (ie. Cycle 2 Day 1 predose timepoint). Subjects with missing concentration values are not included. The T1, T2, and T3 values of ADC Cycle 1 C_{trough} are 0.267, 0.378, and 0.853 µg/mL respectively. Shaded bands indicate 95% confidence intervals.
Source: ECHELON-3, m2.7.2, Figure 2

Figure 7: Applicant- Kaplan-Meier Plots for Progression Free Survival (PFS) by Tertiles of ADC Cycle 1 Trough Concentrations



Included all subjects in the ITT population in Placebo+Len+R arm and subjects in the ITT population with reportable PK values at C2D1 predose in BV+Len+R arm. Subjects in the BV+Len+R arm were categorized into 3 groups based on their ADC Cycle 1 C_{trough} (ie. Cycle 2 Day 1 predose timepoint). Subjects with missing concentration values are not included. The T1, T2, and T3 values of ADC Cycle 1 C_{trough} are 0.267, 0.378, and 0.853 µg/mL respectively. Shaded bands indicate 95% confidence intervals.
Source: ECHELON-3, m2.7.2, Figure 3

The FDA's Assessment:

FDA generally agrees with the Applicant's position that the proposed dosing regimen of 1.2 mg/kg Q3W BV in combination with Len+R is supported by the statistically significant and clinically meaningful improvement in the OS (13.8 months vs 8.5 months) and PFS (47.3% reduction in the risk of disease progress or deaths) compared to placebo+Len+R in ECHELON-3 study.

FDA also agrees that there is no apparent relationships between ADC exposure and efficacy endpoints including OS and PFS in ECHELON-3 based on exposure efficacy analysis with

Cycle 1 ADC C_{EOI} (**Figure 3** and **Figure 4)**. Additionally, significant associations were not observed between ORR and Cycle 1 ADC C_{EOI}. Overall, the E-R analysis for efficacy is supportive of the proposed BV dosage of 1.2 mg/kg Q3W in combination with Len + R. Refer to Section 19.4.2.2 for the detailed E-R efficacy assessment.

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

Yes. 1.2 mg/kg (up to a maximum of 120 mg) Q3W of BV is appropriate for the proposed indication.

Data:

Data supporting the proposed dosing regimen in this patient population is summarized in sections 6.2.2.1, 6.2.2.2, and 6.3.2.1 of the assessment aid. There was no apparent trend between ADC exposure and efficacy endpoints. Consistent OS and PFS benefits were observed in subjects randomized to receive 1.2 mg/kg Q3W BV in combination with lenalidomide and rituximab in ECHELON-3 study (Figure 6 and Figure 7). Exposure tertile analyses were conducted to evaluate the relationships between BV exposures and incidence rate of Grade 3 or higher TEAE, Grade 3 or higher neutropenia, Grade 4 or higher neutropenia, Grade 3 or higher infections, febrile neutropenia, and Grade 2 or higher PN. ADC exposure was found to be a predictor of Grade 2 or higher PN, while MMAE exposure was not predictive of any of the safety endpoints evaluated. As mentioned above, these findings are consistent with the previously established BV ER relationships ((Suri 2019); Table 6, Table 7) and support the dose modification for AE management implemented in ECHELON-3.

Table 6: Applicant- Summary of Incidence of Treatment-Emergent Adverse Events of Interest by Tertiles of ADC Cycle 1 Trough Concentrations

Safety Endpoint	T1	T2	T3	p-value[b]
N of subjects (%)	32	32	33	
≥Grade 3 TEAE	27(84.4)	28(87.5)	29(87.9)	NS
≥Grade 3 Neutropenia[a]	15(46.9)	20(62.5)	17(51.5)	NA
≥Grade 4 Neutropenia [a]	11(34.4)	13(40.6)	5(15.2)	NA
≥Grade 3 Infections	12(37.5)	15(46.9)	12(36.4)	NA
Febrile Neutropenia	2(6.2)	2(6.2)	5(15.2)	NS
≥Grade 2 Peripheral Neuropathy (SMQ)	1(3.1)	4(12.5)	9(27.3)	0.02

NA=Not applicable; NS=not significant; TEAE=treatment-emergent adverse event

Included all subjects in the safety population with reportable PK values at Cycle 2 Day 1 predose in BV+Len+R arm. Subjects with missing PK data were not included. Subjects in the BV+Len+R arm were categorized into 3 groups based on their ADC Cycle 1 trough concentrations (ie. Cycle 2 Day 1 predose timepoint). T1 represents the lowest tertile while T3 represents the highest tertile.

a Including preferred terms of "neutropenia" and "neutrophil count decrease"

b Chi-square contingency table test (α=0.05) for association performed for AE endpoints whereby a numerical trend with higher exposure was noted.

Source: ECHELON-3, m2.7.2, Table 5

Table 7: Applicant- Summary of Incidence of Treatment-Emergent Adverse Events of Interest by Tertiles of Cycle 1 MMAE Trough Concentrations

Safety Endpoint	T1	T2	T3	p-value[b]
N of subjects (%)	31	33	33	
≥Grade 3 TEAE	29(93.5)	28(84.8)	27(81.8)	NA
≥Grade 3 Neutropenia[a]	20(64.5)	15(45.5)	17(51.5)	NA
≥Grade 4 Neutropenia[a]	14(45.2)	7(21.2)	8(24.2)	NA
≥Grade 3 Infections	11(35.5)	12(36.4)	16(48.5)	NS
Febrile Neutropenia	2(6.5)	2(6.1)	5(15.2)	NA
≥Grade 2 Peripheral Neuropathy (SMQ)	7(22.6)	2(6.1)	5(15.2)	NA

NA=Not applicable; NS=not significant; TEAE=treatment-emergent adverse event

Included all subjects in the safety population with reportable PK values at Cycle 2 Day 1 predose in BV+Len+R arm. Subjects with missing PK data were not included. Subjects in the BV+Len+R arm were categorized into 3 groups based on their MMAE Cycle 1 C_{trough} (ie. Cycle 2 Day 1 predose timepoint). T1 represents the lowest tertile while T3 represents the highest tertile.

a Including preferred terms of "neutropenia" and "neutrophil count decrease"

b Chi-square contingency table test (α=0.05) for association performed for AE endpoints whereby a numerical trend with higher exposure was noted.

Source: ECHELON-3, m2.7.2, Table 6

The Applicant's Position:

Collectively, these results support the recommended 1.2 mg/kg Q3W BV dose in combination with lenalidomide and rituximab for the proposed indication.

The FDA's Assessment:

As noted previously in the FDA's assessment for Section 6.3.2.2, the E-R for efficacy did not identify an association between observed Cycle 1 ADC C_{max} and OS, PFS, or ORR among patients receiving BV+Len+R in Study ECHELON-3.

However, the FDA disagrees with the Applicant's position regarding the totality of E-R findings. E-R analysis for safety showed that higher Cycle 1 ADC C_{EOI} (i.e., Cycle 1 ADC C_{max}) was associated with increased incidence of any grade peripheral neuropathy, Grade ≥ 2 peripheral neuropathy, Grade ≥ 3 infection, TEAE leading to any dose modification (i.e., any discontinuation, dose reduction, delay, interruption, hold, or skip) of one or more treatment drug, and TEAE leading to any dose delay, interruption, or elimination of one or more treatment drug in patients receiving BV+Len+R (**Figure 15** in Section 19.4.2.4). Further, clear conclusions could not be made regarding relationship between MMAE exposure and safety given both limited MMAE concentrations collected for C_{EOI} and C_{trough} timepoints, and a lack of MMAE C_{max} or C_{avg} data in ECHELON-3 study.

Overall, E-R analysis did not identify any major concerns with the proposed dosage in the general population, however the risk of worse toxicity with higher MMAE exposure cannot be ruled out given the limited evaluation of MMAE for E-R safety associations in ECHELON-3. Refer to Sections 19.4.2.2 and 19.4.2.4 for the detailed E-R efficacy and safety assessment.

6.3.2.3 Is an alternative dosing regimen or management strategy required for

subpopulations based on intrinsic patient factors (e.g. race, ethnicity, age, performance status, genetic subpopulations, etc.)?

No, 1.2 mg/kg (up to 120mg) Q3W BV given in combination with lenalidomide and rituximab is appropriate for subpopulations based on intrinsic factors.

Data:

The effect of various intrinsic factors including age, race, sex, body weight, baseline albumin, immunogenicity, tumor type on the PK of BV have previously been thoroughly evaluated through population PK analyses (Li 2017; Suri 2018a; Suri 2019). Results indicated body weight is the only clinically relevant intrinsic factor for the PK of BV in the adult population, consistent with the recommended body weight-based dosing (b) (4) (b) (4) Following body weight-based dose of BV, the PK of BV was found to be consistent across tumor types and were similar in both monotherapy and in combination with chemotherapy agents. These findings were also confirmed by the observed BV PK in ECHELON-3.

While hepatic and renal functions were not formally evaluated as covariates, the relationships between hepatic/renal function biomarkers and PK exposures of ADC and MMAE in patients who received 1.2 mg/kg Q3W BV+Len+R regimen were examined. No statistically significant correlations were found between Cycle 1 trough concentrations for ADC and MMAE and the baseline levels of ALT, AST, total bilirubin, serum creatinine, and estimated GFR.

The Applicant's Position:

1.2 mg/kg Q3W BV given in combination with lenalidomide and rituximab is the recommended dose regimen for adult patients for the proposed indication. No alternative dosing regimen or management strategy is required for subpopulations based on intrinsic factors.

The FDA's Assessment:

FDA generally agrees with the Applicant that no alternative dosing regimens are recommended based on intrinsic factors such as bodyweight, age, sex, or race. Following the proposed dosage of 1.2 mg/kg BV, clinically meaningful differences in the observed ADC or MMAE concentrations (Cycle 1 C_{EOI} and Cycle 1 C_{trough}) were not identified across body weight (40 to 123 kg), age (29 to 87 years), male or female sex, or Asian (n=29) or White (n=69) racial category.

It should be noted that there was insufficient data to evaluate potential PK differences due to race or ethnicity due limited number of patients who identified as Hispanic (n=5) or as races other than Asian or White (Black or African American [n=2]) in ECHELON-3. Refer to Section 6.2.2.2 for additional information.

However, as discussed in Section 6.3.1, the FDA disagrees with the Applicant's position with respect to dosage adjustment for intrinsic factor, especially in patients with hepatic impairment.

FDA noted comparable PK exposures of ADC and MMAE (C_{EOI} and C_{trough}) among patients with mild hepatic impairment and normal hepatic function (**Table 4**). However, PK estimates for MMAE including C_{max} or C_{avg} were not assessed in ECHELON-3 study. Therefore, the FDA recommends that a lower starting dosage of 0.9 mg/kg Q3W should be implemented for patients

with mild hepatic impairment. Additionally, given the known hepatotoxicity concerns with BV, patients with moderate and severe hepatic impairment should avoid use.

Tabular comparisons of safety following 1.2 mg/kg Q3W BV in ECHELON-3 study showed that patients with mild hepatic impairment experienced worse safety profile compared to patients with normal hepatic function (See **Table 5**). Further, there is insufficient data in patients with moderate or severe hepatic impairment in ECHELON-3 study to conclude that patients with hepatic impairment would not be at an undue safety risk without implementing appropriate dosage-modifications.

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

Data:

Drug-drug interactions data were previously submitted in BLA125388, SN0218 m2.7.2 and there is no new information.

The Applicant's Position:

BV is intended for IV infusion administration; therefore, food-drug interactions are not expected.

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

X X

Primary Reviewer Team Leader

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

Table 8 shows the clinical studies included in this sBLA that support efficacy and safety of BV+Len+R for the proposed indication.

The Applicant's Position:

Data from ECHELON-3, which compared BV in combination with lenalidomide and rituximab (BV+Len+R) versus placebo+Len+R in patients with R/R DLBCL, are presented as primary evidence for efficacy and safety in the proposed indication. Data from the 3 additional studies, SGN35-012, SGN35-017, SGN35-023, support the findings from ECHELON-3 and offer further

evidence for the activity of BV in DLBCL. Supportive safety data is provided from safety run-in (SRI) portion of ECHELON-3, SGN35-012, SGN35-017, SGN35-023, ECHELON-1 (C25003), and ECHELON-2 (SGN35-014).

The FDA's Assessment:

The FDA agrees with the Applicant that ECHELON-3 was considered the primary study supporting efficacy and safety of BV+Len+R for this application. Studies SGN35-012, SGN35-017, and SGN35-023 are considered supportive for efficacy and safety.

Table 8: Applicant - Clinical Studies Relevant to the sBLA Submission

Trial Identity / NCT no.	Trial Design	Regimen/Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
	Controlled Studies to Support Efficacy and Safety						
SGN35-031 (ECHELON-3) NCT04404283	Phase 3, randomized, double-blind, placebo-controlled, active-comparator	1.2 mg/kg BV + R (375 mg/m2) Q3W + Len (20 mg) qd or placebo + R (375 mg/m2) Q3W + Len (20 mg) qd BV and rituximab: IV Lenalidomide: Oral	Primary: OS Secondary: PFS, ORR, CR rate, and DOR per investigator; incidence, severity, and seriousness of AEs, OS in CD30-positive subjects Exploratory: Association of CD30 expression with ORR and PFS per investigator	Treatment duration until progression or unacceptable toxicity Follow-up Consent withdrawal, study closure, or death.	Total N=240 SRI=10 BV+Len+R = 112 Placebo+Len+R=118	R/R DLBCL	172 Centers; 16 Countries
SGN35-012 NCT01421667	Phase 2, open-label, uncontrolled	Part A/C: 1.8 mg/kg BV q3w Part B: 1.8 mg/kg BV + R q3w first 8 cycles, 1.8 mg/kg BV after 8 cycles IV	Parts A/C Primary: ORR Secondary: Safety, relationship of CD30 expression with antitumor activity, DOR, PFS, CR, PK, PD Additional: OS, changes in disease related symptoms, immunogenicity Part B Primary: Safety Secondary: ORR, CR Additional: DOR, PFS, OS, PK	Treatment duration Parts A/C: until progression, unacceptable toxicity, or study closure. Part B: BV+R for up to 8 cycles. Following this period, or unacceptable toxicity to rituximab, subjects can receive BV as single agent until progression, unacceptable toxicity, or study closure Follow-up Consent withdrawal, study closure, or death.	Total N (DLBCL)= 118 Part A (CD30+) =49 Part B (CD30+) =16 Part C (CD30u) =53	R/R NHL	34 Centers; 2 Countries
SGN35-017 NCT01925612	Phase 2, open-label; Part 1 and 3: randomized	Part 1: 1.2 or 1.8 mg/kg BV+RCHOP q3w, 6 cycles Part 2: 1.8 mg/kg BV+RCHP q3w, 6	Primary: Antitumor activity (CR rate) per investigator assessment, safety Secondary: ORR and PFS per investigator, overall survival	Treatment duration Maximum of 6 cycles (~18 weeks) Follow-up	Total N=87 Part 1 (1.2 mg/kg BV) =29 Part 1 (1.8	FL DLBCL	27 Centers; 4 Countries

Trial Identity / NCT no.	Trial Design	Regimen/Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
	Part 2: non-randomized	cycles Part 3: 1.8 mg/kg BV+RCHP or R-CHOP q3w, 6 cycles BV, rituximab, cyclophosphamide, doxorubicin, vincristine: IV; prednisone: oral	Additional: CD30 expression on tumor specimens, PK	Consent withdrawal, study closure, or death	mg/kg BV) =22 Part 2=11 Part 3 BV+RCHP= 11 RCHOP=12		
SGN35-023 NCT02594163	Phase 2, randomized, open-label	1.8 mg/kg BV+BR q3w for 6 cycles, and 1.8 mg/kg BV up to 16 cycles, or BR for 6 cycles IV	Primary: ORR Secondary: PFS, CR rate, DOR, OS, and safety and tolerability Exploratory: ATA, CD30 expression vs response, subject stratification biomarkers vs response, BV and MMAE exposures when administered in combination with rituximab and bendamustine, PD markers	Treatment duration Maximum of 6 cycles (~4 months) for combination treatment; subjects who respond without excessive toxicity may receive single-agent BV for up to an additional 10 cycles (up to 16 total cycles), or until progression or unacceptable toxicity Follow-up Consent withdrawal, study closure, or death	Total N (BV treated)=25 BV mono=12 BV+BR=13	R/R DLBCL	26 Centers; 7 Countries
	Studies to Support Safety						
C25003 (ECHELON-1) NCT01712490	Phase 3, open-label, randomized	1.2 mg/kg BV(A)+AVD or ABVD on days 1 and 15 of each 28-day cycle, up to 6 cycles	Primary: Modified PFS per IRF assessment Secondary: OS, CR rate per IRF assessment, safety, EFS, DFS, ORR, DOR and DCR per IRF, rate of patients not in CR that received	Treatment duration Maximum of 6 cycles Follow-up Consent withdrawal, have been followed for a minimum of 10 years after randomization, study	Total N=1334 A+AVD=664 ABVD=670	FL cHL	218 Centers; 21 Countries

Trial Identity / NCT no.	Trial Design	Regimen/Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		IV	irradiation, CR rate per IRF at the end of frontline therapy, rate of Cycle 2 PET negativity, PRO, PK, ATA Exploratory: PRO, serum concentrations of AVD, % subjects alive without HL at 3 and 5 years, % subjects switching therapy post Cycle 2 pre-EOT, biomarker expression, serum concentrations of disease markers, utilization of medical resources, incidence of pregnancy at the time of study ; closure	closure/completion, or death			
SGN35-014 (ECHELON-2) NCT01777152	Phase 3, randomized, double-blind, placebo-controlled	1.8 mg/kg BV (A) q3wk + CHP or CHOP, 6-8 cycles BV, cyclophosphamide, doxorubicin, vincristine: IV Prednisone: oral	Primary: PFS per IRF Secondary: PFS per IRF for subjects with sALCL, CR and ORR per IRF, OS, safety, lab abnormalities Additional: ATA MRU based on medical care encounters, QoL	Treatment duration Maximum of 8 cycles (~6 months) Follow-up Consent withdrawal, study closure, or death	Total N=452 A+CHP=226 CHOP=226	FL PTCL	132 Centers; 17 Countries

ABVD=doxorubicin, bleomycin, vinblastine, and dacarbazine; ATA= antitherapeutic antibodies; AVD= doxorubicin, vinblastine, and dacarbazine; BR= bendamustine and rituximab; BV=brentuximab vedotin; R=rituximab, len=lenalidomide; cHL=classical Hodgkin lymphoma; CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone; CHP= cyclophosphamide, doxorubicin, and prednisone; DLBCL= diffuse large B-cell lymphoma; FL=first line; EFS=event-free survival; IRF= independent review facility; MRU= medical resource utilization; NHL= non-Hodgkin lymphoma; PET= positron emission tomography; PTCL= peripheral T-cell lymphoma; Q3W=once every 3 weeks; qd=once daily; QoL=quality of life; RCHP=rituximab, cyclophosphamide, doxorubicin, and prednisone; RCHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R/R= relapsed/refractory

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. ECHELON-3

Trial Design

The Applicant's Description:

ECHELON-3 is a randomized, double-blind, placebo-controlled, active-comparator, multicenter Phase 3 study designed to evaluate the efficacy of BV+Len+R versus placebo+Len+R for the treatment of subjects with R/R DLBCL. Enrolled subjects had R/R DLBCL with eligible subtypes, must have received ≥2 prior lines of therapy and must be ineligible for HSCT or CAR T-cell therapy.

There is no standard of care for R/R DLBCL after 2 or more lines of systemic therapy. Rituximab, lenalidomide, and BV all have manageable individual safety profiles, making this an attractive combination in multiple relapsed and heavily pretreated subjects and may provide a regimen that is specifically suitable for an older population treated in the community setting. In December 2019, the sponsor met with the FDA to discuss the ECHELON-3 study. During that meeting, the sponsor and FDA discussed an add-on study design evaluating BV+Len+R with a control arm of Len+R (Reference ID 4536879) supported by emerging data suggesting added efficacy when lenalidomide is combined with rituximab. This was suggested by the FDA as an alternative to the original proposal from the sponsor (b) (4) (b) (4) The sponsor acknowledges that the treatment landscape has evolved since 2019 and that the chosen control arm of rituximab and lenalidomide has not been further studied in a registrational context; the sponsor has provided relevant data to support the use of Len+R as a comparator in ECHELON-3 with applicability to the US patient population (m2.5, Section 1.4.2).

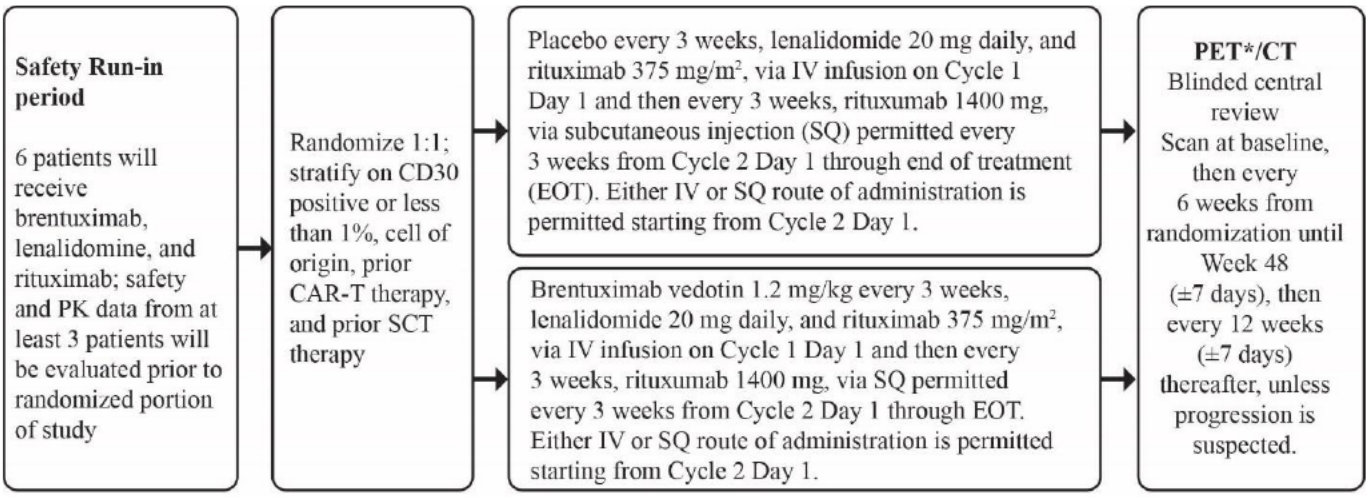
During the December 2019 meeting, the FDA also recommended an initial open-label safety and PK run-in (SRI) since the combination of BV+Len+R had not been evaluated previously. The SRI phase was conducted prior to the randomized portion of the study where safety data from 6 subjects treated with BV+Len+R was reviewed by a safety monitoring committee (SMC), including 3 external members. After these subjects completed the first cycle of treatment, the SMC did not identify any new safety signals or concerns and approved proceeding with the randomized portion of the study.

Subjects were randomized in a 1:1 manner to receive either BV or placebo in combination with Len+R. Randomization was stratified by CD30 expression (positive, ≥1% versus negative, <1%), prior HSCT (received or not), prior CAR T-cell therapy (received or not), and cell of origin (GCB or non-GCB). The primary endpoint was OS in the ITT population. A preplanned interim analysis of OS for both efficacy and futility was to be performed by an independent data

monitoring committee at approximately 128 OS events (0.75 information fraction). The final analysis of OS was planned to be performed after approximately 170 OS events have occurred.

For more details on study design, please see Figure 8.

Figure 8: Applicant-ECHELON-3 Study Design



* Once PET is negative, no futher PET scans are required

The FDA's Assessment:

The Agency agrees with the Applicant's description of the study design, study population and treatment plan; however, the review team had concerns regarding the applicability of the R2 control arm in ECHELON-3 to the general U.S. population with R/R LBCL, given that R2 is not approved for this indication in the U.S. This concern was conveyed to the Applicant during several meetings including April 2023 and during the pre-BLA meeting in May 2024. During the pre-sBLA meeting the Agency stated that "R2 is not an approved regimen for patients with R/R DLBCL. The non-standard control arm makes interpretation of efficacy challenging, and this may pose significant issues for your application." The Applicant acknowledged that R2 is not approved for R/R DLBCL. As noted by the Applicant, information to support the applicability of the R2 control to a U.S. population with R/R LBCL was provided in the BLA.

To support the use and applicability of the R2 control arm, the Applicant provided data from several data sources. During the Type D meeting in May of 2023, the Applicant provided data from a physician survey assessing therapies utilized for patients who had either failed or were not eligible for intensive chemotherapy regimens, ASCT or CAR T therapy. From this data, the use of R2 was 4.5-9%. In addition, the Applicant provided additional literature from real-world data and from claims analysis which reported the use of R2 in 10% and 29% of patients with R/R DLBCL in the third line and post CAR-T setting respectively. At the pre sBLA meeting in May of 2024, the Applicant cited current guidelines that include R2 as a therapeutic option for patients with R/R LBCL not eligible for ASCT or CAR T therapy and single-arm trial data showing comparable responses rates between R2 (ORR 41.5%) and therapies with accelerated approval for R/R LBCL after at 2 prior systemic therapies such as loncastuximab tesirine (ORR 48%) and selinexor (ORR 29%).

A Summary of recent key meetings and discussions with the Applicant is provided in the table below. As noted in Table 9, the ECHELON-3 protocol was amended during the course of the study to include a revision of the primary endpoint from PFS to OS, and the removal of assessment of OS in the CD30+ population from a key secondary endpoint to a prespecified subgroup analysis. These revisions were communicated to the Agency prior to the final SAP submission and study readout. The final design which included an evaluation of overall survival in the ITT population was considered acceptable by the Agency.

Table 9: Summary of Recent Key Meetings with the Applicant

Date	Meeting
12/2019	**Type B Pre-Phase 3 meeting to discuss the design of ECHELON-3 for R/R DLBCL:** • Initial design: (safety run-in first) Bv+Len vs Len: (b) (4) (b) (4) Applicant proposed Bv+R2 vs Pbo+R2: FDA accepted • N=400 with R/R DLBCL, ineligible for CAR-T and HSCT • Dual primary endpoint PFS in ITT (IRC) and CD30+ patients
4/2023	**Type D meeting to discuss major changes in the protocol:** • Revision of the study design from dual primary endpoints of PFS (IRC) in ITT and CD30 positive to single primary endpoint OS in ITT population • Key secondary endpoints changed to PFS (INV) and ORR (INV) • Reduced the number of patients from ~200 CD30-positive and ~200 CD30-negative to ~225 patients • Added a prespecified analysis of OS in the CD30-positive subgroup to the protocol as 1 of the secondary endpoints. • Added an interim futility analysis of OS. Post-meeting the Sponsor updated the interim analysis to also test for superiority. **FDA accepted the major changes but conveyed concerns about the control arm** • The Sponsor provided utilization data on R2 in US: 4.5% use in 3rd line setting for R/R LBCL
5/2024	**Pre-BLA meeting:** FDA conveyed concerns about R2: "R2 is not an approved regimen for patients with R/R DLBCL. The non-standard control arm makes interpretation of efficacy challenging, and this may pose significant issues for your application." • The Sponsor acknowledged that R2 is not approved for R/R DLBCL, referred to the NCCN guidelines and provided updated utilization data indicating that R2 use was 1.4% in the 3rd line setting for R/R LBCL.

Source: FDA review

Eligibility Criteria

The Applicant's Description:

Subjects enrolled into ECHELON-3 were 18 and older with R/R DLBCL with eligible subtypes; subjects must have received ≥2 prior lines of therapy and must be ineligible for HSCT or CAR T-Cell therapy. Subjects must have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 2. Prior HSCT and CAR T-cell therapy was allowed.

The FDA's Assessment:
The Agency agrees with the Applicant's summary of eligibility criteria.

Subjects with relapsed or refractory diffuse and transformed large B-cell lymphoma (R/R DLBCL) were eligible. Lymphoma subtype and cell of origin (GCB versus non-GCB) were histologically determined by the most recent local pathology assessment for the purposes of study eligibility and stratification. The following subtypes of LBCL were eligible for enrollment:

a. DLBCL not otherwise specified (NOS)
b. Intravascular large B-cell Lymphoma
c. DLBCL associated with chronic inflammation
d. EBV-positive NOS
e. ALK-positive
f. T-cell-/histiocyte-rich large B-cell lymphoma
g. Primary mediastinal large B-cell lymphoma
h. High-grade B-cell lymphoma with translocations of MYC and BCL2 and/or BCL6 (double-/triple-hit lymphoma)
i. High-grade NOS B-cell lymphomas
j. Primary cutaneous DLBCL (leg type)
k. DLBCL arising from transformed indolent lymphomas/leukemias
l. Follicular lymphoma Grade 3b

Patients were found to be ineligible for CAR T-cell therapy or HSCT if they met at least one of the qualifications below:

- One or more co-morbidities, including cardiac, pulmonary, renal or hepatic dysfunction that in the opinion of the investigator make the patient medically unfit to receive HSCT or CAR-T therapy.
- Active disease following induction and salvage chemotherapy
- Inadequate stem cell mobilization (for HSCT)
- Relapse following prior HSCT or CAR-T
- Unable to receive CAR-T therapy due to financial, geographic, insurance, or manufacturing issues

Furthermore, patients were enrolled regardless of the CD30 expression status. The eligibility criteria for assessment of CD30 expression are listed below:

- Subjects must have tumor tissue submitted to the central pathology lab for the determination of CD30 expression, which will be centrally determined by visual assessment for any detectable level of CD30 on tumor cells by IHC. The most recent biopsy available that contains viable DLBCL tissue should be submitted. If the CD30 results from the central pathology lab are not available prior to randomization, the subject may be stratified based on % CD30 expression from the local pathology lab. Subjects who are stratified based on local pathology lab results must have the same archived tumor

tissue sent in for central CD30 evaluation within 2 weeks of enrollment.

The efficacy determination may be limited by the lack of central review of the histologic diagnosis and the variability in assessment of CD30 expression status (local versus central).

Study Endpoints

The Applicant's Description:

The primary endpoint was OS in the ITT population. The key secondary endpoints included PFS and ORR per Lugano 2014 by investigator; other secondary endpoints included complete response (CR) rate and DOR per Lugano 2014 by investigator, incidence, severity, and seriousness of adverse events AEs per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0 and OS in CD30-positive subjects. Exploratory endpoints included association of CD30 expression and other biomarkers with ORR and PFS per Lugano 2014 by investigator, BV serum concentrations and ADA incidence, PRO (EQ-5D-5L), NCCN FACT-Lym, and healthcare utilization.

The FDA's Assessment:

The Agency agrees with the Applicant on description of endpoints. A protocol amendment submitted on 8/4/2023 included significant changes to the endpoints which the Agency agreed with as detailed below:

- Changed the primary endpoint from PFS to OS
- Changed the key secondary endpoints to include PFS and ORR
- Changed other secondary endpoints to include CR and DOR per Lugano 2014 by investigator
- Added the secondary endpoint of OS in the CD30-positive population
- Changed response assessment from "per BICR" to "per investigator"

Statistical Analysis Plan and Amendments

The Applicant's Description:

The SAP was finalized on 18-Jan-2024, prior to the database lock for the interim analysis of OS, and no amendments have occurred.

Determination of Sample Size: Approximately 225 subjects were to be enrolled in order to provide sufficient power to compare OS between the treatment arms. The null hypothesis of no difference in OS between the experimental and control arms were to be tested in the ITT population at a 2-sided alpha of 0.05 using a stratified log-rank test. Assuming median OS of 9 months in the control arm and a HR of 0.62, the median OS for the experimental arm was approximately 14.5 months.

The final analysis of OS was planned to be performed after approximately 170 OS events had occurred. An interim analysis of OS for both efficacy and futility was planned to be performed at approximately 128 OS events (0.75 information fraction). A non-binding futility criteria of HR >1.1 was used at the interim analysis. Efficacy boundaries at the interim and final OS

analysis were to be determined using an alpha spending approach with an O'Brien-Fleming boundary in order to maintain type I error control at a 2-sided alpha level of 0.05. Boundaries at the interim and final analysis were to be revised to reflect the actual information available as well as any previous alpha spending.

Under the assumptions above there is approximately 87% power to reject the null hypothesis of no difference in OS in the ITT population. Assuming a 10% risk of drop out from OS follow-up over 12 months, 225 subjects were expected to allow for accumulation of approximately 170 OS events within approximately 18 months of the last subject randomized.

Approximately 155 PFS events were expected to have occurred at the time of the interim analysis and 170 events are expected at the time of the final analysis. Assuming a HR of 0.62 and applying an alpha spending approach at a 2-sided alpha of 0.05 with a Pocock boundary there was approximately 86% power to reject the null hypothesis of no difference in PFS between the treatment arms.

Assuming an ORR of 30% for the control arm and 50% for the experimental arm (equivalent to a common odds ratio of approximately 2.35) and a 2-sided alpha of 0.05 there was approximately 87% power to reject the null hypothesis of no difference in ORR between the treatment arms.

Multiplicity adjustment: Multiplicity adjustment was accounted for in the SAP due to hypothesis testing for the OS primary endpoint and the key secondary endpoints of PFS per investigator and ORR per investigator. The specified approach provided strong control of the family-wise type I error rate at a 2-sided 5% level.

The OS, PFS, and ORR endpoints were to be tested sequentially with full alpha=0.05 initially allocated to OS. Testing of subsequent endpoints would occur when the preceding endpoint was statistically significant. Multiplicity adjustment for the interim analysis was achieved by implementing an alpha spending approach for OS and PFS. An O'Brien Fleming boundary was used for OS and a Pocock boundary was used for PFS. Testing of ORR was to be based on the interim analysis. Details of hypothesis testing and multiplicity are presented in the ECHELON-3 SAP.

Analysis Populations:

Intent-to-Treat (ITT) Analysis Set: Included all randomized subjects. Subjects were included in the treatment group assigned at randomization regardless of the actual treatment received.

Safety Analysis Set: Included all subjects who were randomized and received any amount of study drug (BV, lenalidomide, or rituximab). Treatment groups were determined using the actual treatment received, regardless of the randomization treatment assignment. Subjects receiving any dose of BV were grouped into the experimental group. Subjects who did not receive BV but received any dose of lenalidomide or rituximab were grouped into the control group.

Safety Run-In (SRI) Analysis Set: Included all subjects who were enrolled and received any amount of study drug (BV, lenalidomide, or rituximab) in the SRI part of the study.

Patient Reported Outcomes (PRO) Full Analysis Set: Included all randomized subjects who received any amount of study treatment and completed at least 1 PRO assessment at baseline.

Pharmacokinetics (PK) Analysis Set: Included all subjects who received BV and from whom at least 1 blood sample was collected and assayed for ADC or MMAE concentration.

All Enrolled Subjects Analysis Set: Included all subjects enrolled in the study (both the SRI and randomized portion of the study). Subjects were included in the treatment group assigned at enrollment.

Efficacy analyses: Analysis of OS and other key endpoints were conducted using the ITT analysis set. KM methods were used to estimate OS, with estimates presented by treatment arm. The stratified log rank test was used to obtain a p-value to test the null hypothesis of no difference in OS between the treatment arms. KM estimates of median OS and the 2-sided 95% confidence interval (CI) based on the log-log transformation were presented . Additional KM estimates of OS rates and associated 95% CIs were provided. A stratified Cox proportional hazards regression model was used to estimate a hazard ratio and 95% CI. Sensitivity analyses were also performed and are further described in the SAP.

Formal analyses of the key secondary endpoints of PFS and ORR, including hypothesis testing as appropriate, were conducted once the primary endpoint was significant. PFS was analyzed using similar methods as OS. The ORR and the 2-sided 95% exact CI were calculated for each treatment arm. Additional comparison of ORR between the 2 treatment arms was based on a 2-sided Cochran-Mantel-Haenszel test, stratified by the randomization stratification factors . Additional details of analysis of secondary and exploratory endpoints are included in the SAP.

Subgroup analyses: Subgroup analyses were conducted for OS and PFS endpoints. Prespecified subgroup variables included:

- Age (<65 years old, ≥65 years old)
- Sex (Male, Female)
- Race (White, Asian, other categories with sufficient sample size)
- Region (North America, Europe, Rest of World)
- Variables used for randomization stratification:
    - CD30 expression (<1%, ≥1%)
    - Cell of origin (GCB, non-GCB)
    - Prior HSCT (received, not received)
    - Prior CAR-T therapy (received, not received)
- Baseline ECOG performance status (0-1, 2)
- Bulky disease (1 or more lesions >7.5cm in the longest dimension)
- Baseline International Prognostic Index (IPI) (<3, ≥3)
- Refractory to last prior anti-lymphoma therapy
- Double expressor
- Double- or triple-hit lymphoma

The FDA's Assessment:

The FDA agrees with the Applicant's position. FDA noted that the following rule of pooling of strata is important and affected the stratified analyses of primary and key secondary endpoints. Section 6.9 of the SAP (Amendment 6, dated 23 Aug 2023) stated that "Pooling of strata will occur if <5% of the subjects in the ITT population are present in a specific stratum or if the stratified model otherwise fails to converge. Pooling will be performed sequentially in the following order until the above criteria are met for the remaining strata: (1) Prior hematopoietic stem cell transplant, (2) Prior CAR-T therapy, (3) CD30 expression (4) Cell of origin."

Protocol Amendments

The Applicant's Description:

The original version of the protocol was approved on 29-Jan-2020. The protocol was amended 6 times during the course of the study. Table 10 only includes amendments where substantial changes were made.

Table 10: Applicant- Key Changes made to the ECHELON-3 Study Protocol

Amendment	Date	Key Changes
Original	29-Jan-2020	Not applicable
1	24-Apr-2020	• Inclusion criteria modified • Added dose modifications for lenalidomide based on renal impairment • Subjects now must receive primary G-CSF prophylaxis
3	24-Mar-2021	Inclusion criteria modified
5	04-Aug-2023	• Changed primary endpoint to OS and changed key and other secondary • Changed response assessment from "per BICR" to "per investigator" for PFS and ORR • Reduced planned number of subjects to 225 (approximately 113 per arm) • Added new statistical considerations for updated study design, including interim analysis for efficacy and futility and final analysis for OS Provided lenalidomide dose modification guidance for patients with renal impairment

The FDA's Assessment:

The FDA agrees with the Applicant's position. See Table 9 for details regarding interactions with the Applicant regarding protocol amendments.

8.1.2. Study Results

Compliance with Good Clinical Practices

Data:

Investigator sites and service provider audits were conducted by the sponsor to assess compliance with Good Clinical Practice (GCP) and the ECHELON-3 protocol. Audit certificates for this study are included in Appendix 16.1.8 of the CSR.

The Applicant's Position:

The protocol for this study was designed in accordance with the general ethical principles outlined in the Declaration of Helsinki . The conduct of all aspects of the study, including methods for obtaining informed consent, were also in accordance with principles enunciated in the declaration, the International Council for Harmonization Good Clinical Practices, and applicable regional regulations/guidelines.

The FDA's Assessment:

The Agency agrees with the Applicant's description of methods used to evaluate compliance with Good Clinical Practices.

Financial Disclosure

Data:

There are no investigators with disclosable financial and equity interests/arrangements in the ECHELON-3 study (Form FDA 3454, m1.3.4).

The Applicant's Position:

The integrity of ECHELON-3 data is not affected by the financial and equity interests of the investigators.

The FDA's Assessment:

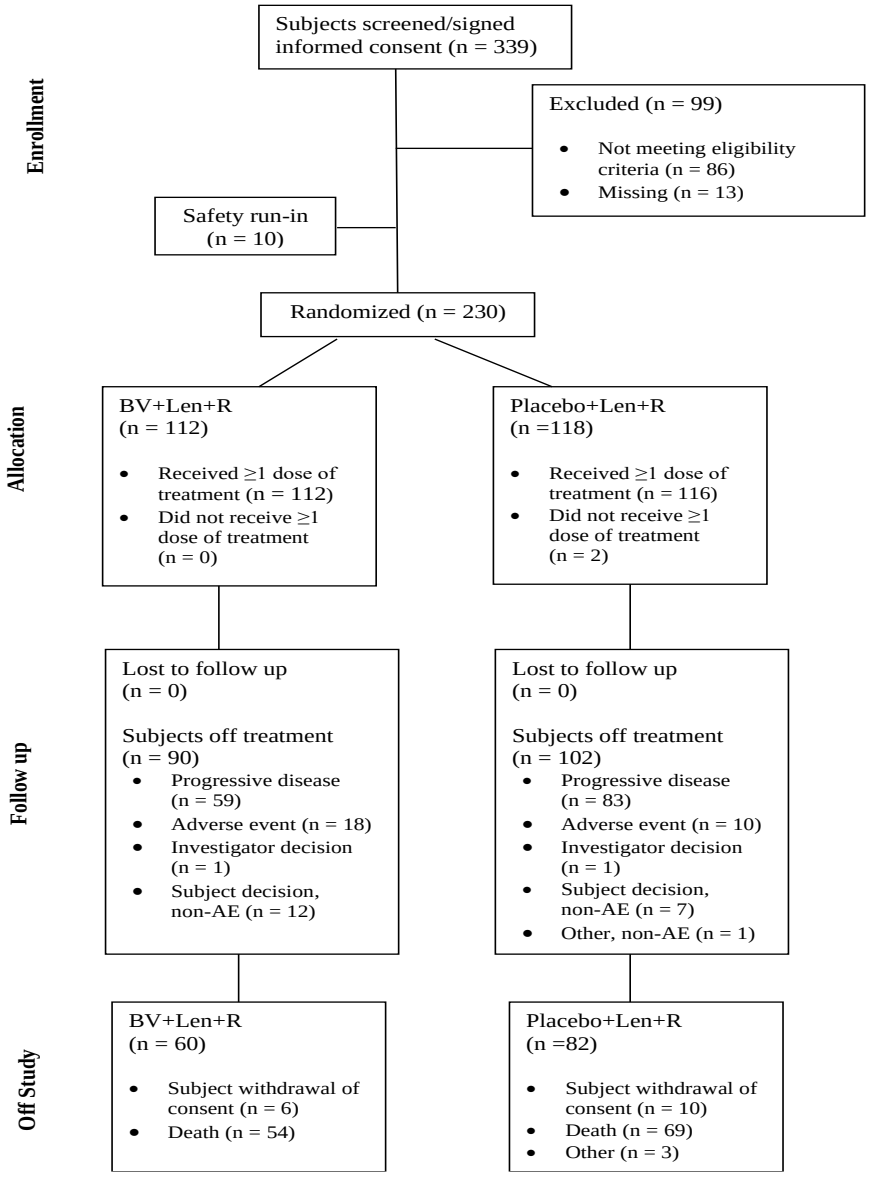
The Agency agrees that the financial disclosure information provided do not indicate a conflict of interest and measures to mitigate potential for investigator bias were undertaken. See also section 19.2.

Patient Disposition

Data:

Subjects disposition is summarized in Figure 9.

Figure 9: Applicant-Summary of Subject Disposition



Source: m5.3.5.1, ECHELON-3 CSR, Table 14.1.1.1.1, Table 14.1.1.1.2, and Table 14.1.2

The Applicant's Position:

Of the 230 subjects randomized, 112 were randomized to BV+Len+R arm and 118 subjects were randomized to placebo+Len+R arm. In the BV+Len+R arm, 112 (100%) subjects received at least 1 dose of BV+Len+R and 116 (98%) subjects received at least 1 dose of placebo+Len+R in the placebo+Len+R arm. At the time of the data cutoff, 22 (20%) subjects in the BV+Len+R arm and 14 (12%) subjects in the placebo+Len+R arm were still on treatment. Of the 90 (80%) subjects off treatment in the BV+Len+R arm, 30 (27%) were in long-term follow up; in the placebo+Len+R arm, of the 102 (86%) subjects off treatment, 22 (19%) subjects were in long-term follow up. For subjects that discontinued treatment, progressive disease (62%) and AEs (12%) were the most common primary reasons. The most frequent reasons for

discontinuation from the study were death (54 subjects [48%] and 69 subjects [58%] in BV+Len+R arm and placebo+Len+R arm, respectively) and subject withdrawal (6 subjects [5%] and 10 subjects [8%] in BV+Len+R arm and placebo+Len+R arm, respectively).

The FDA's Assessment:

The Agency agrees with the Applicant's position. Progressive Disease was the leading reason for treatment discontinuation in both arms. The Agency revised the number of patients that withdrew due to non-AE reasons after reviewing the narratives. Table 11 and Table 12 below provide the breakdown of patient disposition and review of non-AE withdrawals.

Table 11: Patient Disposition in ECHELON-3

	Bv+R2 N=112	Pbo+R2 N=118
Treatment status, n (%)		
Treatment ongoing	22 (20)	14 (12)
Treatment discontinued	90 (80)	102 (86)
PD	59 (53)	84 (71)
AE	21 (19)	10 (8)
Withdrawal by patient (non-AE)	9 (8)	6 (6)
Physician decision	1 (0.8)	0 (0)
Other	0 (0)	1 (0.8)
Study status, n (%)		
Study discontinued	60 (54)	82 (69)

Source: FDA analysis

Table 12: Patient Withdrawal for Non-AE Reasons in ECHELON-3

Arm	Most recent response	Reason for discontinuation by patient
BV+R2	PD (n=3)	• Became eligible for HSCT • Impaired QoL • Wanted to stop
	CR (n=3)	• Unhappy with study • Want to stop (2)
	No assessment (n= 3)	• Withdrawal of consent

Arm	Most recent response	Reason for discontinuation by patient
Pbo+R2	PD (n=2)	• reduced QoL • withdrawal of consent
	CR (n=2)	• distance is too far
	PR (n=1)	• withdrawal of consent
	No assessment (n= 1)	• patient requested hospice

Source: FDA analysis

Reviewer comment: The Applicant's analysis included 18 patients in the BV arm who had discontinued treatment due to patient decision and were considered non-AE related discontinuations. Upon review of the narratives and reasons for the patient withdrawal, these were considered AE-related per the FDA analysis.

Protocol Violations/Deviations

Data:

Of the 230 subjects randomized in this study, 12 subjects (11%) in the BV+Len+R arm and 16 subjects (14%) in the placebo+Len+R arm had an important protocol deviation (IPD or protocol violation). The most common IPD was "concomitant medications" (12 [including 9 missed G-CSF administration, and 3 administration of a prohibited concomitant medication]), followed by "study conduct" (6 out of 230 [1 accidental subject unblinding, 1 missed protocol-required assessments, 4 missed G-CSF administration]) and "informed consent" (5 out of 230 [all due to delayed reconsenting to updated informed consent forms]). No IPD's due to lack of investigator oversight were reported in the study (m5.3.5.1, ECHELON-3 CSR, Listing 16.2.2.1). A summary of IPDs is presented in m5.3.5.1, ECHELON-3 CSR, Table 14.1.5.1.

Per the study clinical monitoring plan, IPD criteria were defined for the study and periodically assessed per ICH E3 guidance.

The Applicant's Position:

A sensitivity analysis for OS and PFS was performed excluding subjects with IPDs. The results of these sensitivity analyses were generally consistent with the overall study results. Therefore, the deviations that occurred in the ECHELON-3 trial were assessed to have negligible impact on the overall interpretation of the trial results.

The FDA's Assessment:

The Agency agrees with the Applicant's position that the protocol deviations are unlikely to impact the overall study results and conclusions.

Table of Demographic Characteristics

Data:

Demographics in ECHELON-3 study are provided in Table 13.

Table 13: Applicant-Demographics- ITT Analysis Set

	BV+Len+R (N=112) n (%)	Placebo+Len+R (N=118) n (%)	Total (N=230) n (%)
Age (yrs)			
N	112	118	230
Mean (STD)	69.2 (12.7)	65.8 (14.5)	67.4 (13.8)
Median	74.0	70.0	71.0
Min, Max	29, 87	21, 89	21, 89
Age arm, n (%)			
< 65 years	33 (29.5)	42 (35.6)	75 (32.6)
≥ 65 years	79 (70.5)	76 (64.4)	155 (67.4)
Gender, n (%)			
Male	60 (53.6)	70 (59.3)	130 (56.5)
Female	52 (46.4)	48 (40.7)	100 (43.5)
Ethnicity, n (%)			
Hispanic, Latino/a, or of Spanish Origin	4 (3.6)	5 (4.2)	9 (3.9)
Not of Hispanic, Latino/a, or Spanish Origin	90 (80.4)	84 (71.2)	174 (75.7)
Unknown	0	1 (0.8)	1 (0.4)
Not Reportable	18 (16.1)	28 (23.7)	46 (20.0)
Race, n (%)			
American Indian or Alaska Native	0	1 (0.8)	1 (0.4)
Asian	28 (25.0)	32 (27.1)	60 (26.1)
White	65 (58.0)	56 (47.5)	121 (52.6)
Other	0	1 (0.8)	1 (0.4)
Unknown	1 (0.9)	0	1 (0.4)
Not Reportable	18 (16.1)	28 (23.7)	46 (20.0)
ECOG Performance Status[a], n (%)			
Grade 0	42 (37.5)	41 (34.7)	83 (36.1)
Grade 1	58 (51.8)	64 (54.2)	122 (53.0)

	BV+Len+R (N=112) n (%)	Placebo+Len+R (N=118) n (%)	Total (N=230) n (%)
Grade 2	12 (10.7)	13 (11.0)	25 (10.9)

ECOG= Eastern Cooperative Oncology Group; STD= standard deviation
a. Values presented are the last non-missing value on or before the first dose date. If a subject did not receive any dose, the randomization/enrollment date is used in place of the first dose date.
Source: m5.3.5.1, ECHELON-3 CSR, Table 14.2.1.1

The Applicant's Position:

Overall, the demographics of subjects in ECHELON-3 were similar between treatment arms.

The median age in ECHELON-3 ranged from 70 to 74. This is consistent with epidemiological data, which shows the average age at diagnosis in DLBCL is approximately 65 years old, and DLBCL in children is rare (Kanas 2022). In the US, the incidence of DLBCL is generally higher in males and highest in Hispanics (7.2/100,000), non-Hispanic Whites (6.7/100,000) and non-Hispanic Asian/Pacific Islanders (Kanas 2022; National Cancer Institute 2024)). Similarly, the majority of the subjects in ECHELON-3 were male and non-Hispanic white, followed by Asian. As the majority of patients were enrolled outside of the US, race was "not reportable" in approximately 20% of subjects due to local regulations limiting collection of race data.

The FDA's Assessment:
The Agency agrees with the Applicant on the general description of patient demographics in ECHELON-3. The demographics of the trial population were not fully representative of a United States R/R LBCL patient population with only 9% of patients enrolled in the US. Further, there was limited representation of African American and Hispanic patients. Table 14 below shows a summary of pertinent demographics data in ECHELON-3.

Table 14: Key Demographics Elements in ECHELON-3

Demographics	Bv+R2 N=112	Pbo+R2 N=118
Age (years)		
Median	74	70
≥ 65y (%)	71	64
Race (%)		
White	58	48
Black/AA	0	0
Asian	25	27
Not reportable	16	24
Ethnicity, Hispanic (%)	3.6	4.2
Geographic region (%)		
US	10	8
Europe	45	51

Demographics	Bv+R2 N=112	Pbo+R2 N=118
Asia-Pacific	29	33
North America	27	16

Source: FDA analysis

In response to an FDA information request, the Applicant provided additional safety and efficacy data for a pool of patients with LBCL treated with BV monotherapy or BV in combination and a separate pool of patients who received BV in combination in any Phase 3 trial Applicant-sponsored trial to address the limitations of the ECHLON-3 trial and its applicability to a US population. This analysis provided additional data to address the limited data in Hispanic patients (n = 23 with DLBCL and 65 in phase 3 trials) and Black patients (N = 13 with DLBCL and 28 in phase 3 trials) noted in the ECHELON-3 trial. There were no substantial differences in the safety or efficacy observed across these subgroups and the data is supportive to demonstrate applicability of a US R/R population.

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

Data:

Subject baseline characteristics in ECHELON-3 study are provided in Table 15.

Table 15: Applicant- Baseline Characteristics-ITT Analysis Set

	BV+Len+R (N=112) n (%)	Placebo+Len+R (N=118) n (%)	Total (N=230) n (%)
Disease diagnosis, n (%)			
ALK-positive DLBCL	0	1 (0.8)	1 (0.4)
DLBCL arising from transformed follicular lymphoma or marginal zone lymphoma	23 (20.5)	18 (15.3)	41 (17.8)
DLBCL associated with chronic inflammation	1 (0.9)	1 (0.8)	2 (0.9)
DLBCL, NOS	63 (56.3)	64 (54.2)	127 (55.2)
EBV-positive DLBCL, NOS	3 (2.7)	5 (4.2)	8 (3.5)
High-grade B-cell lymphoma with translocations of MYC or BCL2 and/or BCL6 (double-/triple-hit lymphoma)	12 (10.7)	15 (12.7)	27 (11.7)
High-grade NOS B-cell lymphoma	2 (1.8)	4 (3.4)	6 (2.6)
Primary cutaneous DLBCL (leg type)	2 (1.8)	4 (3.4)	6 (2.6)
Primary mediastinal large B-cell lymphoma	5 (4.5)	2 (1.7)	7 (3.0)
T-cell-/histiocyte-rich large B-cell lymphoma	1 (0.9)	4 (3.4)	5 (2.2)
Time from initial diagnosis of DLBCL to randomization/enrollment (months)			
N	110	113	223
Mean (STD)	32.38 (35.11)	39.39 (48.71)	35.93 (42.59)

	BV+Len+R (N=112) n (%)	Placebo+Len+R (N=118) n (%)	Total (N=230) n (%)
Median	20.39	18.79	19.65
Min, Max	3.3, 186.7	2.6, 218.7	2.6, 218.7
Disease status in relation to most recent systemic therapy for DLBCL[a], n (%)			
Refractory	98 (87.5)	96 (81.4)	194 (84.3)
Relapsed	13 (11.6)	21 (17.8)	34 (14.8)
Unknown	1 (0.9)	1 (0.8)	2 (0.9)
Disease status in relation to initial systemic therapy for DLBCL[a], n (%)			
Refractory	64 (57.1)	64 (54.2)	128 (55.7)
Relapsed	47 (42.0)	49 (41.5)	96 (41.7)
Unknown	1 (0.9)	5 (4.2)	6 (2.6)
Chromosomal or molecular abnormalities in BCL-2, BCL-6, or MYC[b], n (%)			
BCL-2 rearrangement	23 (20.5)	21 (17.8)	44 (19.1)
BCL-6 rearrangement	16 (14.3)	16 (13.6)	32 (13.9)
MYC rearrangement	18 (16.1)	16 (13.6)	34 (14.8)
BCL-2 protein overexpression	43 (38.4)	45 (38.1)	88 (38.3)
BCL-6 protein overexpression	45 (40.2)	39 (33.1)	84 (36.5)
MYC protein overexpression	23 (20.5)	21 (17.8)	44 (19.1)
None of the above	38 (33.9)	47 (39.8)	85 (37.0)
Transformed DLBCL, n (%)			
Yes	32 (28.6)	27 (22.9)	59 (25.7)
No	80 (71.4)	91 (77.1)	171 (74.3)
Prior disease diagnosis for transformed DLBCL, n (%)			
Chronic Lymphocytic Leukemia (CLL)	6 (5.4)	5 (4.2)	11 (4.8)
Small Lymphocytic Leukemia (SLL)	0	1 (0.8)	1 (0.4)
Follicular Lymphoma	21 (18.8)	16 (13.6)	37 (16.1)
Marginal Zone Lymphoma	4 (3.6)	3 (2.5)	7 (3.0)
Mucosa-associated lymphoid tissue lymphoma (MALT)	1 (0.9)	0	1 (0.4)
Other	0	2 (1.7)	2 (0.9)
Not Applicable	80 (71.4)	91 (77.1)	171 (74.3)
Diagnosed with HIV, n (%)			
Yes	1 (0.9)	1 (0.8)	2 (0.9)
No	111 (99.1)	117 (99.2)	228 (99.1)

	BV+Len+R (N=112) n (%)	Placebo+Len+R (N=118) n (%)	Total (N=230) n (%)
IPI score at time of enrollment, n (%)			
0	2 (1.8)	2 (1.7)	4 (1.7)
1	16 (14.3)	14 (11.9)	30 (13.0)
2	27 (24.1)	31 (26.3)	58 (25.2)
3	33 (29.5)	38 (32.2)	71 (30.9)
4	29 (25.9)	27 (22.9)	56 (24.3)
5	5 (4.5)	6 (5.1)	11 (4.8)
Ann Arbor Stage at Study Entry, n (%)			
Stage I	14 (12.5)	7 (5.9)	21 (9.1)
Stage II	15 (13.4)	13 (11.0)	28 (12.2)
Stage III	14 (12.5)	33 (28.0)	47 (20.4)
Stage IV	69 (61.6)	65 (55.1)	134 (58.3)
Extranodal Disease involvement at Study Entry, n (%)			
No involvement	25 (22.3)	33 (28.0)	58 (25.2)
1 site	31 (27.7)	30 (25.4)	61 (26.5)
> 1 site	56 (50.0)	55 (46.6)	111 (48.3)
Elevated lactate dehydrogenase at study entry, n (%)			
Yes	67 (59.8)	76 (64.4)	143 (62.2)
No	44 (39.3)	39 (33.1)	83 (36.1)
Unknown	1 (0.9)	3 (2.5)	4 (1.7)
Bulky disease at study entry[c], n (%)			
Yes	16 (14.3)	35 (29.7)	51 (22.2)
No	95 (84.8)	82 (69.5)	177 (77.0)
Unknown	1 (0.9)	1 (0.8)	2 (0.9)
CD30 Status[d], n (%)			
≥1%	36 (32.1)	38 (32.2)	74 (32.2)
<1%	76 (67.9)	80 (67.8)	156 (67.8)
Cell of Origin[e], n (%)			
GCB	51 (45.5)	54 (45.8)	105 (45.7)
Non-GCB	61 (54.5)	64 (54.2)	125 (54.3)
Prior hematopoietic stem cell transplant[e], n (%)			
Received	10 (8.9)	18 (15.3)	28 (12.2)
Not Received	102 (91.1)	100 (84.7)	202 (87.8)

	BV+Len+R (N=112) n (%)	Placebo+Len+R (N=118) n (%)	Total (N=230) n (%)
Prior CAR-T Therapy[e], n (%)			
Received	32 (28.6)	35 (29.7)	67 (29.1)
Not Received	80 (71.4)	83 (70.3)	163 (70.9)

a. Relapsed refractory status is derived from prior therapy data. Refractory: no response or response lasting less than 6 months from last treatment end date; relapsed: response lasting at least 6 months from last treatment end date.
b. Subjects may appear in multiple categories.
c. Bulky disease is defined as at least 1 target lesions with longest diameter >7.5 cm by investigator assessment.
d. CD30 status per central result. When central result is not available local result is used.
e. Based on post randomization corrected values.
Data cutoff: 22JAN2024 Snapshot: 21FEB2024
Source: m5.3.5.1, ECHELON-3 CSR, Table 14.2.2.1

The Applicant's Position:

Baseline disease characteristics were generally balanced between treatment arms and represent R/R DLBCL subjects with high unmet need. The distribution of DLBCL diagnoses in ECHELON-3 is consistent with the WHO Classification which identified large B-cell lymphomas as a heterogenous collection of clinicopathological entities in which DLBCL-NOS is the most frequently occurring (Kurz 2023). Most subjects had advanced disease at study entry with 74% and 83% of subjects in the BV+Len+R and placebo+Len+R, respectively, having Stage III/IV disease and approximately 60% of subjects in both arms having high-intermediate to high IPI.

Other biological factors associated with poor outcomes in patients with DLBCL include non-GCB subtype, (Li 2018) and double- or triple-hit lymphoma involving rearrangements of MYC and BCL2 or BCL6 (Sehn 2021). In ECHELON-3, the majority of subjects had non-GCB subtype (54% across both arms), and approximately 11% across both arms had high-grade double- or triple- hit lymphoma with rearrangements in MYC and BCL2 or BCL6.

The majority of subjects in both arms were refractory to their last line of prior therapy and had primary refractory disease. This is consistent with recent and historical data showing approximately 70% of subjects will be R/R after the second line of treatment within 5 years and approximately 50% of subjects are R/R to frontline treatment (Susanibar-Adaniya 2021). The number of subjects who received prior CAR-T is consistent with recent real-world data which reports that approximately 38% of subjects receive CAR-T in the third line . Approximately 50% to 60% of patients do not respond to or relapse after CAR-T therapy (Zheng 2022).

In summary, the baseline disease characteristics observed in ECHELON-3 are generally representative of a contemporary population of R/R DLBCL subjects with poor prognosis and high unmet need in the third-line setting.

The FDA's Assessment:

FDA agrees with the Applicant's presentation of patients' baseline characteristics. The patient population is heterogeneous with respect to histology, with the majority having DLBCL NOS

and few patients having high-grade B-cell lymphoma and other LBCL subtypes. Additionally, there is lack of central review of the histologic diagnosis which limits the interpretation of results. Furthermore, central CD30 assessment was conducted in only 80% of the patients which may raise some uncertainty with the projected CD30 expression status. Table 16 below demonstrates the key baseline characteristics of patients in ECHELON-3.

Table 16: Key Baseline Characteristics in ECHELON-3

Disease Characteristics	Bv+R2 N=112 %	Pbo+R2 N=118 %
Stage III-IV	74	83
Bulky disease at study entry[a]	14	30
CD30 Status ≥1%[b]	32	32
Lines of systemic tx for LBCL (median)	2	3
Prior HSCT	9	15
Prior CAR-T	29	30
Transformed LBCL	29	23
FL, MZL	23	18
Richter's Transformation	5	5
DLBCL, NOS	76	68
Non-GCB[c]	43	37
HGBL (DH/TH)	14	18
PMBCL	4.5	1.7
Other	5.5	12.3

a Bulky disease was defined as at least 1 target lesion with longest diameter >7.5 cm by investigator assessment.
b Central CD30 assessment in 80% of the patients
c Local assessment
Source: FDA analysis

Patients in the Pbo+R2 arm were more heavily treated and had higher number of prior HSCT. There were comparable number of prior CAR-T in the 2 arms. Table 17 below shows a summary of prior therapies in ECHELON-3.

Table 17: Prior Therapies >5% in ECHELON-3

Prior Tx >5%	Bv+R2 N=112 %	Pbo+R2 N=118 %
Prior therapies		
Median	2	3
0	0.9[a]	0

Prior Tx >5%	Bv+R2 N=112 %	Pbo+R2 N=118 %
1[b]	7	6
2	46	40
3	26	36
>3	21	18
Prior therapy description		
RCHOP +/- 2 cycles of R	76	71
Prior CAR-T	29	30
R-GemOx	14	24
Bispecifics	13	17
Prior HSCT	9	15
Pola+R-CHP	0	0.8
LEN containing regimen	0	0
BV containing regimen	0	0

a one patient with transformed disease mistakenly enrolled without prior systemic therapy
b For subjects with transformed LBCL at least the last systemic therapy used must have been for LBCL
RCHOP: rituximab, cyclophosphamide, doxorubicin, prednisone, rituximab and vincristine;
GemOx: gemcitabine, oxaliplatin; Len: lenalidomide
Source: FDA and Applicant's analyses

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data/The Applicant's Position:

Site staff administered study treatment at the site, thus ensuring treatment compliance. Median RDI for BV was 94.4% (m5.3.5.1 ECHELON-3 CSR, Table 14.4.2.1). Concomitant medications for individual subjects are presented in m5.3.5.1, ECHELON-3 CSR, Listing 16.2.10.6. All subjects were required to take low-dose aspirin (at least 50 mg daily) as prophylactic anticoagulation, anti-viral prophylaxis (subjects at high risk for hepatitis B reactivation), and G-CSF prophylaxis starting 1 to 3 days after each BV/placebo administration (filgrastim, pegfilgrastim, or filgrastim biosimilars were allowed; G-CSF type, formulation, dose, and duration per institutional guidelines). All supportive measures consistent with optimal subject care were provided throughout the study according to institutional standards.

The FDA's Assessment:

The Agency agrees with the Applicant's position.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

The OS analysis based on the data cutoff date of 22-Jan-2024 is presented in Table 18 and Figure 10. With a median follow-up time of 16.4 months, the risk of death was reduced by 37.1% in the

BV+Len+R arm vs the placebo+Len+R arm (stratified HR=0.629; 95% CI: 0.445, 0.891; 2-sided p=0.0085). The prespecified O'Brien Flemming efficacy boundary (2-sided p=0.0232) was crossed. The median OS was 13.8 months (95% CI: 10.3, 18.8) for the BV+Len+R arm vs 8.5 months (95% CI: 5.4, 11.7) for the placebo+Len+R arm. The estimated percentage of subjects alive at 12 months was 55.4 % (95% CI: 44.9%, 64.7%) for the BV+Len+R arm and 36.8% (95% CI: 27.1%, 46.6%) for the placebo+Len+R arm. This trend of improved survival in patients on the BV+Len+R arm continues out beyond 24 months. SAP defined sensitivity analyses of OS were also performed; the results generally support the results of OS analysis and demonstrate robustness of the primary analysis data.

Table 18: Applicant-Overall Survival- ITT Analysis Set

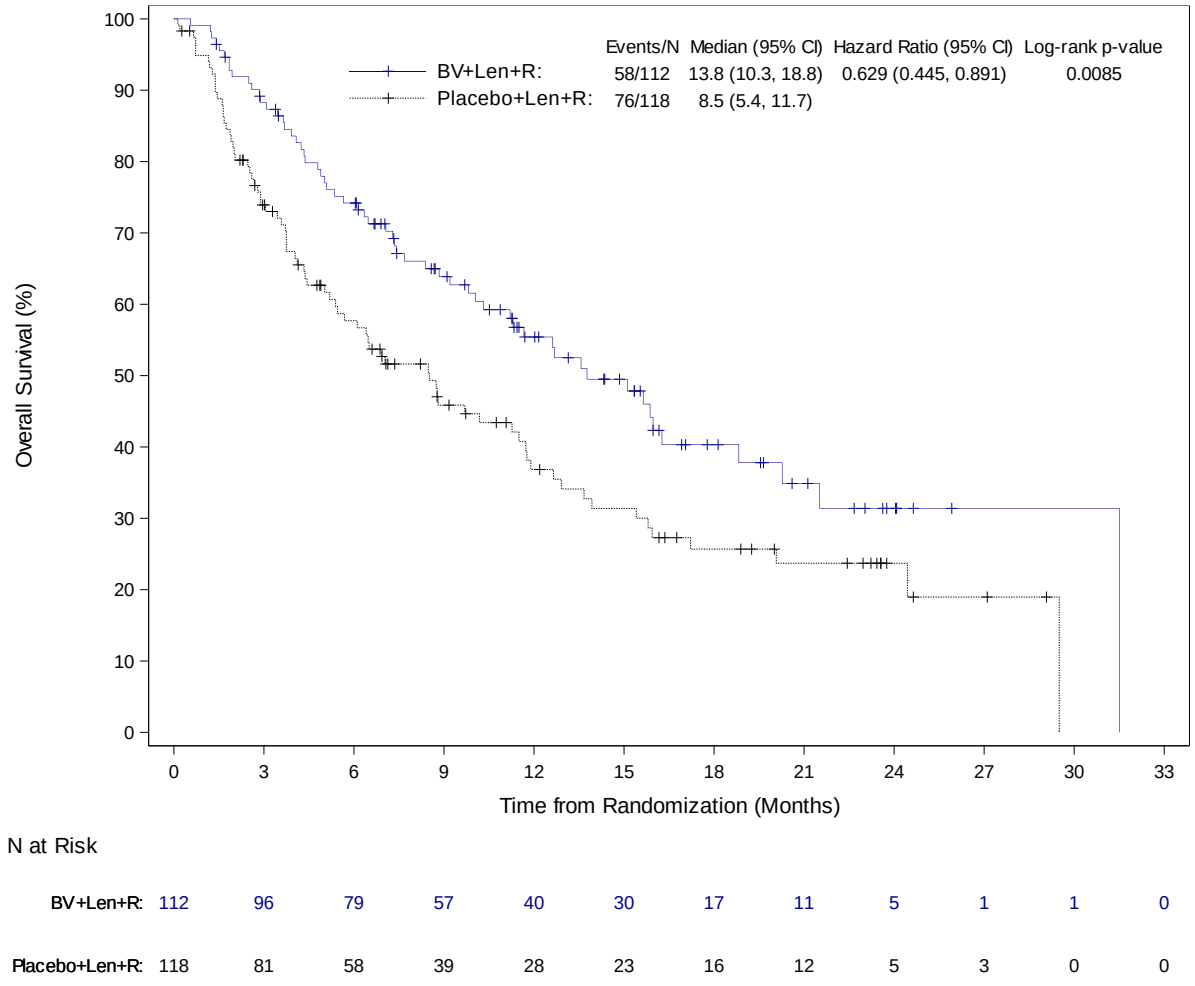
	BV+Len+R (N=112)	Placebo+Len+R (N=118)	Total (N=230)
Number of deaths, n (%)	58 (51.8)	76 (64.4)	134 (58.3)
Hazard ratio (95% CI) [a]	0.629 (0.445, 0.891)		
P-value [b]	0.0085		
Duration of OS (months)			
Median (95% CI) [c]	13.8 (10.3, 18.8)	8.5 (5.4, 11.7)	11.3 (8.7, 13.6)
Q1, Q3	5.7, 31.5	2.9, 20.1	4.0, 24.4
Min, Max[d]	0.6, 31.5	0.1, 29.5	0.1, 31.5
OS rate at			
3 months (95% C.I.) [c]	88.2% (80.6%, 93.0%)	73.9% (64.9%, 81.0%)	81.0% (75.2%, 85.5%)
6 months (95% C.I.) [c]	74.2% (64.8%, 81.4%)	57.7% (47.9%, 66.3%)	65.8% (59.1%, 71.7%)
9 months (95% C.I.) [c]	63.9% (53.8%, 72.3%)	45.9% (36.0%, 55.2%)	54.8% (47.7%, 61.3%)
12 months (95% C.I.) [c]	55.4% (44.9%, 64.7%)	36.8% (27.1%, 46.6%)	46.0% (38.8%, 52.9%)
15 months (95% C.I.) [c]	49.5% (38.7%, 59.4%)	31.4% (22.0%, 41.2%)	40.3% (33.0%, 47.4%)
18 months (95% C.I.) [c]	40.3% (29.1%, 51.2%)	25.7% (16.8%, 35.4%)	32.9% (25.6%, 40.3%)
21 months (95% C.I.) [c]	34.9% (23.2%, 46.8%)	23.7% (15.0%, 33.6%)	29.4% (22.1%, 37.1%)
24 months (95% C.I.) [c]	31.4% (19.4%, 44.1%)	23.7% (15.0%, 33.6%)	28.1% (20.7%, 35.9%)
27 months (95% C.I.) [c]	31.4% (19.4%, 44.1%)	19.0% (9.3%, 31.2%)	24.6% (15.9%, 34.2%)
30 months (95% C.I.) [c]	31.4% (19.4%, 44.1%)	-	12.3% (1.6%, 34.7%)
Duration of OS follow-up (months) [e]			
Median (95% CI) [c]	15.5 (12.2, 18.1)	18.9 (12.2, 23.2)	16.4 (14.4, 19.3)
Q1, Q3	10.9, 22.7	8.2, 23.6	9.2, 23.2
Min, Max[d]	0.6+, 31.5+	0.1+, 29.5+	0.1+, 31.5+

Overall survival (OS) is time from randomization to death due to any cause. OS is estimated using Kaplan-Meier method.

a. Hazard ratio and 95% CI based on a stratified cox regression model with stratification factors cell of origin (GCB, non-GCB) and CD30 status (≥1%, <1%) at randomization. Hazard ratio <1 favors BV+Len+R. Nonbinding futility boundary HR=1.1.

b. Two-sided p-value from a stratified log-rank test with stratification factors cell of origin (GCB, non-GCB) and CD30 status (≥1%, <1%) at randomization. O'Brien Flemming efficacy boundary 2-sided p value=0.0232.
c. Calculated using the complementary log-log transformation method (Collett, 1994).
d. + indicates a censored observation.
e. Duration of follow-up calculated using reverse Kaplan-Meier method.
Source: m5.3.5.1, ECHELON-3 CSR, Table 14.3.4.1

Figure 10: Applicant- Kaplan-Meier Plot of Overall Survival- ITT Analysis Set

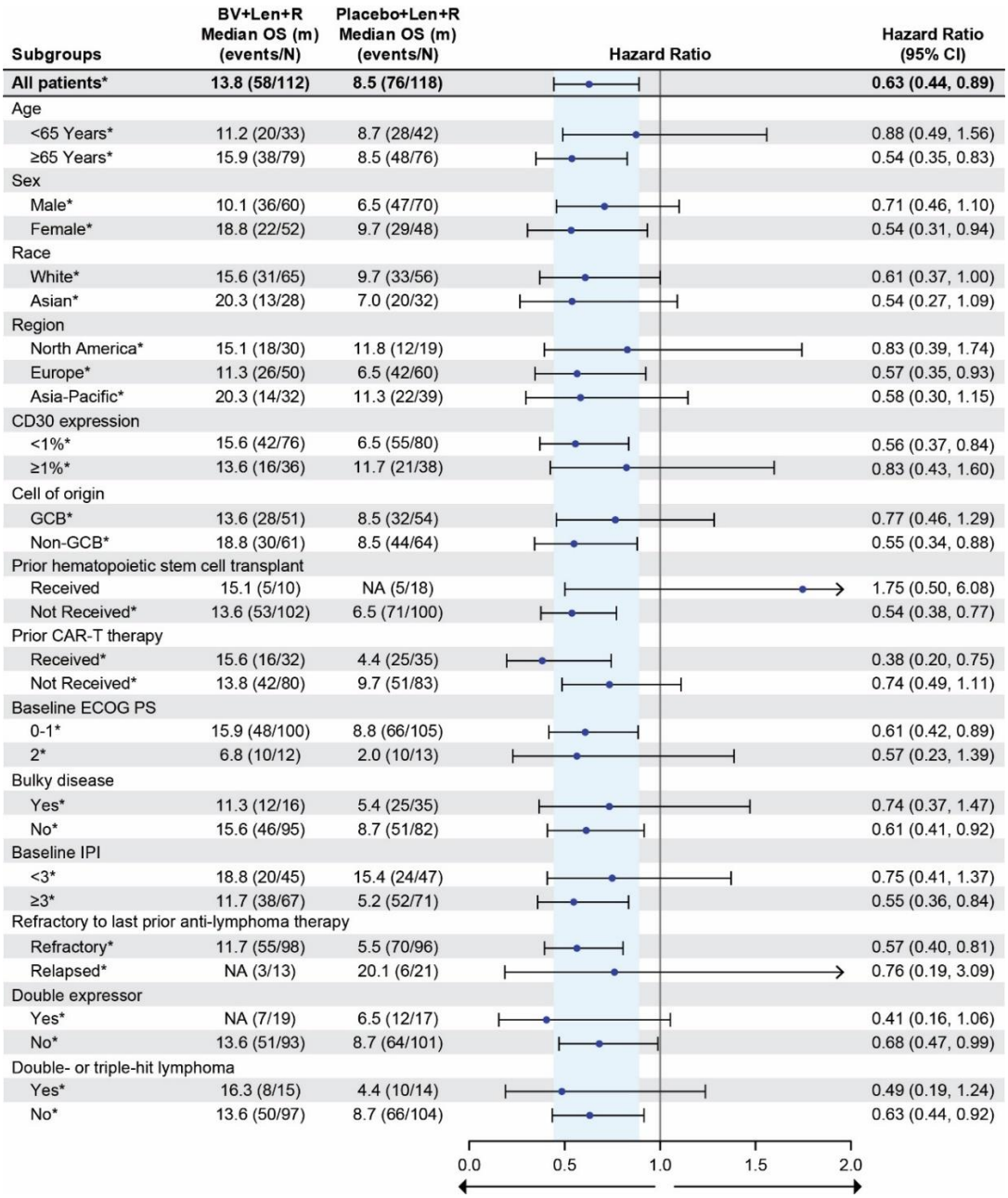


Source: m5.3.5.1, ECHELON-3 CSR, Figure 14.3.4.1

Subgroup analysis: Analyses of OS by selected baseline characteristics, prognostic factors, and histological subtype in ECHELON-3 is presented in Figure 11. HR point estimates for OS are less than 1 for all prespecified subgroups defined by stratification factors including CD30 expression, cell of origin, prior CAR T-cell therapy, and prior HSCT (not received), with the exception of HSCT received. The HR for OS in subjects who received HSCT was 1.75 (95% CI:

0.50, 6.08), though the number of subjects was small with a wide 95% CI (10 subjects in the BV+Len+R arm and 18 subjects in the placebo+Len+R arm). While subgroup analyses may be helpful in assessing consistency in treatment effect, interpretation of individual subgroup results has limitations due to small sample size

Figure 11: Applicant- Subgroup Analysis of Overall Survival (ITT) Analysis Set



* indicates subgroup with HR<1.
Source: m5.3.5.1, ECHELON-3 CSR, Figure 14.3.4.2

The Applicant's Position:

Results from the ECHELON-3 study demonstrated clinically meaningful and statistically significant survival benefit with BV+Len+R compared to that observed with placebo+Len+R. The results of SAP-defined sensitivity analysis support the results of OS analysis and demonstrate robustness of the primary analysis data. Additionally, the OS benefit among subjects in BV+Len+R arm was generally consistent across prespecified subgroups.

The FDA's Assessment:

FDA agrees with the Applicant's position regarding the OS primary analyses results at the pre-specified interim analysis. FDA did additional subgroup analyses among the ITT population by including the baseline variables of the following: number of prior lines of therapy, histologic diagnosis, diagnosis of transformed lymphoma, and prior lymphoma diagnosis before transformed lymphoma). These were included in the adbase.xpt dataset submitted on 08/07/2024.

Figure 12

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Figure 12 shows the subgroup analyses of OS by FDA.

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Figure 12: FDA- Subgroup Analysis of Overall Survival (ITT) Analysis Set

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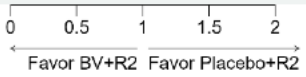
Subgroup	BV+R2 Median OS (m) (events / N)	Placebo+R2 Median OS (m) (events / N)	HR (95% CI)
All patients	13.8 (58 / 112)	8.5 (76 / 118)	0.63 (0.44, 0.89)
Age			
<65 Years	11.2 (20 / 33)	8.7 (28 / 42)	0.88 (0.49, 1.56)
>=65 Years	15.9 (38 / 79)	8.5 (48 / 76)	0.54 (0.35, 0.83)
Sex			
Male	10.1 (36 / 60)	6.5 (47 / 70)	0.71 (0.46, 1.10)
Female	18.8 (22 / 52)	9.7 (29 / 48)	0.54 (0.31, 0.94)
Race			
White	15.6 (31 / 65)	9.7 (33 / 56)	0.61 (0.37, 1.00)
Asian	20.3 (13 / 28)	7.0 (20 / 32)	0.54 (0.27, 1.09)
Region			
North America	15.1 (18 / 30)	11.8 (12 / 19)	0.83 (0.39, 1.74)
Europe	11.3 (26 / 50)	6.5 (42 / 60)	0.57 (0.35, 0.93)
Asia-Pacific	20.3 (14 / 32)	11.3 (22 / 39)	0.58 (0.30, 1.15)
Lines therapy			
2	16.3 (21 / 48)	8.5 (30 / 46)	0.56 (0.32, 0.98)
3	11.3 (22 / 33)	9.7 (27 / 45)	0.67 (0.38, 1.20)
>3	10.3 (15 / 31)	6.5 (19 / 27)	0.68 (0.34, 1.34)
CD30 expression			
<1%	15.6 (42 / 76)	6.5 (55 / 80)	0.56 (0.37, 0.84)
>=1%	13.6 (16 / 36)	11.7 (21 / 38)	0.83 (0.43, 1.60)
DLBCL,NOS COO			
GCB	13.6 (19 / 37)	8.8 (20 / 36)	0.66 (0.35, 1.26)
Non-GCB	18.8 (22 / 48)	8.8 (30 / 43)	0.53 (0.30, 0.92)
Prior CAR-T			
Received	15.6 (16 / 32)	4.4 (25 / 35)	0.38 (0.20, 0.75)
Not Received	13.8 (42 / 80)	9.7 (51 / 83)	0.74 (0.49, 1.11)
Prior Transplant			
Received	15.1 (5 / 10)	NA (5 / 18)	1.75 (0.50, 6.08)
Not Received	13.6 (53 / 102)	6.5 (71 / 100)	0.54 (0.38, 0.77)
LBCL subtypes			
DLBCL, NOS	15.1 (41 / 85)	8.8 (51 / 80)	0.56 (0.37, 0.85)
HGBL	15.9 (10 / 15)	5.2 (14 / 21)	0.80 (0.35, 1.81)
Primary mediastinal LBCL	4.1 (3 / 5)	4.4 (2 / 2)	0.76 (0.10, 5.51)
Others	7.3 (4 / 7)	6.5 (9 / 15)	1.28 (0.37, 4.42)
Transformed lymphoma			
Y	15.6 (18 / 32)	15.8 (16 / 27)	1.03 (0.51, 2.07)
N	13.8 (40 / 80)	6.9 (60 / 91)	0.54 (0.36, 0.81)
Prior Diag for Transformed LBCL			
FL, MZL	16.3 (12 / 26)	17.2 (11 / 21)	1.09 (0.46, 2.60)
Richter's	7.4 (6 / 6)	2.3 (5 / 6)	1.08 (0.30, 3.89)



Source: FDA analysis

The Applicant included a prespecified subgroup analysis of patients based on CD30 expression (<1% and ≥1%). In both the Applicant's and the FDA's subgroup analysis of the primary endpoint based on CD30 expression, the results favored the Bv+R2 arm compared to the placebo +R2 arm.

Reviewer's Comment: Study ECHELON-3 was not designed to assess differential OS in any particular subgroup, the subgroup analyses results presented above should be regarded as exploratory only. Results of this exploratory analysis should be interpreted with caution.

Data Quality and Integrity

Data:

N/A

The Applicant's Position:

The sponsor's representatives conducted monitoring visits as frequently as deemed necessary to determine that protocol adherence and data recording were satisfactory. Appropriate measures to protect subject confidentiality were employed during monitoring. The case report forms (CRFs) and related source documents were typically reviewed in detail by the monitor at each site visit. Original source documents or certified copies were needed for review. This review included inspection of data acquired as a requirement for participation in this study and other medical records as required to confirm that the information collected was correct. Other study records, such as correspondence with the sponsor and the institutional review board/independent ethics committee (IRB/IEC) and screening and drug accountability logs were also inspected. All source data and study records were available for inspection by representatives of regulatory authorities and the IRB/IEC. The investigator was responsible to ensure accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports. Any change or correction to a CRF was maintained in an audit trail within the electronic data capture system. Data changes were only made by those individuals so authorized. The investigator retained records of the changes and corrections, written and/or electronic.

The FDA's Assessment:

FDA agrees with the Applicant's Position. No concerns regarding data integrity were identified during the review of this application.

Efficacy Results – Secondary and other relevant endpoints

Data:

Progression-free survival per Lugano 2014 by Investigator: Data for PFS are presented in

Table 19 and Figure 13. PFS was superior for the BV+Len+R arm vs the placebo+Len+R arm with a 47.3% reduction in the risk of disease progression or death (stratified HR=0.527; 95% CI: 0.380, 0.729; 2-sided p=<.0001). The median PFS was 4.2 months (95% CI: 2.9, 7.1) in the BV+Len+R arm compared to 2.6 months (95% CI: 1.4, 3.1) in the placebo+Len+R arm.

Analyses of PFS by selected baseline characteristics, prognostic factors, and histological subtype in ECHELON-3 was conducted (m5.3.5.1, ECHELON-3 CSR, Figure 14.3.3.2). Overall, the PFS benefit among subjects in BV+Len+R arm was generally consistent across prespecified subgroups.

Table 19: Applicant-Progression- Free Survival per Lugano 2014 by Investigator (ITT Analysis Set)

	BV+Len+R (N=112)	Placebo+Len+R (N=118)	Total (N=230)
Subjects with progressive disease (PD) or death, n (%)	71 (63.4)	85 (72.0)	156 (67.8)
PD	56 (50.0)	71 (60.2)	127 (55.2)
Death	15 (13.4)	14 (11.9)	29 (12.6)
Hazard ratio (95% CI) [a]	0.527 (0.380, 0.729)		
P-value [b]	<0.0001		
Duration of PFS (months)			
Median (95% CI) [c]	4.2 (2.9, 7.1)	2.6 (1.4, 3.1)	3.0 (2.7, 4.1)
Q1, Q3	2.6, 16.8	1.3, 5.5	1.4, 9.7
Min, Max[d]	0.0+, 31.5	0.0+, 24.8+	0.0+, 31.5
PFS rate at			
2 months (95% C.I.) [c]	75.8% (66.4%, 83.0%)	53.0% (43.0%, 62.0%)	64.3% (57.4%, 70.4%)
4 months (95% C.I.) [c]	55.1% (44.9%, 64.1%)	35.5% (26.3%, 44.8%)	45.3% (38.3%, 51.9%)
6 months (95% C.I.) [c]	42.7% (32.9%, 52.1%)	20.4% (12.8%, 29.2%)	31.7% (25.3%, 38.3%)
8 months (95% C.I.) [c]	39.1% (29.4%, 48.6%)	16.6% (9.7%, 25.0%)	28.1% (21.9%, 34.6%)
10 months (95% C.I.) [c]	33.3% (23.8%, 43.1%)	13.0% (6.7%, 21.5%)	23.5% (17.4%, 30.0%)
12 months (95% C.I.) [c]	33.3% (23.8%, 43.1%)	13.0% (6.7%, 21.5%)	23.5% (17.4%, 30.0%)
Duration of PFS follow-up (months) [e]			
Median (95% CI) [c]	11.1 (8.6, 14.2)	8.8 (6.9, 10.9)	10.2 (8.6, 11.2)
Q1, Q3	7.0, 16.6	4.3, 14.2	5.7, 16.4
Min, Max[d]	0.0, 31.5+	0.0, 24.8	0.0, 31.5+

Progression-Free survival (PFS) is time from randomization to earliest occurrence of PD per Lugano 2014 or death. PFS is estimated using Kaplan-Meier method.

a. Hazard ratio and 95% CI based on a stratified cox regression model with stratification factors cell of origin (GCB, non-GCB) and CD30 status (≥1%, <1%) at randomization. Hazard ratio <1 favors BV+Len+R.

b. 2-sided p-value from a stratified log-rank test with stratification factors cell of origin (GCB, non-GCB) and CD30 status (≥1%, <1%) at randomization.

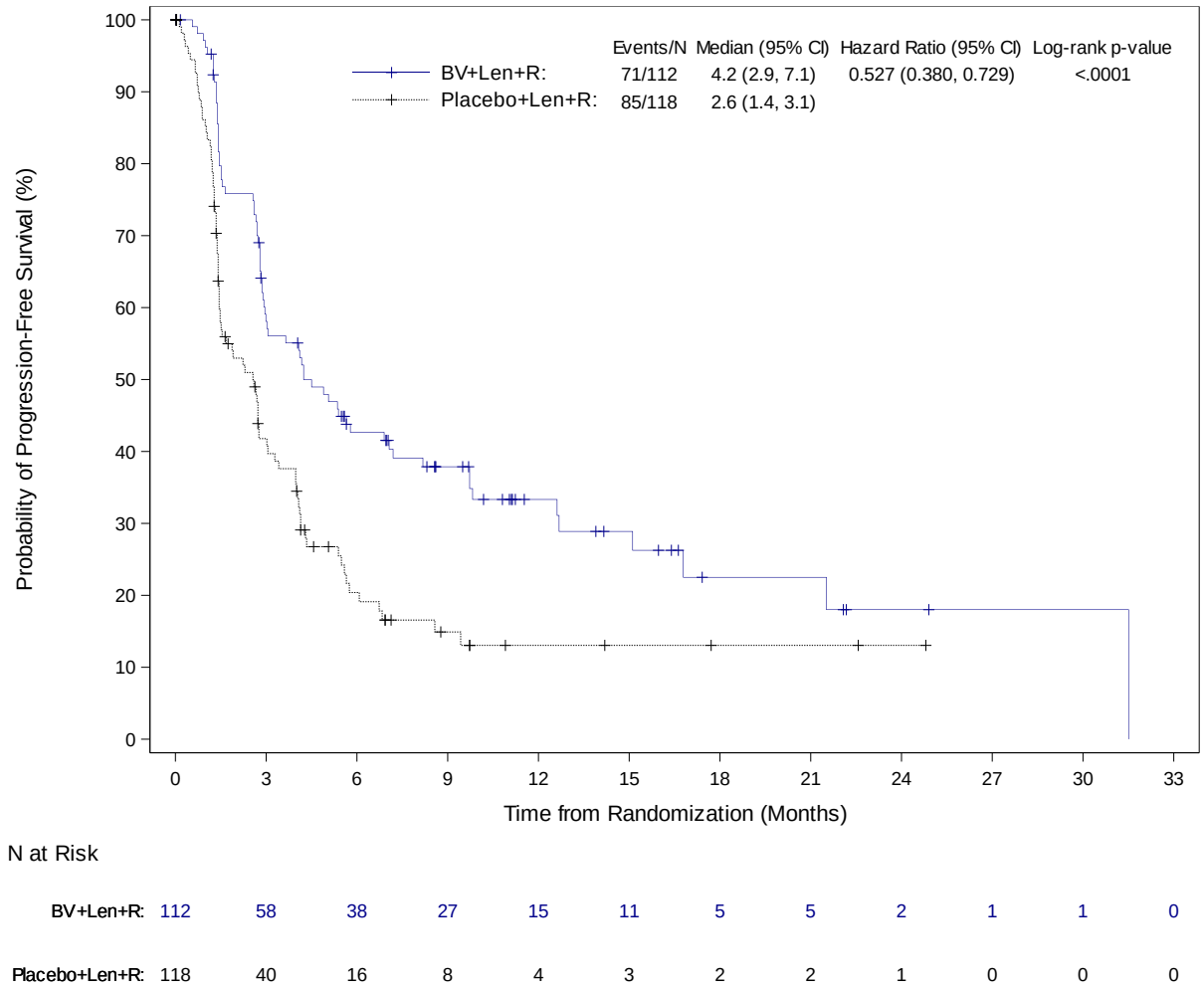
c. Calculated using the complementary log-log transformation method (Collett, 1994).

d. + indicates a censored observation.

e. Duration of follow-up calculated using reverse Kaplan-Meier method.

Source: m5.3.5.1, ECHELON-3 CSR, Table 14.3.3.1

Figure 13: Applicant- Kaplan-Meier Plot of Progression- Free Survival per Lugano 2014 by Investigator (ITT Analysis Set)



Source: m5.3.5.1, ECHELON-3 CSR, Figure 14.3.3.1

Overall Response per Lugano 2014 per Investigator: A significantly higher ORR (64.3% [95% CI: 54.7, 73.1], 2-sided p=0.0006) was observed in BV+Len+R arm compared with placebo+Len+R arm (41.5% [95% CI: 32.5, 51.0]). Best overall response noted in the BV+Len+R arm vs placebo+Len+R arm included CR in 45 subjects vs 22 subjects, and partial response (PR) in 27 subjects in each arm.

Duration of response: DOR is defined as the time from start of the first documentation of objective tumor response (CR or PR) to the first documentation of tumor progression per the Lugano 2014 response criteria as assessed by the investigator or death due to any cause, whichever occurs first. The median DOR was 8.3 months (95% CI: 4.2, 15.3) with BV+Len+R and 3.0 months (95% CI: 2.8, 5.4) with placebo+Len+R arm.

The Applicant's Position:

In the ECHELON-3 study, statistically significant and clinically meaningful improvements were noted for the secondary endpoints of PFS and ORR in the BV+Len+R arm compared with the placebo+Len+R arm in subjects with R/R DLBCL.

The FDA's Assessment:

FDA agrees with the Applicant's position regarding the primary analyses results for key secondary endpoints (investigator assessed PFS and investigator assessed ORR) and secondary endpoint DOR at the pre-specified interim analysis.

The key secondary endpoints of PFS and ORR were also evaluated by blinded independent central review (BICR). Progression free survival per BICR was assessed as a sensitivity analysis.

Per the FDA's analysis, PFS per BICR was similar to the PFS as assessed by investigator. The median PFS per BICR in the Bv+R2 arm was 6.9 months (95% CI: 4.0, 13.6) vs. 2.5 months (95% CI: 1.4, 4.0) in the Pbo+R2 arm, HR 0.523 (0.364, 0.751), p value 0.0004.

Response assessments were also performed by BICR and included in the datasets as part of the application. Response per investigator and BICR are displayed in Table 20 below.

Table 20: Response as Assessed by Investigator and BICR

Response Parameter	INV		BICR	
	Bv + R2 N=112 n (%)	Pbo+R2 N=118 n (%)	Bv + R2 N=112 n (%)	Pbo+R2 N=118 n (%)
OR (CR +PR) 95% CI	72 (64.3) (54.7, 73.1)	49 (41.5) (32.5, 51.0)	70 (62.5) (52.9, 71.5)	43 (36.4) (27.8, 45.8)
CR 95% CI	45 (40.2) (31.0, 49.9)	22 (18.6) (12.1, 26.9)	48 (42.9) (33.5, 52.6)	26 (22.0) (14.9, 30.6)
PR	27 (24.1)	27 (22.9)	22 (19.6)	17 (14.4)
SD	7 (6.3)	8 (6.8)	9 (8.0)	12 (10.2)
PD	23 (20.5)	40 (33.9)	21 (18.8)	40 (33.9)
NE	0	0	1 (0.9)	3 (2.5)
NV[a]	10 (8.9)	21 (17.8)	11 (9.8)	20 (16.9)

Source: FDA analysis
BICR = blinded independent review committee, OR = objective response, CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable, NV = not available
[a] Subjects without a post-baseline assessment

An information request was sent to Applicant to clarify the reasons for patients being not evaluable or not available for response. The Applicant provided narratives for these patients. The responses provided were treatment discontinuation prior to first assessment either due to adverse event, clinical progression without radiologic assessment or death. This is detailed in Table 21 below for the patients assessed as NV (not available) per investigator.

Table 21: Reasons for Response Assessments that were Non Evaluable (NE) or Not Available (NV)

Reason for no response assessment per investigator	Bv + R2	Pbo+R2
	N=21	N=10
	n	n
Clinical Disease Progression per investigator prior to first disease assessment	14	4
Death prior to first disease assessment	3	1
Treatment discontinuation due to AE prior to first disease assessment	2	1
Treatment discontinuation due to pt decision prior to first disease assessment	1	3
Not treated, death prior to first disease assessment	1	0
No post baseline imaging at the time of data cutoff	0	1

Source: FDA analysis of Applicant response or IR received on 9/24/2024

In general, the objective response rate and complete response rate were similar when assessed by investigator or by BICR. Both analyses demonstrated a higher ORR and CRR in the Bv+R2 arm compared to the Pbo+R2 arm. The Agency does not agree that patients who were assessed by investigators to have clinical progression should be considered non evaluable, as these patients should be considered to have PD. This would not impact the ORR and CRR rate, however and therefore does not change the overall assessment of efficacy based on objective response.

FDA did additional subgroup analyses for key secondary endpoints among ITT population by including the baseline variables of the following: histologic diagnosis per WHO criteria, number of lines of prior systemic therapy, transformed from indolent lymphoma, and histology prior to transformation. These were included in the adbase.xpt submitted 08/07/2024.

Figure 14 shows the subgroup analyses of investigator assessed PFS by FDA. The observed ORR were in general consistently higher in BV+R2 compared with the Placebo+R2 arm across

subgroups with the exception of where numbers of patients in the subgroups were low. Table 22 shows the subgroup analyses of investigator assessed ORR per FDA.

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Figure 14: FDA- Subgroup Analysis of PFS by investigator (ITT) Analysis Set

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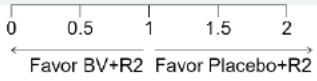
Subgroup	BV+R2 Median PFS (m) (events / N)	Placebo+R2 Median PFS (m) (events / N)	HR (95% CI)
All patients	4.2 (71 / 112)	2.6 (85 / 118)	0.53 (0.38, 0.73)
Age			
<65 Years	2.9 (25 / 33)	1.4 (33 / 42)	0.69 (0.41, 1.17)
>=65 Years	5.7 (46 / 79)	2.8 (52 / 76)	0.48 (0.32, 0.72)
Sex			
Male	2.9 (41 / 60)	2.2 (54 / 70)	0.56 (0.37, 0.85)
Female	7.2 (30 / 52)	3.3 (31 / 48)	0.55 (0.33, 0.92)
Race			
White	5.1 (41 / 65)	2.7 (37 / 56)	0.54 (0.34, 0.86)
Asian	9.7 (16 / 28)	2.8 (24 / 32)	0.51 (0.27, 0.97)
Region			
North America	4.1 (22 / 30)	1.4 (12 / 19)	0.65 (0.32, 1.34)
Europe	3.6 (31 / 50)	1.5 (44 / 60)	0.48 (0.30, 0.77)
Asia-Pacific	9.7 (18 / 32)	3.0 (29 / 39)	0.50 (0.28, 0.91)
Lines therapy			
2	7.1 (29 / 48)	2.7 (34 / 46)	0.46 (0.28, 0.76)
3	2.9 (26 / 33)	1.5 (30 / 45)	0.56 (0.32, 0.99)
>3	3.1 (16 / 31)	2.6 (21 / 27)	0.61 (0.32, 1.17)
CD30 expression			
<1%	3.1 (49 / 76)	1.9 (57 / 80)	0.57 (0.38, 0.84)
>=1%	6.9 (22 / 36)	2.7 (28 / 38)	0.49 (0.28, 0.86)
DLBCL,NOS COO			
GCB	5.1 (24 / 37)	3.1 (26 / 36)	0.54 (0.30, 0.94)
Non-GCB	4.5 (31 / 48)	2.3 (30 / 43)	0.53 (0.32, 0.88)
Prior CAR-T			
Received	3.0 (21 / 32)	1.4 (25 / 35)	0.41 (0.22, 0.76)
Not Received	5.1 (50 / 80)	2.8 (60 / 83)	0.58 (0.40, 0.85)
Prior Transplant			
Received	5.4 (6 / 10)	5.6 (10 / 18)	1.00 (0.36, 2.79)
Not Received	4.2 (65 / 102)	1.5 (75 / 100)	0.46 (0.33, 0.64)
LBCL subtypes			
DLBCL, NOS	5.1 (55 / 85)	2.7 (57 / 80)	0.53 (0.36, 0.77)
HGBL	3.6 (9 / 15)	1.6 (14 / 21)	0.51 (0.21, 1.23)
Primary mediastinal LBCL	2.8 (4 / 5)	2.0 (2 / 2)	0.46 (0.06, 3.31)
Others	1.6 (3 / 7)	2.6 (12 / 15)	0.70 (0.19, 2.50)
Transformed lymphoma			
Y	3.6 (21 / 32)	4.1 (18 / 27)	0.83 (0.44, 1.56)
N	5.4 (50 / 80)	1.9 (67 / 91)	0.48 (0.33, 0.69)
Prior Diag for Transformed LBCL			
FL, MZL	4.2 (15 / 26)	5.5 (13 / 21)	0.82 (0.39, 1.74)
Richter's	2.7 (6 / 6)	1.2 (5 / 6)	0.95 (0.26, 3.42)



Source: FDA analysis

Table 22: FDA- Subgroup Analysis of ORR by investigator (ITT) Analysis Set

Subgroup	BV+R2		Placebo+R2	
	ORR (n) / N	ORR (%) (95% CI)	ORR (n) / N	ORR (%) (95% CI)
All patients	72 / 112	64.3 (54.7, 73.1)	49 / 118	41.5 (32.5, 51.0)
Age				
<65 Years	16 / 33	48.5 (30.8, 66.5)	14 / 42	33.3 (19.6, 49.5)
>=65 Years	56 / 79	70.9 (59.6, 80.6)	35 / 76	46.1 (34.5, 57.9)
Sex				
Male	33 / 60	55.0 (41.6, 67.9)	26 / 70	37.1 (25.9, 49.5)
Female	39 / 52	75.0 (61.1, 86.0)	23 / 48	47.9 (33.3, 62.8)
Race				
White	44 / 65	67.7 (54.9, 78.8)	24 / 56	42.9 (29.7, 56.8)
Asian	19 / 28	67.9 (47.6, 84.1)	17 / 32	53.1 (34.7, 70.9)
Region				
North America	21 / 30	70.0 (50.6, 85.3)	4 / 19	21.1 (6.0, 45.6)
Europe	28 / 50	56.0 (41.3, 70.0)	22 / 60	36.7 (24.6, 50.1)
Asia-Pacific	23 / 32	71.9 (53.3, 86.3)	23 / 39	59.0 (42.1, 74.4)
Lines therapy				
2	33 / 48	68.8 (53.7, 81.3)	20 / 46	43.5 (28.9, 58.9)
3	22 / 33	66.7 (48.2, 82.0)	16 / 45	35.6 (21.9, 51.2)
>3	17 / 31	54.8 (36.0, 72.7)	13 / 27	48.1 (28.7, 68.1)
CD30 expression				
<1%	46 / 76	60.5 (48.6, 71.6)	30 / 80	37.5 (26.9, 49.0)
>=1%	26 / 36	72.2 (54.8, 85.8)	19 / 38	50.0 (33.4, 66.6)
DLBCL, NOS COO				
GCB	29 / 37	78.4 (61.8, 90.2)	18 / 36	50.0 (32.9, 67.1)
Non-GCB	31 / 48	64.6 (49.5, 77.8)	17 / 43	39.5 (25.0, 55.6)
Prior CAR-T				
Received	21 / 32	65.6 (46.8, 81.4)	9 / 35	25.7 (12.5, 43.3)
Not Received	51 / 80	63.8 (52.2, 74.2)	40 / 83	48.2 (37.1, 59.4)
Prior Transplant				
Received	5 / 10	50.0 (18.7, 81.3)	14 / 18	77.8 (52.4, 93.6)
Not Received	67 / 102	65.7 (55.6, 74.8)	35 / 100	35.0 (25.7, 45.2)
LBCL subtypes				
DLBCL, NOS	60 / 85	70.6 (59.7, 80.0)	35 / 80	43.8 (32.7, 55.3)
HGBL	8 / 15	53.3 (26.6, 78.7)	6 / 21	28.6 (11.3, 52.2)
Primary mediastinal LBCL	2 / 5	40.0 (5.3, 85.3)	1 / 2	50.0 (1.3, 98.7)
Others	2 / 7	28.6 (3.7, 71.0)	7 / 15	46.7 (21.3, 73.4)
Transformed lymphoma				
Y	19 / 32	59.4 (40.6, 76.3)	14 / 27	51.9 (31.9, 71.3)
N	53 / 80	66.3 (54.8, 76.4)	35 / 91	38.5 (28.4, 49.2)
Prior Diag for Transformed LBCL				
FL, MZL	17 / 26	65.4 (44.3, 82.8)	13 / 21	61.9 (38.4, 81.9)
Richter's	2 / 6	33.3 (4.3, 77.7)	1 / 6	16.7 (0.4, 64.1)

Source: FDA analysis

Reviewer's Comment: Study ECHELON-3 was not designed to assess differential PFS or ORR in any particular subgroup, the subgroup analyses results presented above should be regarded as exploratory only. Results of this exploratory analysis should be interpreted with caution.

Dose/Dose Response

No relevant data for this submission.

The FDA's Assessment:

Refer to the Clinical Pharmacology review in Section 6.

Durability of Response

The Applicant's Position:

DOR is presented as a secondary endpoint. See Section 8.1.2 for secondary endpoints.

The FDA's Assessment:

Refer to the FDA's Assessment under Section 8.1.2 Efficacy Results – Secondary and other relevant endpoints.

Persistence of Effect

The Applicant's Position:

The persistence of efficacy of BV is demonstrated by the prolonged OS and PFS compared to the control arm. OS and PFS rates at milestone timepoints are presented in Table 18 and

Table 19**.**

The FDA's Assessment:

FDA does not agree with the Applicant's position. Since the study was not designed to evaluate the persistence of efficacy, and the treatment may continue as long as there is clinical benefit (stable disease [SD] or better) without progression or unacceptable toxicity. As such, this section is not applicable to the study.

Efficacy Results – Secondary or Exploratory COA (PRO) Endpoints

Data/The Applicant's Position:

PRO data from the ECHELON-3 study was an exploratory endpoint and is included in ECHELON-3 CSR Section 14. Analyses were not discussed due to low compliance rates, impacting interpretability of the data. Low compliance was likely driven by usability of electronic PRO devices in the elderly population.

The FDA's Assessment:

The exploratory PRO endpoints included in the ECHELON-3 study were EuroQol-5 dimension-5 level (EQ-5D-5L) and National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy-Lymphoma (NCCN FACT-Lym). The assessment frequency for the FACT-Lym was every two weeks until EOT. Compliance rate is defined as the proportion of subjects who completed the instrument among those were expected to complete it at each visit. Patients were expected to complete the instrument if they had not discontinued treatment by the scheduled visit.

The baseline compliance rate for the NCCN FACT-Lym for the ECHELON-3 trial population was 42.6% and was similar between arms. The compliance rate for NCCN FACT-Lym across study visits rarely was above 70%. For example, at Week 4, the compliance rate was 67% in the BV+Len+R arm and 47% in the Placebo+Len+R arm.

The FDA generally agrees with the Applicant that the low compliance rates in the ECHELON-3 study negatively impacts the ability to interpret the PRO data. Therefore, no conclusions or interpretation could be made based on this data. The reasons for this degree of PRO missingness are unclear.

Additional Analyses Conducted on the Individual Trial

Data:

As part of additional secondary and exploratory endpoints, OS, PFS, and ORR subgroup analyses per CD30 expression were conducted.

The Applicant's Position:

The treatment benefit with BV+Len+R compared to placebo+Len+R was observed for primary endpoint of OS and key secondary endpoints of PFS and ORR regardless of CD30 expression.

The FDA's Assessment:

OS in the CD30-positive population was revised to a secondary objective since study Protocol Amendment 5 dated 08/04/2023. Analyses that were not specified under the hypothesis testing plan are generally considered to be descriptive. Refer to section 8.1.2 Efficacy Results – Primary Endpoint and Secondary and other relevant endpoints for analyses per CD30 expression by FDA.

Reviewer's Comment: While ECHELON-3 was originally designed to evaluate PFS in the ITT and CD30+ populations, testing in a biomarker-positive and ITT populations is typically not adequate to demonstrate consistency of treatment effect between the two populations. For biomarkers thought to portend differential treatment effects (i.e., predictive biomarkers), an

appropriate design would feature formal analyses of the biomarker-positive and biomarker-negative subgroups.

CD30 positivity in LBCL has been reported to be associated with favorable outcomes (Pierce 2017), however, because of differences in the threshold for CD30 positivity, disease setting (treatment naïve vs relapsed or refractory), and therapy setting, conclusions are limited regarding the role of CD30 positivity in response to BV + R2 therapy. Prior to ECHELON-3, whether treatment with BV in combination with R2 would yield differential treatment effects based on CD30 expression was unknown.

In Study SGN35-012, which included CD30+ and CD30 undetectable (CD30u) patients, higher response rates were demonstrated in the CD30+ cohort (44%) versus the CD30u cohort (31%), refer to Section 8.1.4 for additional information. The difference in response rates was modest at 13%. Given the potential prognostic role of CD30 expression, as well as differences in baseline characteristics, it was unclear whether this difference was indicative of a differential treatment effect.

The original design of ECHELON-3 required 280 PFS events, 140 of which were expected to be observed in the CD30-positive population. A minimum number of events was not required for the CD30-positive population. Per Applicant Table 15, 32.2% of patients enrolled had ≥1% CD30 expression vs. 67.8% of patients with <1% CD30 expression. The subgroup results for the efficacy endpoints do not suggest differential efficacy between these two subgroups (Figures 12 and 14).

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:

The primary evaluation of efficacy is based on the single, phase III study ECHELON-3. Further discussion is provided in the Integrated Assessment of Effectiveness.

8.1.4. Assessment of Efficacy Across Trials

Primary Endpoints

Data:

Efficacy results from the ECHELON-3 primary endpoint of OS are presented alongside data from SGN35-012 in Table 23; these studies both explored subjects with R/R DLBCL and support the contribution of components using BV, R, and Len. Owing to the differences in disease settings and treatment regimens among ECHELON-3 and the supporting studies, efficacy data were not pooled.

Secondary and Other Endpoints

Data:

Results from the ECHELON-3 secondary endpoints of PFS, ORR, and DOR are presented alongside data from SGN35-012 in Table 24.

The Applicant's Position:

BV shows single-agent activity in R/R DLBCL and is supported by consistent activity across all DLBCL studies. The combination of BV+Len+R in ECHELON-3 shows significant improvement in OS, PFS, and ORR, demonstrating that the addition of BV to Len+R improves efficacy in R/R DLBCL. In conclusion, BV+Len+R offers a clinically meaningful therapeutic option to patients with R/R DLBCL who have received 2 or more prior lines of systemic therapy.

The FDA's Assessment:

The FDA does not agree with the Applicant's position regarding the time to event endpoint (OS, PFS) comparison across trials and therefore, only response data from supporting trials are considered supportive for this application. The ORR data from part A and C of study SGN35-012 provide data supporting single agent activity of BV in patients with DLBCL with high and low CD30+ expression.

Study SGN35-012 was a 3-part, phase 2, open-label, multicenter study, which evaluated BV as monotherapy or in combination with rituximab in patients with R/R NHL, including PTCL and B-cell lymphoma. The primary objective of the study was to determine the antitumor activity of treatment with BV as measured by the ORR. The study also aimed to characterize the relationship between CD30 expression and antitumor activity.

Parts A and C investigated the antitumor activity of BV as a single agent, whereas Part B investigated the safety of BV+R. Assessment of CD30 expression to determine eligibility was performed by visual assessment of immunohistochemistry (vIHC) (using the anti-CD30 Ber-H2 antibody) at the local (institutional or external) laboratory. In Parts A and B, patients were required to have histologically-confirmed CD30-positive (CD30+) disease, and in Part C, patients were required to have histologically-confirmed disease with undetectable CD30 expression (CD30u). The primary endpoint for Parts A and C was to determine activity of treatment with BV as measured by the ORR, and the primary endpoint for Part B was to assess the safety of BV when given in combination with rituximab.

To support the efficacy evaluation of ECHELON-3 study, the BV arm (N = 100) of Study SGN35-012 included efficacy evaluable subjects from Part A and Part C. While the BV+R arm (N = 12) of Study SGN35-012 included efficacy evaluable subjects from Part B. The data cutoff date of CSR was 27 AUG 2015. The efficacy results of OS, PFS and ORR endpoints were summarized from Study SGN35-012. Per the FDA analysis of Study SGN35-012 (adeff.xpt dataset submitted under SN 0252) Part A, which included patients with B cell lymphomas that were CD30+, 49 patients with CD30+ R/R DLBCL were treated with BV monotherapy. Of the 48 efficacy evaluable patients, the ORR was 43.8% (95% CI: 29.5%, 58.8%) and the CR rate was 18.8% (95% CI: 8.95%, 32.6%). In Part C of the study, 52 subjects with CD30 undetectable DLBCL were treated with BV monotherapy. The ORR in this population was 30.8% (95% CI: 18.7%, 45.1%) and the CRR was 11.5% (95% CI: 4.35%, 23.4%).

Reviewer's Comment: Due to the differences in disease settings and treatment regimens, the comparison between ECHELON-3 and study SGN35-012 is not able to isolate the contribution of effect of Len+R in addition to BV monotherapy. In addition, the results of BV arm in SGN35-012 were conducted by integrating Parts A and C of the study. The results of BV+R was conducted based on limited sample size (N = 12) from Part B of the study. As such, the supportive evidence of effectiveness based on study SGN35-012 should be interpreted with caution. In addition, cross trial comparison of time to event endpoints is limited.

The ORR of 37% observed in study SGN35-012 with BV monotherapy (combined Part A and Part C), support activity of BV in patients with relapsed and refractory NHL.

Table 23: Applicant- Comparison of Efficacy Results- OS (ITT Analysis Set)

	Analysis	ECHELON-3		SGN35-012	
		BV+Len+R (N=112)	Placebo+Len+R (N=118)	BV (N=100)	BV + R (N=12)
OS	Number of deaths, n (%)	58 (51.8)	76 (64.4)	64 (64.0)	4 (33.3)
	Duration of OS (months)				
	Median (95% CI) [a] (months)	13.8 (10.3, 18.8)	8.5 (5.4, 11.7)	8.1 (5.5, 10.2)	- (9.4, -)
	Q1, Q3	5.7, 31.5	2.9, 20.1	3.8, -	10.8, -
	Min, Max[b]	0.6, 31.5	0.1, 29.5	0.7, 43.5+	6.2, 20.7+
	Duration of OS follow-up (months) [c]				
	Median (95% CI)	15.5 (12.2, 18.1)	18.9 (12.2, 23.2)	21.3 (12.5, 33.1)	17.4 (13.4, 20.0)
	Q1, Q3	10.9, 22.7	8.2, 23.6	11.1, 35.2	15.8, 19.1
	Min, Max[b]	0.6+, 31.5+	0.1+, 29.5+	0.7+, 43.5	6.2+, 20.7

a. Calculated using the complementary log-log transformation method (Collett, 1994).
b. + indicates a censored observation.
c. Duration of follow-up calculated using reverse Kaplan-Meier method.
d. Exact 95% CI computed using the Clopper-Pearson method (Clopper 1934)
Source: m5.3.5.3, ECHELON-3 ISE, Table 14.3.1, Table 14.3.2, Table14.3.3. Table 14.3.4

Table 24: Applicant- Comparison of Efficacy Results- PFS and ORR (ITT Analysis Set)

	Analysis	ECHELON-3		SGN35-012	
		BV+Len+R (N=112)	Placebo+Len+R (N=118)	BV (N=100)	BV + R (N=12)
PFS	Subjects with a PFS event, n (%)	71 (63.4)	85 (72.0)	78 (78.0)	8 (66.7)
	PD	56 (50.0)	71 (60.2)	76 (76.0)	8 (66.7)
	Death	15 (13.4)	14 (11.9)	2 (2.0)	0
	Duration of PFS (months)				
	Median (95% CI) [a]	4.2 (2.9, 7.1)	2.6 (1.4, 3.1)	2.1 (1.5, 3.0)	3.3 (1.3, 9.7)
	Q1, Q3	2.6, 16.8	1.3, 5.5	1.3, 6.0	2.7, 9.7

	Analysis	ECHELON-3		SGN35-012	
		BV+Len+R (N=112)	Placebo+Len+R (N=118)	BV (N=100)	BV + R (N=12)
	Min, Max[b]	0.0+, 31.5	0.0+, 24.8+	0.4, 24.0+	1.2, 12.0+
	Duration of PFS follow-up (months) [c]				
	Median (95% CI)	11.1 (8.6, 14.2)	8.8 (6.9, 10.9)	9.0 (7.7, 22.8)	12.0 (2.7, -)
	Q1, Q3	7.0, 16.6	4.3, 14.2	5.6, 22.8	3.1, 12.0
	Min, Max[b]	0.0, 31.5+	0.0, 24.8	0.4+, 24.0	1.2+, 12.0
BOR	Complete response (CR), n (%)	45 (40.2)	22 (18.6)	15 (15.0)	2 (16.7)
	95% CI for CR rate [d]	(31.0, 49.9)	(12.1, 26.9)	(8.6, 23.5)	(2.1, 48.4)
	Partial response (PR), n (%)	27 (24.1)	27 (22.9)	22 (22.0)	4 (33.3)
	Stable disease (SD), n (%)	7 (6.3)	8 (6.8)	18 (18.0)	4 (33.3)
	Progressive disease (PD), n (%)	23 (20.5)	40 (33.9)	45 (45.0)	2 (16.7)
	Not evaluable (NE), n (%)	0	0	0	0
	Not available, n (%)	10 (8.9)	21 (17.8)	0	0
ORR	CR or PR, n (%)	72 (64.3)	49 (41.5)	37 (37.0)	6 (50.0)
	95% CI for ORR [d]	(54.7, 73.1)	(32.5, 51.0)	(27.6, 47.2)	(21.1, 78.9)
DOR	Duration of response (months)				
	Median (95% CI) [a]	8.3 (4.2, 15.3)	3.0 (2.8, 5.4)	4.7 (3.3, 11.6)	2.1 (1.4, -)
	Q1, Q3	2.8, 30.1	1.8, -	1.8, 16.6	1.6, 7.1
	Min, Max [b]	0.9, 30.1	0.0+, 23.5+	0.0+, 22.7+	1.4, 10.7+

a. Calculated using the complementary log-log transformation method (Collett, 1994).
b. + indicates a censored observation.
c. Duration of follow-up calculated using reverse Kaplan-Meier method.
d. Exact 95% CI computed using the Clopper-Pearson method (Clopper 1934)
Source: m5.3.5.3, ECHELON-3 ISE, Table 14.3.1, Table 14.3.2, Table 14.3.3. Table 14.3.4

Subpopulations

The Applicant's Position:

Analysis of prespecified subgroups for OS is provided under Section 8.1.2 Efficacy Results-Primary Endpoint.

The FDA's Assessment:

Refer to Section 8.1.2 Efficacy Results – Primary Endpoint, Secondary and other relevant endpoint for the subgroup analyses for ECHELON-3 study by FDA.

According to the CSR of study SGN35-012, exploratory subgroup analyses were carried out for selected endpoints. The subgroups that were examined were NHL classification and disease subtype; CD30 expression, intensity, and the combination of expression and intensity; age and

sex; disease status relative to the frontline therapy (primary refractory vs non-primary refractory) and relative to the most recent therapy (relapsed vs refractory); IPI score at initial disease diagnosis (0–2 vs 3–5); and tumor size at baseline (< median tumor size vs ≥ median tumor size).

Reviewer's Comment: Due to the differences in disease settings and treatment regimens between ECHELON-3 and the study SGN35-012, the subgroup analyses of study SGN35-012 are not applicable to the assessment.

8.1.5. Integrated Assessment of Effectiveness

Data:

At the prespecified interim analysis, ECHELON-3 met its primary efficacy endpoint of OS with significant reduction in the risk of death in BV+Len+R arm by 37.1% compared to the placebo+Len+R (stratified HR=0.629, 95% CI: 0.445, 0.891; 2-sided P=0.0085), leading to an improvement of 5.3 months in median OS (13.8 months vs. 8.5 months). This study also demonstrated a statistically significant and clinically meaningful improvement in the key secondary endpoint of investigator assessed PFS and ORR. A 47.3% reduction in the risk of disease progression or death was observed in BV+Len+R arm compared to the placebo+Len+R arm (stratified HR=0.527; 95% CI: 0.380, 0.729; 2-sided p<0.0001). The investigator-assessed ORR in the BV+Len+R arm was 64.3% [95% CI: 54.7, 73.1] compared to 41.5% (95% CI: 32.5, 51.0; 2-sided P=0.0006) in the placebo+Len+R arm. The ECHELON-3 interim analysis demonstrated further improvements in OS, PFS, and ORR, compared to the results observed in SGN35-012, supporting the hypothesis that combining BV with additional chemotherapy agents leads to increased efficacy in R/R DLBCL patients.

The Applicant's Position:

BV shows single-agent activity in R/R DLBCL and is supported by consistent activity across all DLBCL studies. Substantial evidence of effectiveness was demonstrated in ECHELON-3, an adequate and well controlled investigation, where the combination of BV+Len+R shows significant improvement in OS, PFS, and ORR, demonstrating that the addition of BV to Len+R improves efficacy in R/R DLBCL. In conclusion, BV+Len+R offers a clinically meaningful therapeutic option to patients with the proposed indication.

The FDA's Assessment:

The FDA agrees that the efficacy results from the ECHELON-3 study indicate that BV+R2 has clinically meaningful activity in patients with R/R LBCL including DLBCL NOS, DLBCL arising from indolent lymphoma, or HGBL, after two or more lines of systemic therapy who are not eligible for auto-HSCT or CAR T-cell therapy.

The pre-specified interim analysis of ECHELON-3 study met the primary objective in OS in the ITT population, where the risk of death in BV+R2 arm reduced by 37.1% compared to the Placebo+R2 arm (stratified HR=0.629, 95% CI: 0.445, 0.891; 2-sided P=0.0085). The median OS was 13.8 months (95% CI: 10.3, 18.8) in the BV+R2 arm compared to 8.5 months (95% CI: 5.4, 11.7) in the Placebo+R2 arm.

The ECHELON-3 study exhibited statistically significant results in the key secondary endpoints (investigator assessed PFS and investigator-assessed ORR) in the ITT population. Comparing to the Placebo+R2 arm, a 47.3% reduction in the risk of disease progression or death in BV+R2 arm was observed (stratified HR=0.527; 95% CI: 0.380, 0.729; 2-sided p<0.0001). The median PFS was 4.2 months (95% CI: 2.9, 7.1) in the BV+R2 arm compared to 2.6 months (95% CI: 1.4, 3.1) in the Placebo+R2 arm. In addition, investigator-assessed ORR in the BV+R2 arm was statistically higher compared to the Placebo+R2 arm (64.3% [95% CI: 54.7, 73.1] vs. 41.5% [95% CI: 32.5, 51.0]; 2-sided P=0.0006).

The study SGN35-012 was submitted as the supportive study, where the BV monotherapy arm (N = 100) of Study SGN35-012 included efficacy evaluable subjects from Part A and Part C and the BV+R arm (N = 12) of Study SGN35-012 included efficacy evaluable subjects from Part B. Due to the differences in disease settings and treatment regimens, and limitations to cross trial comparisons, the ability of the data from SGN35-012 to support efficacy is limited to the BV monotherapy arms in patients with R/R DLBCL. In Part A (CD30 ≥1%), in patients with DLBCL, the ORR was 43.8% (95% CI: 29.5%, 58.8%) and the CR rate was 18.8% (95% CI: 8.95%, 32.6%). In Part C of the study (CD30 < 1%) the ORR was 30.8% (95% CI: 18.7%, 45.1%) and the CRR was 11.5% (95% CI: 4.4%, 23.4%). This data supports the activity of BV in patients with R/R DLBCL regardless of CD30 expression. The efficacy data from the SGN35-012 trial, an adequate and well-controlled trial, in patients with relapsed or refractory large B-cell lymphoma treated with brentuximab vedotin provides confirmatory evidence in support of the new indication.

8.2. Review of Safety

Data:

The primary clinical data to support the evaluation of safety of BV in R/R DLBCL population are based on the randomized portion of pivotal study ECHELON-3 (SGN35-031), with supportive safety data from SRI portion of ECHELON-3, 3 additional DLBCL clinical studies SGN35-012, SGN35 017, and SGN35-023, and 2 phase 3 randomized studies of BV in combination therapy: ECHELON-1 (C25003) in subjects with cHL and ECHELON-2 (SGN35-014) in subjects with PTCL.

The FDA's Assessment:

The Agency agrees that the safety review for the proposed R/R LBCL indication is primarily based on the results from the randomized portion of pivotal study ECHELON-3 (SGN35-031).

8.2.1. Safety Review Approach

Data:

The following 5 safety analysis sets contribute to the integrated safety analysis (ISS).

- ECHELON-3 – This population includes all subjects with R/R DLBCL who received either BV or placebo in combination with multi-agent chemotherapy. This randomization portion

of this study includes a total of 228 randomized and treated subjects (112 in BV+Len+R arm and 116 in placebo+Len+R arm).

- DLBCL Combo Other –Includes all subjects with DLBCL who received at least 1 dose of BV in combination with multi-agent chemotherapy, regardless of chemotherapy backbone, dose level or schedule, in the clinical studies of SGN35-012 Part B, SGN35-017, SGN35-023, and the SRI portion of ECHELON-3. This analysis set includes a total of 112 subjects.

- DLBCL Mono – Includes all subjects with DLBCL who received at least 1 dose of BV monotherapy, regardless of dose level or schedule, in the clinical study SGN35-012 Part A and Part C. This analysis set includes a total of 102 subjects.

- DLBCL Total – Includes all subjects with DLBCL who received at least 1 dose of BV or BV in combination with multi-agent chemotherapy, regardless of chemotherapy, dose level or schedule, in studies ECHELON-3 (both randomization and SRI portions), SGN35-012, SGN35-017, and SGN35-023. This analysis set includes a total of 326 subjects. Data pooled from these DLBCL studies will provide a comprehensive evaluation of the overall safety profile of BV, either as combination therapy or monotherapy, in the DLBCL setting.

- Phase 3 BV Combo – Includes all subjects who received at least 1 dose of BV in combination with multi-agent chemotherapy, regardless of indication, in the 3 large phase 3 studies ECHELON-1, ECHELON-2, and ECHELON-3 (randomized portion only). This analysis set includes a total of 997 subjects. Data pooled from these 3 large phase 3 trials will allow an overall assessment of the safety profile in combination therapies across different disease settings.

Safety data from the randomized and treated subjects in the pivotal R/R DLBCL study ECHELON-3 will be presented by actual treatment regimen, and side-by-side with the 4 ISS populations mentioned above in tabular format.

The Applicant's Position:

The primary clinical data to support the evaluation of safety of BV in R/R DLBCL population are based on the pivotal study ECHELON-3.

The FDA's Assessment:

The Agency agrees that the safety review for the proposed R/R LBCL indication is primarily based on the results from the randomized portion of pivotal study ECHELON-3 (SGN35-031). Patients in the treatment arm (n=112) received BV, 1.2 mg/kg via intravenous infusion every 3 weeks, lenalidomide, and a rituximab product. Placebo replaced BV in the placebo plus lenalidomide and rituximab arm (n = 116). AE reporting period was defined as new or worsening AE from the first dose of any study drug through 30 days after last dose of brentuximab vedotin or lenalidomide or 110 days after last dose of rituximab, whichever is later. Toxicity was graded using NCI CTCAE version 5.0.

The safety and tolerability evaluation included an assessment of:

- Incidence and severity of all-cause treatment-emergent adverse events (TEAEs)
- Grade 3-5 TEAEs

- Serious adverse events
- TEAEs leading to treatment modification or discontinuation
- Adverse events of special Interest

AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 26.0. To inform the safety review, FDA used grouped preferred terms for more sensitive and informative safety analyses. The FDA preferred terms are listed in the Appendix 19.5, Table 41.

Throughout this document, the safety and efficacy analysis has been verified by the Agency for Study ECHELON-3 and not the other additional supportive studies mentioned by the Applicant.

8.2.2. Review of the Safety Database

Overall Exposure

Data:

BV administration and exposure by integrated safety analysis set is summarized in Table 25.

Table 25: Applicant-Summary of Treatment Administration- BV Integrated Safety Analysis Set

	ECHELON-3					
Duration of study treatment[a] (months)	BV+Len+R (N=112)	Placebo+Len+R (N=116)	DLBCL Combo Other (N=112)	DLBCL Mono (N=102)	DLBCL Total (N=326)	P3 BV Combo (N=997)
N	112	116	112	102	326	997
Mean (STD)	5.9 (5.6)	3.5 (4.3)	3.9 (2.3)	3.4 (3.1)	4.5 (4.1)	5.3 (2.3)
Median	3.6	2.0	4.3	2.0	3.6	5.5
Min, Max	0, 26	0, 27	0, 17	1, 15	0, 26	0, 26
Number of cycles[b] administered						
N	112	116	112	102	326	997
Mean (STD)	7.6 (7.3)	4.9 (5.7)	5.3 (3.0)	4.6 (4.0)	5.9 (5.3)	5.9 (2.8)
Median	5.0	3.0	6.0	3.0	5.0	6.0
Min, Max	1, 34	1, 37	1, 22	1, 19	1, 34	1, 34

a. ECHELON-3: duration of treatment is time from first dose of any study treatment to the earliest of the following: 21 days from last dose of BV or rituximab, last dose date of lenalidomide, date of death, start of subsequent anticancer therapy, or data cutoff date; SGN35-012/-017/-023 and ECHELON-2: duration of treatment is from first dose date of any study treatment to the earlier of 21 days from day 1 of last dosing cycle or death date; ECHELON-1: duration of treatment is time from first study dose to 14 days after the last dose date.
b. Cycle with any amount (>0) of any component of study treatment received.

Source: m5.3.5.3, ECHELON-3 ISS, Table 14.4.1

The Applicant's Position:

The median duration of treatment and number of cycles observed in the BV+Len+R arm in ECHELON-3 was similar to the DLBCL Combo Other analysis group (4.3 months and 6.0 cycles). Compared to the BV+Len+R arm and the DLBCL Combo Other analysis group, the median duration of treatment and number of cycles in the DLBCL Mono analysis group (2.0 months and 3.0 cycles) and the placebo+Len+R arm (2.0 months and 3.0 cycles) was expectedly lower. Together, these data suggests that the addition of BV to combination therapy may result in longer treatment durations for subjects with DLBCL.

The FDA's Assessment:

The FDA disagrees with The Applicant's approach in prioritizing the comparison of BV+R2 versus the groups other than the placebo arm of the ECHELON-3. Overall, there is a limited duration of exposure for both the BV+R2 arm (median 3.6 months) and the control arm (median 2 months), and there is an observed increase in serious and fatal AE and AE driven dosage modifications in recipients of BV + R2. We acknowledge that several factors such as the aggressive nature of R/R LBCL, and the expected toxicities from an active ADC add-on agent (compared to the placebo arm) could contribute to this limited exposure data.

Relevant characteristics of the safety population:

Data:

Baseline subject and disease characteristics are summarized for the integrated safety analysis sets in Table 26. Within the DLBCL population, the results of the pivotal ECHELON-3 study demographic characteristics were generally similar to all DLBCL analysis groups. There was a higher percentage of White subjects in the DLBCL Combo Other, DLBCL Mono, and DLBCL Total analysis groups compared to both arms of ECHELON-3. However, the percentage of White subjects was similar when comparing the DLBCL Total and P3 BV Combo analysis groups.

Table 26: Applicant- Baseline Subject and Disease Characteristics- BV Integrated Safety Analysis Set

	ECHELON-3					
	BV+Len+R (N=112) n (%)	Placebo+Len+R (N=116) n (%)	DLBCL Combo Other (N=112) n (%)	DLBCL Mono (N=102) n (%)	DLBCL Total (N=326) n (%)	P3 BV Combo (N=997) n (%)
Age (yr)						
N	112	116	112	102	326	997
Mean (STD)	69.2 (12.7)	65.7 (14.6)	62.8 (13.4)	61.3 (16.6)	64.5 (14.7)	45.9 (18.6)
Median	74.0	70.0	67.0	64.0	68.0	44.0
Min, Max	29, 87	21, 89	21, 81	17, 91	17, 91	18, 87

	ECHELON-3					
	BV+Len+R (N=112) n (%)	Placebo+Len+R (N=116) n (%)	DLBCL Combo Other (N=112) n (%)	DLBCL Mono (N=102) n (%)	DLBCL Total (N=326) n (%)	P3 BV Combo (N=997) n (%)
Age category, n (%)						
<65 years old	33 (29.5)	41 (35.3)	47 (42.0)	52 (51.0)	132 (40.5)	790 (79.2)
≥65 years old	79 (70.5)	75 (64.7)	65 (58.0)	50 (49.0)	194 (59.5)	207 (20.8)
Sex, n (%)						
Male	60 (53.6)	68 (58.6)	66 (58.9)	54 (52.9)	180 (55.2)	568 (57.0)
Female	52 (46.4)	48 (41.4)	46 (41.1)	48 (47.1)	146 (44.8)	429 (43.0)
Race, n (%)						
American Indian or Alaska Native	0	1 (0.9)	0	2 (2.0)	2 (0.6)	0
Asian	28 (25.0)	32 (27.6)	3 (2.7)	5 (4.9)	36 (11.0)	129 (12.9)
Black or African American	0	0	6 (5.4)	8 (7.8)	14 (4.3)	32 (3.2)
Native Hawaiian or Other Pacific Islander	0	0	0	1 (1.0)	1 (0.3)	1 (0.1)
White	65 (58.0)	56 (48.3)	95 (84.8)	83 (81.4)	243 (74.5)	759 (76.1)
Other	0	1 (0.9)	1 (0.9)	3 (2.9)	4 (1.2)	21 (2.1)
Not Reported	18 (16.1)	26 (22.4)	0	0	18 (5.5)	28 (2.8)
Missing unknown	1 (0.9)	0	7 (6.3)	0	8 (2.5)	27 (2.7)
Ethnicity, n (%)						
Hispanic or Latino	4 (3.6)	5 (4.3)	10 (8.9)	9 (8.8)	23 (7.1)	65 (6.5)
Not Hispanic or Latino	90 (80.4)	84 (72.4)	96 (85.7)	93 (91.2)	279 (85.6)	842 (84.5)
Not reported	18 (16.1)	26 (22.4)	0	0	18 (5.5)	60 (6.0)
Missing/unknown	0	1 (0.9)	6 (5.4)	0	6 (1.8)	30 (3.0)
ECOG Performance Status, n (%)						
0	42 (37.5)	41 (35.3)	33 (29.5)	27 (26.5)	102 (31.3)	501 (50.3)
1	58 (51.8)	63 (54.3)	53 (47.3)	59 (57.8)	170 (52.1)	406 (40.7)
2	12 (10.7)	12 (10.3)	26 (23.2)	16 (15.7)	54 (16.6)	89 (8.9)
Missing	0	0	0	0	0	1 (0.1)
Disease stage at enrollment[a], n (%)						
Stage I	14 (12.5)	7 (6.0)	1 (0.9)	3 (2.9)	18 (5.5)	26 (2.6)
Stage II	15 (13.4)	13 (11.2)	11 (9.8)	17 (16.7)	43 (13.2)	45 (4.5)
Stage III	14 (12.5)	32 (27.6)	27 (24.1)	22 (21.6)	63 (19.3)	307 (30.8)
Stage IV	69 (61.6)	64 (55.2)	73 (65.2)	57 (55.9)	199 (61.0)	618 (62.0)
Not applicable/unknown	0	0	0	3 (2.9)	3 (0.9)	1 (0.1)

a. Stage includes Stage A and Stage B.
Source: m5.3.5.3, ECHELON-3 ISS, Table 14.2.1

The Applicant's Position:

Patient demographics and baseline disease characteristics in the safety population were generally consistent with that seen in the ECHELON-3 study. As described in Section 8.1.2, the ECHELON-3 population is generally representative of the R/R DLBCL population based on demographics and disease characteristics.

The FDA's Assessment:
The Agency agrees with the Applicant's assessment regarding the demographics and baseline characteristics of the safety population in ECHELON-3. Notably, there is inadequate representation of racial and ethnic minorities, with no African American representation, only 4% of the enrolled study population being Hispanic, and 9% of patients being enrolled from the US. Refer to section 8.1.1 for more details on the demographics and baseline characteristics of ECHELON-3.

Adequacy of the safety database:

Data:

Data from 6 studies (ECHELON-3, with supportive safety data from SRI portion of ECHELON-3, SGN35-012, SGN35 017, SGN35-023, ECHELON-1 and ECHELON-2) contributing to 5 pooled populations were used to provide a comprehensive assessment and to fully characterize the safety of BV in subjects with DLBCL. The pools described in detail in Section 8.2.1 include 112 subjects in the BV+Len+R arm of ECHELON-3 (116 in placebo+Len+R arm), 112 subjects in DLBCL Combo Other (BV+multi-agent chemo in subjects with DLBCL), 102 subjects in DLBCL Mono (BV monotherapy in subjects with DLBCL), 326 subjects in DLBCL Total (BV or BV+ multi-agent chemotherapy in subjects with DLBCL), and 997 subjects in Phase 3 BV Combo (BV+ multi-agent therapy in subjects across different disease settings).

The Applicant's Position:

The overall safety database is adequate to support the characterization of the safety profile of BV in subjects with R/R DLBCL.

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

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:

The sponsor representative(s) made periodic site visits to review the progress of the studies. The Clinical Quality Assurance group or its designee conducted audits at the clinical sites or other study-related facilities and organizations. Database management was performed by the sponsor.

An electronic data capture system was employed for the studies. The sponsor provided eCRF completion guidelines to study site personnel. Queries resulting from edit checks and/or data verification procedures were posted electronically in the eCRF. Site audits were conducted in all trials as outlined in the respective CSRs.

The Applicant's Position:

No issues with data integrity and/or analysis were identified that precluded inclusion of data in the analysis or conclusions regarding the safety assessment.

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

Categorization of Adverse Event

Data:

For ECHELON-3, a TEAE is defined as any newly occurring or worsening AE after the first dose of study treatment through the end of safety reporting period (30 days after last dose of BV or lenalidomide or 110 days after last dose of rituximab, whichever is later). There were minor differences across studies in the definition of TEAEs; these are captured in each study specific CSR and the ISS SAP. All AEs were coded to standard "Preferred Terms" (PT) and system organ classifications (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA, Version 26.0) for all studies.

AE grades were based on the grades reported in each of the studies. Safety was evaluated according to the following versions of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE):

- SGN35-012, SGN35-017, SGN35-023, ECHELON-1, ECHELON-2: version 4.03
- ECHELON-3: version 5.0

Subject incidence of AEs was summarized by SOC and/or preferred term in descending frequency in the ECHELON-3 BV treatment arm, and then by alphabetical order of PTs or severity, as applicable. In the summary tables, a subject was counted only once for each preferred term at the worse grade of severity. Similarly, if a subject had more than 1 AE within a body system, the subject was counted only once in that body system.

PN is an event of clinical interest for BV. Classification of PN events will be based on the standardized MedDRA query broad. PN events may be divided into peripheral sensory neuropathy and peripheral motor based on neuropathy based on special search query.

The Applicant's Position:

The approach to categorization of AEs was consistent with Health Authority guidance and appropriate for evaluation of the safety data.

The FDA's Assessment:
The Agency agrees with the Applicant's assessment. For more details on the FDA grouping of preferred terms such as peripheral neuropathy (PN), refer to Table 41.

Routine Clinical Tests

Data:

Abnormal clinical laboratory values were reported as TEAEs if they were considered a clinically significant change from baseline or led to premature discontinuation of study drug, dose modification, or other therapeutic intervention. An integrated analysis of clinical laboratory data wasn't conducted, but relevant information is detailed in individual CSRs when applicable. Hematologic and clinical chemistry values are included in m5.3.5.1, ECHELON-3 CSR, Section 11.2.2.

The Applicant's Position:

Overall, no new safety concerns emerged from clinical laboratory evaluations in ECHELON-3. Findings aligned with the established safety profiles of BV, lenalidomide, and rituximab.

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

8.2.4. Safety Results

Deaths

Data:

A summary of deaths within /after 30 days of last dose of study treatment is provided in Table 27. Across all analysis groups of DLBCL, subjects treated with BV, most deaths were disease related and occurred >30 days after last dose of study treatment.

Table 27: Applicant-Summary of Deaths- BV Integrated Safety Analysis Set

	ECHELON-3					
	BV+Len+R (N=112) n (%)	Placebo+Len+R (N=116) n (%)	DLBCL Combo Other (N=112) n (%)	DLBCL Mono (N=102) n (%)	DLBCL Total (N=326) n (%)	P3 BV Combo (N=997) n (%)
Overall death	58 (52)	74 (64)	34 (30)	65 (64)	157 (48)	136 (14)
Primary cause of death						
Disease related death	40 (36)	59 (51)	24 (21)	56 (55)	120 (37)	89 (9)
Not disease related death	13 (12)	11 (9)	8 (7)	7 (7)	28 (9)	38 (4)
Missing/unknown	5 (4)	4 (3)	2 (2)	2 (2)	9 (3)	9 (1)

	ECHELON-3					
	BV+Len+R (N=112) n (%)	Placebo+Len+R (N=116) n (%)	DLBCL Combo Other (N=112) n (%)	DLBCL Mono (N=102) n (%)	DLBCL Total (N=326) n (%)	P3 BV Combo (N=997) n (%)
Deaths within 30 days of last dose of study treatment	10 (9)	15 (13)	4 (4)	9 (9)	23 (7)	27 (3)
Disease related death	5 (4)	12 (10)	0	8 (8)	13 (4)	12 (1)
Not disease related death	5 (4)	3 (3)	3 (3)	1 (1)	9 (3)	15 (2)
Missing/unknown	0	0	1 (1)	0	1 (<1)	0
Deaths after 30 days of last dose of study treatment	48 (43)	59 (51)	30 (27)	56 (55)	134 (41)	109 (11)
Disease related death	35 (31)	47 (41)	24 (21)	48 (47)	107 (33)	77 (8)
Not disease related death	8 (7)	8 (7)	5 (4)	6 (6)	19 (6)	23 (2)
Missing/unknown	5 (4)	4 (3)	1 (1)	2 (2)	8 (2)	9 (1)

Source: m5.3.5.3, ECHELON-3 ISS, Table 14.7.1

The Applicant's Position:

The incidence of overall death in the BV+Len+R arm in ECHELON-3 was generally similar to the DLBCL analysis groups. The overall death rate was higher when comparing the BV+Len+R arm and DLBCL Total analysis group to the P3 BV Combo analysis group. The variance in death rates is expected due to differences in demographic characteristics and disease settings between the populations studied. Subjects with R/R DLBCL are typically older and heavily pre-treated, increasing the likelihood of reduced fitness levels, treatment-related comorbidities, and pre-existing conditions compared to newly diagnosed patients. Most deaths were due to disease related factors more than 30 days after last dose of study treatment.

The FDA's Assessment:

For the death analysis, the FDA has used the predefined duration of safety reporting period (versus the 30 days in the Applicant's analysis) which is from the first dose of any study drug through 30 days after last dose of brentuximab vedotin or lenalidomide or 110 days after last dose of rituximab, whichever is later. Reasons for death have been revised based on narratives of deaths that occurred within the safety reporting period. Progressive disease was the leading cause of death in both arms (higher percentage in the placebo arm) followed by AEs. There were no deaths due to progressive disease within 30 days of last dose of study treatment or deaths due to TEAE which were reported in the safety update period.

Table 28: Deaths Within and Beyond the Safety Reporting Period

Cause of Death	Bv+R2 (N=112) n (%)	Pbo+R2 (N=116) n (%)

All deaths	58 (52)	74 (64)
PD	37 (33)	57 (49)
AE	15 (13)	8 (7)
Unknown	5 (4.5)	3 (2.6)
Other	1 (0.9)	6 (5)
Deaths within 30/110 days of last dose	32 (29)	41 (35)
PD/NALT	19 (17) • 15/18: after NALT	34 (29) • 26/34: after NALT
AE	12 (11) • n=5: COVID-19 • n=1 each: AKI, asphyxia, confusional state, health deterioration, PNA, subdural hematoma, urosepsis	5 (4.3) • n=2: COVID-19 • n=1 each: MI, viral hepatitis, intestinal perforation
Unknown	1	1 (death)
Other	0	1 Cardiac disorder

Source: Reviewer analysis of ADAE.xpt and death narratives
NALT: next anti lymphoma therapy
*Data cutoff: 1/22/2024

Serious Adverse Events

Data:

TESAEs occurring in ≥2% of BV+Len+R subjects across studies in the integrated safety analysis set are presented in Table 29.

Table 29: Applicant- Treatment-Emergent Serious Adverse Events by Preferred Term (occurring in ≥2% of BV+Len+R subjects) –BV Integrated Safety Analysis Set

	ECHELON-3					
Preferred Term	BV+Len+R (N=112) n (%)	Placebo+Len+R (N=116) n (%)	DLBCL Combo Other (N=112) n (%)	DLBCL Mono (N=102) n (%)	DLBCL Total (N=326) n (%)	P3 BV Combo (N=997) n (%)
Subjects with any event	67 (60)	58 (50)	57 (51)	48 (47)	172 (53)	437 (44)
Pneumonia	12 (11)	6 (5)	6 (5)	9 (9)	27 (8)	45 (5)
COVID-19	8 (7)	6 (5)	0	0	8 (2)	8 (1)
COVID-19 pneumonia	8 (7)	4 (3)	0	0	8 (2)	8 (1)
Febrile neutropenia	7 (6)	6 (5)	19 (17)	4 (4)	30 (9)	152 (15)

	ECHELON-3					
Preferred Term	BV+Len+R (N=112) n (%)	Placebo+Len+R (N=116) n (%)	DLBCL Combo Other (N=112) n (%)	DLBCL Mono (N=102) n (%)	DLBCL Total (N=326) n (%)	P3 BV Combo (N=997) n (%)
General physical health deterioration	4 (4)	3 (3)	0	0	4 (1)	4 (<1)
Septic shock	4 (4)	1 (1)	0	0	4 (1)	9 (1)
Urinary tract infection	4 (4)	0	1 (1)	1 (1)	6 (2)	8 (1)
Sepsis	3 (3)	1 (1)	4 (4)	3 (3)	10 (3)	22 (2)
Thrombocytopenia	3 (3)	1 (1)	0	2 (2)	5 (2)	5 (1)
Atrial fibrillation	2 (2)	2 (2)	1 (1)	0	3 (1)	5 (1)
Clostridium difficile infection	2 (2)	1 (1)	0	0	2 (1)	4 (<1)
Femoral neck fracture	2 (2)	0	0	0	2 (1)	2 (<1)
Myelodysplastic syndrome	2 (2)	1 (1)	1 (1)	0	3 (1)	2 (<1)
Pancytopenia	2 (2)	2 (2)	3 (3)	0	5 (2)	4 (<1)
Pneumonitis	2 (2)	0	1 (1)	0	3 (1)	9 (1)
Pyrexia	2 (2)	5 (4)	2 (2)	5 (5)	9 (3)	55 (6)
Respiratory failure	2 (2)	1 (1)	2 (2)	2 (2)	6 (2)	7 (1)
Urosepsis	2 (2)	0	0	0	2 (1)	2 (<1)

Source: m5.3.5.3, ECHELON-3 ISS, Table 14.5.7

The Applicant's Position:

The safety profile and incidence of TESAEs in the BV+Len+R arm of ECHELON-3 was generally consistent to the other DLBCL analysis groups treated with BV. In the setting of the pivotal ECHELON-3 study being conducted during the COVID-19 pandemic and infection being a known adverse reaction for BV, lenalidomide, and rituximab (BV, Len, and R); serious pneumonia, COVID-19, and COVID-19 pneumonia were reported at a higher frequency (≥5% difference) in the BV+Len+R arm compared to the DLBCL Combo Other analysis group. A similar trend was noted for treatment-related TESAEs.

Overall, the profile of TESAEs across the integrated safety analysis groups was generally consistent with the known adverse reactions of the individual study drugs and/or underlying diseases and study populations.

The FDA's Assessment:

The Agency agrees with the Applicant that SAEs occurred in 67 (60%) of the patients in the BV+R2 arm. The FDA analysis focused on the comparison between the BV and Pbo arm of the ECHELON-3 study. In general, as expected for this add-on trial, SAEs were higher in the BV+R2 arm. Of note, during the labeling negotiations the Applicant requested (b) (4) (b) (4) and the Agency agreed (b) (4) - (b) (4) (b) (4) Infections (pneumonia, sepsis and COVID-19 were the most common SAEs in the BV+R2 arm.

Table 30: Serious Adverse Events in Echelon-3

Serious AEs and ≥ Grade 3		
	BV+R2 N=112 %	**Pbo+R2 N=116 %**
Any SAE	60	50
≥ Grade 3 AE	88	77
Grade 5	11	8
SAEs ≥ 5% in Bv+R2 arm (%)		
Pneumonia	21	8
Sepsis	8	2.6
COVID-19	7	5
Febrile neutropenia	7	5
Hemorrhage	5	1.7

Source: FDA analysis

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

TEAEs leading to permanent treatment discontinuation of all study drugs (SGN35-012, SGN35-017, SGN35-023, ECHELON2, and ECHELON-3) and/or any study drug (ECHELON-1) are summarized and presented by preferred term across studies in the integrated safety analysis groups in Table 31.

Table 31: Applicant- Treatment-Emergent Adverse Events Leading to Treatment Discontinuation by Preferred Term (Occurring in ≥1% of BV+Len+R subjects) – BV Integrated Safety Analysis Set

	ECHELON-3					
Preferred Term	BV+Len+R (N=112) n (%)	Placebo+Len+R (N=116) n (%)	DLBCL Combo Other (N=112) n (%)	DLBCL Mono (N=102) n (%)	DLBCL Total (N=326) n (%)	P3 BV Combo (N=997) n (%)
Subjects with any event	17 (15)	10 (9)	18 (16)	10 (10)	45 (14)	119 (12)
COVID-19	2 (2)	2 (2)	0	0	2 (1)	2 (<1)
COVID-19 pneumonia	2 (2)	1 (1)	0	0	2 (1)	2 (<1)
General physical health deterioration	2 (2)	0	0	0	2 (1)	2 (<1)
Myelodysplastic syndrome	2 (2)	1 (1)	1 (1)	0	3 (1)	2 (<1)
Pneumonitis	2 (2)	0	0	0	2 (1)	4 (<1)
Asphyxia	1 (1)	0	0	0	1 (<1)	1 (<1)
Gastrointestinal haemorrhage	1 (1)	0	1 (1)	0	2 (1)	1 (<1)
Leukopenia	1 (1)	0	0	0	1 (<1)	1 (<1)
Paraesthesia	1 (1)	0	0	0	1 (<1)	2 (<1)
Pneumonia	1 (1)	0	0	0	1 (<1)	3 (<1)
Respiratory failure	1 (1)	0	0	0	1 (<1)	3 (<1)
Urosepsis	1 (1)	0	0	0	1 (<1)	1 (<1)

Source: m5.3.5.3, ECHELON-3 ISS, Table 14.5.10

The Applicant's Position:

The incidence of TEAEs leading to permanent treatment discontinuation of all study drugs (SGN35-012, SGN35-017, SGN35-023, ECHELON-2, and ECHELON-3) and/or any study drug (ECHELON-1) for subjects with any event was similar across the integrated safety analysis groups.

Overall, the TEAEs leading to permanent discontinuation of all study drugs (SGN35-012, SGN35-017, SGN35-023, ECHELON-2, and ECHELON-3) and/or any study drug

(ECHELON-1) were generally consistent with the known adverse reactions of the respective study treatments in each study and/or preexisting comorbidities, and study populations.

The FDA's Assessment:

The FDA mainly focused the analysis on the AEs leading to dose discontinuation of BV or placebo in the BV+R2 and Pbo+R2 arms, respectively and did not conduct this analysis in the proposed safety pool populations above. Adverse reactions led to discontinuation of BV in 20% of patients. Adverse reactions that led to treatment discontinuation in 3 or more patients include peripheral neuropathy (4.5%) and pneumonia (2.7%). For the FDA grouping of preferred terms refer to Table 41. We agree with the Applicant that TEAEs were generally consistent with the known adverse reactions of BV in the previous FDA approvals.

Dose Interruptions, Delays, and/or Reductions Due to Adverse Effects

Data:

In the ECHELON-3 study, BV+Len+R was administered for a longer duration of treatment compared to placebo. Therefore, differences in the frequency of each dose modification (and overall) between treatment arms were anticipated. As such, the percentage of subjects that required any dose modification due to AEs was higher in the BV+Len+R arm versus the placebo+Len+R arm (76% and 48%, respectively).

TEAEs leading to dose delay and reduction occurred at a higher frequency in the BV+Len+R arm when compared to the other DLBCL analysis groups treated with BV. For dose delays, this observation was primarily driven by hematologic abnormalities (which are known adverse reactions for BV, Len, and R) and COVID-19 related events (ECHELON-3 was conducted during the COVID-19 pandemic). For dose reductions, this observation was primarily driven by hematologic abnormalities and reflects the overlapping safety profiles of BV, Len, and R as noted previously. When comparing the BV+Len+R arm and DLBCL Total analysis groups to the P3 BV Combo analysis group, the types and incidence of TEAEs leading to dose delays or reductions was generally similar.

The Applicant's Position:

Overall, the leading reasons for any dose delays or reductions due to TEAE were generally consistent with the known adverse reactions of the respective study treatments.

The FDA's Assessment:

TEAEs leading to dose delay and reduction occurred at a higher frequency in the Bv+R2 compared to Pbo+R2 arm (46% vs 25% and 6% versus 1.7%). Adverse reactions leading to dose delay of BV in more than 5% of patients included neutropenia, COVID-19, pneumonia and thrombocytopenia. Peripheral neuropathy was the only reason for BV dose reduction. As previously noted, we do not agree with the Applicant's position to mainly focus on comparing safety of BV+R2 with the safety pool populations given the limitations of cross trial comparison.

Significant Adverse Events

Grade 3 or higher TEAEs

Data:

The most common Grade 3 or higher TEAEs regardless of causality occurring in ≥5% of BV+Len+R subjects in the integrated safety analysis set are presented in Table 32. The BV+Len+R arm had a slightly higher percentage of subjects experiencing Grade 3 or higher TEAEs (88%) compared to the placebo+Len+R arm (77%). When adjusting for total exposure across both arms, the exposure-adjusted incidence rate for Grade 3 or higher TEAEs was similar. Within the DLBCL analysis groups treated with BV, the safety profile of Grade 3 or higher TEAEs was generally consistent with the BV+Len+R arm in ECHELON-3. Febrile neutropenia occurred ≥10% more frequently in the DLBCL Combo Other group compared to all other DLBCL analysis groups treated with BV, including the BV+Len+R arm. The subject incidence of neutropenia in the BV+Len+R arm (43%) was ≥10% higher than the DLBCL Mono and DLBCL Combo Other analysis groups (31% and 29%, respectively), but was similar to the DLBCL Total analysis group (35%). Due to overlapping safety profiles as previously mentioned, thrombocytopenia occurred more frequently in the BV+Len+R arm (25%) compared to the DLBCL Combo Other and DLBCL Total analysis groups (10% and 14%, respectively). As previously mentioned, hematologic abnormalities (including Grade 3 or higher events) are expected adverse reactions for BV, Len, and R. These were effectively managed with dose modifications per protocol as indicated by a low rate of treatment discontinuation due to hematologic abnormalities.

Table 32: Applicant- Grade 3 or Higher TEAEs by Preferred Term (occurring in ≥5% of BV+Len+R subjects) – BV Integrated Safety Analysis Set

	ECHELON-3					
Preferred Term	BV+Len+R (N=112) n (%)	Placebo+Len+R (N=116) n (%)	DLBCL Combo Other (N=112) n (%)	DLBCL Mono (N=102) n (%)	DLBCL Total (N=326) n (%)	P3 BV Combo (N=997) n (%)
Subjects with any event	99 (88)	89 (77)	80 (71)	78 (76)	257 (79)	795 (80)
Neutropenia	48 (43)	32 (28)	33 (29)	32 (31)	113 (35)	482 (48)
Thrombocytopenia	28 (25)	22 (19)	11 (10)	6 (6)	45 (14)	50 (5)
Anaemia	25 (22)	24 (21)	20 (18)	12 (12)	57 (17)	109 (11)
Pneumonia	12 (11)	6 (5)	8 (7)	9 (9)	29 (9)	45 (5)
Febrile neutropenia	10 (9)	11 (9)	22 (20)	6 (6)	38 (12)	179 (18)
Neutrophil count decreased	9 (8)	7 (6)	5 (4)	1 (1)	15 (5)	92 (9)
COVID-19	8 (7)	6 (5)	0	0	8 (2)	8 (1)

	ECHELON-3					
Preferred Term	BV+Len+R (N=112) n (%)	Placebo+Len+R (N=116) n (%)	DLBCL Combo Other (N=112) n (%)	DLBCL Mono (N=102) n (%)	DLBCL Total (N=326) n (%)	P3 BV Combo (N=997) n (%)
COVID-19 pneumonia	8 (7)	4 (3)	0	0	8 (2)	8 (1)
Fatigue	7 (6)	3 (3)	4 (4)	8 (8)	19 (6)	28 (3)
Hypokalaemia	6 (5)	3 (3)	7 (6)	5 (5)	18 (6)	22 (2)

Source: m5.3.5.3, ECHELON-3 ISS, Table 14.5.9

The Applicant's Position:

Within the DLBCL analysis groups treated with BV, the safety profile of Grade 3 or higher TEAEs was generally consistent with the BV+Len+R arm in ECHELON-3. Hematologic abnormalities (including Grade 3 or higher events) are expected adverse reactions for BV, lenalidomide and rituximab. These were effectively managed with dose modifications per protocol as indicated by a low rate of treatment discontinuation due to hematologic abnormalities.

The FDA's Assessment:

The FDA's analysis showed a higher incidence of Grade 3 and greater TEAEs in the BV+R2 versus Pbo+R2 arm (88% vs. 77%). See Table 36 for the incidence of Grade 3 and 4 TEAEs in both arms. The FDA does not rely on exposure adjusted analyses as the adverse event data is evaluated in the context of the totality of the regimen as administered to patients.

Peripheral Neuropathy

Data:

BV treatment causes a PN that is predominantly sensory. Cases of peripheral motor neuropathy have also been reported. TEAEs of PN summarized by preferred term and maximum severity across studies in the integrated safety analysis set are presented in Table 33.

Table 33: Applicant-Summary of Treatment-Emergent Adverse Events of Peripheral Neuropathy by Preferred Term – BV Integrated Safety Analysis Set

	ECHELON-3					
Preferred Term Maximum Grade	BV+Len+R (N=112) n (%)	Placebo+Len+R (N=116) n (%)	DLBCL Combo Other (N=112) n (%)	DLBCL Mono (N=102) n (%)	DLBCL Total (N=326) n (%)	P3 BV Combo (N=997) n (%)
Subject with any event	35 (31)	28 (24)	68 (61)	42 (41)	145 (44)	594 (60)
Grade 1	18 (16)	18 (16)	33 (29)	23 (23)	74 (23)	335 (34)

	ECHELON-3					
Preferred Term Maximum Grade	BV+Len+R (N=112) n (%)	Placebo+Len+R (N=116) n (%)	DLBCL Combo Other (N=112) n (%)	DLBCL Mono (N=102) n (%)	DLBCL Total (N=326) n (%)	P3 BV Combo (N=997) n (%)
Grade 2	10 (9)	8 (7)	26 (23)	14 (14)	50 (15)	173 (17)
Grade 3	7 (6)	2 (2)	9 (8)	5 (5)	21 (6)	84 (8)
Grade 4	0	0	0	0	0	2 (<1)
Peripheral sensory neuropathy	22 (20)	9 (8)	49 (44)	29 (28)	100 (31)	311 (31)
Peripheral motor neuropathy	7 (6)	3 (3)	15 (13)	7 (7)	29 (9)	57 (6)
Muscular weakness	5 (4)	5 (4)	7 (6)	6 (6)	18 (6)	47 (5)
Paraesthesia	5 (4)	6 (5)	8 (7)	2 (2)	15 (5)	99 (10)
Hypoaesthesia	3 (3)	3 (3)	4 (4)	7 (7)	14 (4)	39 (4)
Neuropathy peripheral	2 (2)	2 (2)	2 (2)	0	4 (1)	176 (18)
Gait disturbance	1 (1)	1 (1)	1 (1)	1 (1)	3 (1)	4 (<1)
Areflexia	0	0	0	0	0	1 (<1)
Autonomic neuropathy	0	0	0	0	0	1 (<1)
Burning sensation	0	1 (1)	0	0	0	2 (<1)
Dysaesthesia	0	0	1 (1)	0	1 (<1)	6 (1)
Guillain-Barre syndrome	0	0	1 (1)	0	1 (<1)	0
Muscle atrophy	0	0	0	0	0	2 (<1)
Neuralgia	0	2 (2)	0	2 (2)	2 (1)	8 (1)
Neurotoxicity	0	0	0	0	0	2 (<1)
Peripheral sensorimotor neuropathy	0	0	0	0	0	6 (1)
Peroneal nerve palsy	0	0	1 (1)	1 (1)	2 (1)	2 (<1)
Polyneuropathy	0	0	0	0	0	11 (1)
Skin burning sensation	0	0	0	1 (1)	1 (<1)	1 (<1)
Toxic neuropathy	0	0	0	0	0	3 (<1)

Source: m5.3.5.3, ECHELON-3 ISS, Table 14.5.18

The Applicant's Position:

PN events were mainly low grade (Grade 2 or lower), predominantly sensory, and manageable as evidenced by a low rate of dose modifications due to PN. These results are consistent with the established safety profile of BV in combination therapy.

The FDA's Assessment:

In ECHELON-3, 27% of patients treated with BV+R2 experienced peripheral neuropathy of any grade (by maximum grade, 14% Grade 1, 7% Grade 2, 5% Grade 3). The peripheral neuropathy was predominantly sensory and had a median time to onset of 3 months (range, <1-10). Peripheral neuropathy resulted in BV dose reduction in 6% of treated patients, and permanent discontinuation in 4.5%. At last evaluation, 7% of the patients who experienced peripheral neuropathy had complete resolution of neuropathy, 10% had partial improvement, and 83% had no improvement. For those with resolution, the median time was 2 months (range <1-3). The median time to improvement was 4 months (range, 3-4). Of patients who experienced peripheral neuropathy, 93% had ongoing peripheral neuropathy (47% had Grade 1, 33% had Grade 2, and 13% had Grade 3). The FDA disagrees with the Applicant that the PN events were mainly manageable given the high number of unresolved peripheral neuropathy but agrees that in general the PN events were consistent with the established safety profile of BV in a combination therapy.

Of note, the Applicant has included terms such as burning sensation, muscle weakness and gait disturbance throughout this document but revised it to the FDA's preferred grouping (b) (4) (b) (4)

Treatment Emergent Adverse Events and Adverse Reactions

Data:

In ECHELON-3, BV in combination with lenalidomide and rituximab was well tolerated with a manageable safety profile that was consistent with the known adverse reactions of the individual treatment components and/or underlying disease, preexisting comorbidities, and age of the study population. The subject incidence in the BV+Len+R arm was higher than in the placebo+Len+R arm for the following events: Grade 3 or higher TEAEs, serious TEAEs (TESAEs), TEAEs leading to death, and TEAEs leading to treatment discontinuations. When assessing number of events/person-year (E/PY) across both arms, the PY exposure-adjusted incidence rates for overall TEAEs, Grade 3 or higher TEAEs, TESAEs, TEAEs leading to death, and TEAEs leading to treatment discontinuation were similar. PN events were mainly low grade (Grade 2 or lower), predominantly sensory, and manageable. The main safety findings were hematologic abnormalities and infection related events, both of which are part of the established safety profiles of BV, lenalidomide, and rituximab with appropriate management and supportive care guidelines included in each product label, respectively.

No new adverse reactions were identified (see m2.5, Appendix A for further details).

An overview of TEAEs reported per the study protocols, across safety analysis groups is presented in Table 34.

Table 34: Applicant- Overall Summary of Treatment-Emergent Adverse Events – BV Integrated Safety Analysis Set

	ECHELON-3		ECHELON-3 Exposure-Adjusted					
	BV+ Len+R (N=112) n (%)	Placebo+ Len+R (N=116) n (%)	BV+Len+R (PY=72.54) E (100*E/PY)	Placebo+Len+R (PY=52.36) E (100*E/PY)	DLBCL Combo Other (N=112) n (%)	DLBCL Mono (N=102) n (%)	DLBCL Total (N=326) n (%)	P3 BV Combo (N=997) n (%)
Subjects with any TEAE	109 (97)	113 (97)	1367 (1884.5)	926 (1768.5)	112 (100)	101 (99)	322 (99)	983 (99)
Treatment-related TEAE	98 (88)	88 (76)	697 (960.8)	396 (756.3)	107 (96)	83 (81)	288 (88)	949 (95)
Subjects with Grade 3 or higher TEAE	99 (88)	89 (77)	463 (638.3)	290 (553.9)	80 (71)	78 (76)	257 (79)	795 (80)
Grade 3 or higher treatment-related TEAE	79 (71)	58 (50)	306 (421.8)	148 (282.7)	69 (62)	53 (52)	201 (62)	731 (73)
Subjects with any TESAE	67 (60)	58 (50)	146 (201.3)	109 (208.2)	57 (51)	48 (47)	172 (53)	437 (44)
Treatment-related TESAE	36 (32)	19 (16)	58 (80.0)	28 (53.5)	41 (37)	19 (19)	96 (29)	343 (34)
Subjects who discontinued treatment[a] due to TEAE	17 (15)	10 (9)	17 (23.4)	10 (19.1)	18 (16)	10 (10)	45 (14)	119 (12)
Discontinued treatment[a] due to treatment-related TEAE	8 (7)	5 (4)	8 (11.0)	5 (9.5)	11 (10)	6 (6)	25 (8)	99 (10)
Subjects with TEAE leading to death	13 (12)	9 (8)	13 (17.9)	9 (17.2)	7 (6)	15 (15)	35 (11)	30 (3)
Treatment-related TEAE leading to death	4 (4)	0	4 (5.5)	0	3 (3)	0	7 (2)	16 (2)

E=number of events; PY=person-year. PY are computed as sum of exposure period (minimum of (last BV/placebo + 30, last lenalidomide + 30, last rituximab + 110, death date, data cutoff date) - first dose date + 1); SAE=serious adverse event; TE=treatment-emergent; TEAE=treatment-emergent adverse event.

a. Permanent discontinuation of all ongoing study treatments (SGN35-012/-017/-023, ECHELON-2, and ECHELON-3) or permanent discontinuation of any study drug (ECHELON-1).

Source: m5.3.5.3, ECHELON-3 ISS, Table 14.5.1 and Table 14.5.1.1a

TEAEs occurring in ≥ 10% of BV+Len+R subjects regardless of causality in the integrated safety analysis set are presented in Table 35.

Table 35: Applicant- Treatment-Emergent Adverse Events by Preferred Term (≥10% of BV+Len+R Subjects) – BV Integrated Safety Analysis Set

	ECHELON-3					
Preferred Term	BV+Len+R (N=112) n (%)	Placebo+Len+R (N=116) n (%)	DLBCL Combo Other (N=112) n (%)	DLBCL Mono (N=102) n (%)	DLBCL Total (N=326) n (%)	P3 BV Combo (N=997) n (%)
Subjects with any event	109 (97)	113 (97)	112 (100)	101 (99)	322 (99)	983 (99)
Neutropenia	52 (46)	37 (32)	36 (32)	35 (34)	123 (38)	519 (52)
Thrombocytopenia	36 (32)	25 (22)	13 (12)	10 (10)	59 (18)	75 (8)
Diarrhoea	35 (31)	27 (23)	51 (46)	34 (33)	120 (37)	301 (30)
Anaemia	32 (29)	31 (27)	29 (26)	20 (20)	81 (25)	218 (22)
Fatigue	27 (24)	20 (17)	54 (48)	43 (42)	124 (38)	292 (29)
COVID-19	26 (23)	18 (16)	0	0	26 (8)	26 (3)
Asthenia	24 (21)	14 (12)	19 (17)	10 (10)	53 (16)	116 (12)
Peripheral sensory neuropathy	22 (20)	9 (8)	49 (44)	29 (28)	100 (31)	311 (31)
Constipation	19 (17)	21 (18)	31 (28)	27 (26)	77 (24)	362 (36)
Decreased appetite	19 (17)	11 (9)	27 (24)	25 (25)	71 (22)	176 (18)
Pneumonia	19 (17)	8 (7)	9 (8)	10 (10)	38 (12)	74 (7)
Cough	17 (15)	11 (9)	18 (16)	12 (12)	47 (14)	141 (14)
Nausea	17 (15)	19 (16)	58 (52)	37 (36)	112 (34)	468 (47)
Pruritus	17 (15)	7 (6)	12 (11)	10 (10)	39 (12)	68 (7)
Pyrexia	17 (15)	17 (15)	25 (22)	26 (25)	68 (21)	254 (25)
Hypokalaemia	15 (13)	9 (8)	21 (19)	14 (14)	50 (15)	89 (9)
Weight decreased	15 (13)	6 (5)	22 (20)	13 (13)	50 (15)	189 (19)
Rash	14 (13)	9 (8)	5 (4)	4 (4)	23 (7)	59 (6)
Dyspnoea	13 (12)	15 (13)	24 (21)	14 (14)	51 (16)	127 (13)
Hypotension	11 (10)	7 (6)	8 (7)	3 (3)	22 (7)	40 (4)

Source: m5.3.5.3, ECHELON-3 ISS, Table 14.5.3

The Applicant's Position:

Overall, the rate of subjects experiencing any category of TEAEs is similar across the integrated safety analysis groups. Since the durations of exposure, treatment regimens (ie, RCHOP, RCHP, AVD, bendamustine, rituximab, lenalidomide), and disease settings were different across the studies included in the integrated safety analysis groups, some variations in the frequency of certain categories and events were anticipated.

The FDA's Assessment:

The FDA's analysis of common TEAEs in patients in ECHELON-3 varied slightly from the Applicant's based on revised grouping of PTs. No new safety signals were identified. See the Appendix for definitions of the FDA's grouped terms. The revised table using FDA grouping is provided below. The most common TEAEs in the BV+R2 arm were fatigue, diarrhea, peripheral neuropathy, pneumonia, COVID-19 and rash.

Clinically relevant ARs in <10% of patients who received BV+R2 included febrile neutropenia, edema, hypotension, urinary tract infection, respiratory tract infection, vomiting, back pain, dizziness, arthralgia, herpes virus infection, bone pain, atrial fibrillation or flutter, lower respiratory tract infection, and cardiac failure.

The 120-day safety update did not identify any new or unanticipated safety signals. The Agency's primary evaluated of safety was based on the ECHELON-3 trial population. The FDA does not rely on exposure adjusted analyses as the adverse event data is evaluated in the context of the totality of the regimen as administered to patients.

Table 36: TEAEs in ≥10% of Patients in the BV + R2 Arm in ECHELON-3

	BV+R2 N=112		Pbo+R2 N=116	
Body System Adverse Reaction	**All Grades %**	**Grade 3-4 %**	**All Grades %**	**Grade 3-4 %**
General disorders and Administration Site Conditions				
Fatigue	46	10	29	5
Pyrexia	15	1.8	15	0.9
Gastrointestinal disorders				
Diarrhea	31	4.5	23	1.7
Constipation	17	1.8	18	0
Nausea	15	0.9	16	0.9
Abdominal pain	12	1.8	12	1.7
Stomatitis	11	0	7	0
Nervous system disorders				
Peripheral neuropathy	27	5	21	0
Infections and Infestations				
COVID-19	27	13	16	8
Pneumonia	27	21	10	9
Upper respiratory tract infection	12	2.7	5	0
Skin and subcutaneous tissue disorders				
Rash	27	2.7	16	0.9
Pruritus	17	0	6	0
Renal and urinary disorders				
Renal insufficiency	20	3.6	14	4.3
Respiratory, thoracic and mediastinal disorders				
Cough	17	0	9	0
Dyspnea	12	0.9	14	2.6

	BV+R2 N=112		Pbo+R2 N=116	
Body System Adverse Reaction	**All Grades %**	**Grade 3-4 %**	**All Grades %**	**Grade 3-4 %**
Metabolism and nutrition disorders				
Decreased appetite	17	0.9	9	0
Investigations				
Weight decreased	13	0.9	5	0.9

Source: FDA analysis of the ADAE.xpt dataset

Laboratory Findings

Data:

An integrated analysis of clinical laboratory data wasn't conducted, but relevant information is detailed in individual CSRs when applicable. Hematologic and clinical chemistry values for subjects in ECHELON-3 are included in m5.3.5.1, ECHELON-3 CSR, Section 11.2.2.

The Applicant's Position:

Overall, no new safety concerns emerged from clinical laboratory evaluations in ECHELON-3. Findings are aligned with the established safety profiles of BV, lenalidomide, and rituximab.

The FDA's Assessment:

The most common lab abnormality TEAEs in ≥20% of the patients in the BV+R2 arm were neutrophils decreased, lymphocyte decreased, platelets decreased, hemoglobin decreased, alanine aminotransferase increased, potassium decreased, albumin decreased, creatinine increased and calcium decreased. No new safety signals were identified.

Table 37: Select Laboratory Abnormalities (≥20%) that Worsened from Baseline in Patients Who Received BV in ECHELON-3

Laboratory Abnormality[a]	Bv + R2 N = 112[a]		Pbo+R2 N = 116[a]	
	All Grades (%)	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Hematology				
Neutrophils decreased	77	49	63	42
Lymphocyte decreased	65	38	53	30
Platelets decreased	65	29	54	18
Hemoglobin decreased	54	19	49	14
Chemistry				
Alanine aminotransferase increased	31	0.9	17	0

Laboratory Abnormality[a]	Bv + R2 N = 112[a]		Pbo+R2 N = 116[a]	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3 or 4 (%)
Potassium decreased	31	7	29	2.9
Albumin decreased	29	0.9	25	1
Creatinine increased	26	2.8	23	0
Calcium decreased	21	0.9	7	0

Source: FDA analysis

[a] The denominator used to calculate the rate varied from 105 to 107 in the Bv+R2 arm, and from 97 to 103 in the R2 arm based on the number of patients with at least one post-baseline value.

Vital Signs

The Applicant's Position:

Vital sign parameters were listed by visit for each subject in m5.3.5.1, ECHELON-3 CSR, Listing 16.2.10.1. In general, any clinically significant changes in vital signs (per investigator) were captured as AEs as part of a unifying diagnosis.

The FDA's Assessment:

The Agency agrees with the Applicant's assessment. There were no new safety signals identified based on vital sign analysis from this submission.

Electrocardiograms (ECGs)

The Applicant's Position:

ECG data including interpretation and clinical significance, were listed for each subject in m5.3.5.1, ECHELON-3 CSR, Listing 16.2.10.3. In general, any clinically significant changes in ECG (per investigator) were captured as AEs as part of a unifying diagnosis.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

QT

N/A

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Immunogenicity

Data:

In the ECHELON-3 study, 97 subjects (87%) were evaluable for ADA status. Overall, 8 of 97 subjects (8%) had treatment emergent ADA. Subjects that were positive on treatment tended to

become positive on Cycle 2 and all subjects decrease in titer or tested negative in later cycles. The highest titer was 1400 on Cycle 3 Day 1 but was down to 180 on Cycle 4 Day 1.

The Applicant's Position:

The immunogenicity of BV in the ECHELON-3 study was similar to or below that observed with BV monotherapy in other trials.

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

8.2.5. Analysis of Submission-Specific Safety Issues

The Applicant's Position:

No submission-specific safety issues were identified.

The FDA's Assessment:
The Agency conducted analysis of selected AEs of special interest including peripheral neuropathy, cytopenias and infections.

- **Peripheral neuropathy:** As mentioned above, in ECHELON-3, 27% of patients treated with BV+R2 experienced peripheral neuropathy of any grade (by maximum grade, 14% Grade 1, 7% Grade 2, 5% Grade 3). The peripheral neuropathy was predominantly sensory and had a median onset time of 3 months (range, <1-10). Peripheral neuropathy resulted in BV dose reduction in 6% of treated patients, and permanent discontinuation in 4.5%. At last evaluation, 7% of the patients who experienced peripheral neuropathy had complete resolution of neuropathy, 10% had partial improvement, and 83% had no improvement. For those with resolution, the median time was 2 months (range <1-3). The median time to improvement was 4 months (range, 3-4). Of patients who experienced peripheral neuropathy, 93% had ongoing peripheral neuropathy (47% had Grade 1, 33% had Grade 2, and 13% had Grade 3). The considerable percentage of unresolved PN is notable and concerning but not a new safety signal with BV. Of note, the Applicant has included terms such as burning sensation, muscle weakness and gait disturbance throughout this document but revised it to the FDA's preferred grouping terms (b) (4)

- **Cytopenias:** As shown in the lab shift analysis table, incidence of all grade and grade 3-4 was higher in the BV arm with regards to decreased neutrophils, lymphocytes, platelets, hemoglobin, potassium, albumin, calcium and increased ALT and creatinine which are not unexpected based on the mechanism of action of BV in this add-on clinical trial. Febrile neutropenia occurred in 10% of the patients in both arms. Of note, granulocyte colony-stimulating factor (G-CSF) primary prophylaxis was required and administered to 98% of patients in the BV+R2 arm and 91% of patients in the Pbo+R2 arm.

- **Infections:** Infections, mainly respiratory, occurred in a higher percentage of patients in the BV arm compared to the Pbo+R2 arm (All grades 62% versus 49%, Grade 3-4 39% versus

23%). The most common infections in ≥ 10% of patients in the BV arm included pneumonia, COVID-19, URTI and in Pbo+R2 arm included COVID-19 and pneumonia.

Table 38: Adverse Events of Special Interest by Category in ECHELON-3

Selected AESIs	BV+R2 (N=112)		Pbo+R2 (N=116)	
	All %	G3-4 %	All %	G3-4 %
Infections	62	39	49	23
Neutropenia	77	49	63	42
Thrombocytopenia	65	29	54	18
Anemia	54	19	49	14
Peripheral neuropathy	27	5	21	0
Febrile neutropenia	10	10	10	10

*Cytopenias are based on lab shift analysis.
Source: FDA analysis

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

The Applicant's Position:

N/A

The FDA's Assessment:

See section 8.1.2 for FDA's assessment of patient-reported outcomes. The low completion rate of PRO questionnaires in ECHELON-3 limited the interpretation of data. Of note, per the Applicant, low compliance was likely driven by usability of electronic PRO devices in the trial population.

8.2.7. Safety Analyses by Demographic Subgroups

Data:

A subgroup safety analysis was conducted using the safety data of subjects randomized to receive BV+Len+R treatment in the ECHELON-3 study to confirm the lack of impact from age on safety in R/R DLBCL subjects. Given the median age being 74.0 years and the majority (70%) of subjects being ≥65 years old on the BV+Len+R arm in ECHELON-3, the data observed in the sub-group analysis by age is largely consistent with the data previously presented.

When comparing the age groups within the BV+Len+R arm, the rate of treatment discontinuation was higher in the subjects ≥65 years old. However, the rates of treatment discontinuation were similar across all analysis groups in subjects ≥65 years old.

When comparing the age groups within the P3 BV Combo analysis group, the rate of TESAEs was expectedly higher in subjects ≥65 years.

These differences are anticipated given age-related comorbidities and/or lines of treatment.

The Applicant's Position:

No clinically meaningful trends by age were identified.

The FDA's Assessment:

In ECHELON-3, 79 (71%) of BV-treated patients were age 65 and older. We agree with the Applicant that no meaningful differences in safety or efficacy were observed between these patients and younger patients.

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:

No specific safety concerns were identified; hence, no specific study or clinical trial was conducted to evaluate such concerns.

The FDA's Assessment:

Not applicable

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

N/A

The FDA's Assessment:
Not applicable.

Human Reproduction and Pregnancy

The Applicant's Position:

There are no available human data on BV use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. BV can cause fetal harm based upon findings from animal studies of MMAEs. Female subjects of childbearing potential treated with BV should be advised of the potential risk to the fetus.

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

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

A full waiver was granted by the FDA for pediatric study in R/R DLBCL (Reference ID: 4727983).

The FDA's Assessment:
This section is not applicable. There was no pediatric safety information included in this application. See section 10.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

Overdose: No AEs related to overdose of BV were reported for the pivotal ECHELON-3 study. Overdoses were reported in individual studies according to each study's protocol requirements.
Drug Abuse: BV is not likely a drug of abuse potential. The potential for BV abuse and dependence is unknown.

Withdrawal and Rebound: N/A.

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

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Data:

The periodic benefit-risk evaluation report addendum included in the sBLA presents an analysis of safety data for the period from 19-Aug-2022 to 18-Aug-2023, cumulative adverse drug reactions since the first worldwide approval of BV on 19-Aug-2011, and safety data on cumulative SAEs from clinical trials since the international birth date.

The Applicant's Position:

Cumulative review of all the safety data from the post-marketing period has not identified any new safety concerns.

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

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

BV has been marketed since Aug 2011; no new safety signals have been identified and the existing safety management approaches are sufficient measures in the post-marketing setting.

The FDA's Assessment:

The Agency agrees that safety information from the postmarket setting is expected to be consistent with the current safety characterization of BV. Additional safety signals might emerge with longer follow-up and greater exposure and ongoing pharmacovigilance monitoring is warranted.

8.2.11. Integrated Assessment of Safety

Data:

The integrated safety profile of BV presented in this sBLA is based on a total of 228 subjects in the pivotal trial ECHELON-3, 112 subjects in the DLBCL Combo Other, 102 subjects in DLBCL Mono, 326 subjects in the DLBCL Total, and 997 subjects in the P3 BV Combo analysis groups. In the subject populations included in these analysis groups, the doses administered were 1.2 to 1.8 mg/kg. Overall, there was variation in the duration of exposure to BV due to differences in treatment regimens; however, the median number of cycles administered were generally similar across all analysis groups.

The safety profile of BV+Len+R in ECHELON-3 was generally consistent with that of the DLBCL Total group and the established safety profile of BV in combination with multi-agent chemotherapy. As expected, there were some variations in the overall frequencies of certain events across the analysis groups, likely reflecting the diverse chemotherapy combinations and disease populations studied, including R/R DLBCL and frontline DLBCL, cHL, and PTCL.

No new safety signals were identified in the DLBCL population.

The Applicant's Position:

Based on the safety results observed in the trials included in this application, BV at the recommended dose of 1.2 mg/kg Q3W in combination with lenalidomide and rituximab had a manageable and tolerable safety profile in R/R DLBCL subjects.

The FDA's Assessment:

The Agency agrees that BV at the recommended dose of 1.2 mg/kg Q3W in combination with lenalidomide and rituximab carries an acceptable safety profile in the intended population and that the safety profile of BV observed in ECHELON-3 was generally consistent with the safety profile of BV observed in the previous approvals. No new safety findings were identified. The Agency agrees, overall, that expected AEs with BV can be adequately addressed with labeling.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

The efficacy results from the ECHELON-3 study indicated that BV+R2 has clinically meaningful activity in patients with R/R LBCL including DLBCL NOS, DLBCL arising from indolent lymphoma, or HGBL, after two or more lines of systemic therapy who are not eligible for auto-HSCT or CAR T-cell therapy. The pre-specified interim analysis of ECHELON-3 study met the primary objective in OS in the ITT population and exhibited statistically significant results in the key secondary endpoints of investigator assessed PFS and ORR in the ITT population.

The study SGN35-012 was submitted as the supportive study, where the BV monotherapy arm (N = 100) of Study SGN35-012 included efficacy evaluable subjects from Part A (CD30 +) and Part C (CD30 -) and the BV+R arm (N = 12) of Study SGN35-012 included efficacy evaluable subjects from Part B. Due to the differences in disease settings and treatment regimens, and the limitations of single-arm data, comparisons between ECHELON-3 and study SGN35-012 are limited. Supportive data from SGN-012 are limited to the ORR and CRR data from the BV monotherapy arm in patients with R/R DLBCL which support activity of BV in CD30+ and CD30 negative DLBCL.

No major statistical issues were identified in this application.

8.4. Conclusions and Recommendations

The FDA's Assessment:

Relapsed or refractory LBCL is a serious and life-threatening condition for which BV+R2 demonstrated meaningful clinical activity. The ECHELON-3 study was a randomized, blinded, placebo-controlled trial evaluating BV or placebo in combination with rituximab and lenalidomide with a primary endpoint of overall survival. The median OS for patients who were randomized to the BV+R2 arm was 13.8 months (95% CI: 10.3, 18.8) compared to 8.5 months (95% CI: 5.4, 11.7) for those randomized to the Pbo+R2 arm. The OS hazard ratio (HR) was 0.63 (95% CI: 0.45, 0.89), with a log-rank p-value of 0. 0085 (two-sided α=0.0232).

The key secondary endpoints of progression free survival per investigator and overall response rate per investigator were also met. The median PFS was 4.2 months (95% CI: 2.9, 7.1) with BV+R2 vs. 2.6 months (95% CI: 1.4, 3.1) with Pbo+R2. The PFS HR was 0.53 (95% CI: 0.38, 0.73; p-value <0.0001). Treatment with BV+R2 also resulted in significantly higher ORR of 64.3% (95% CI: 54.7, 73.1) compared to the Pbo+R2 arm of 41.5% (95% CI: 32.5, 51.0); 2-sided P=0.0006.

The statistically significant OS difference between arms, supported by PFS and ORR, provides substantial evidence of effectiveness and demonstrates clinical benefit in patients with R/R

LBCL including DLBCL NOS, DLBCL arising from indolent lymphoma, or HGBL, after two or more lines of systemic therapy who are not eligible for auto-HSCT or CAR T-cell therapy. The safety profile of BV was generally acceptable and was consistent with the safety profile in the prior approved indications. While R2 is not an approved regimen for patients with R/R LBCL, the use of R2 as the control arm for the ECHELON-3 trial was considered reasonable given the lack of a standard of care regimen for patients with R/R disease who are ineligible for ASCT and CAR T cell therapy. Furthermore, usage data and current guidelines support that R2 is utilized in this population and supports applicability to a U.S. population.

The Applicant's proposed indication did not include ineligibility for auto-HSCT or CAR T-cell therapy, however, this was included in the revised indication statement to be consistent with the patient population enrolled in ECHELON-3.

Additionally, the efficacy data from the SGN35-012 trial, an adequate and well-controlled trial, in patients with relapsed or refractory large B-cell lymphoma treated with brentuximab vedotin provides confirmatory evidence in support of the new indication.

Overall, based on the totality of data, the review team concluded that BV+R2 has a favorable benefit-risk determination and supports the recommendation for traditional approval for BV in combination with R2 for the treatment of adult patients R/R LBCL, including DLBCL NOS, DLBCL arising from indolent lymphoma, or HGBL, after two or more lines of systemic therapy who are not eligible for auto-HSCT or CAR T-cell therapy.

8.4.1. Approach to Substantial Evidence of Effectiveness

Select from the options below to indicate how substantial evidence of effectiveness (SEE) was established (if applicable). If there are multiple indications, repeat items 1–3 for each indication.

1. Verbatim indication *(enter approved indication if the application was approved and the Applicant's proposed indication if the application received a complete response)*:

Brentuximab vedotin is indicated for treatment of adult patients with relapsed or refractory large B-cell lymphoma (LBCL), including diffuse large B-cell lymphoma (DLBCL) NOS, DLBCL arising from indolent lymphoma, or high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy who are not eligible for auto-HSCT or CAR T-cell therapy, in combination with lenalidomide and a rituximab product

2. SEE was established with *(check **one** of the options for traditional or accelerated approval pathways and complete response not due to lack of demonstrating SEE)*
   a. Adequate and well-controlled clinical investigation(s):
      i. ☐ Two or more adequate and well-controlled clinical investigations, **OR**
      ii. ☐ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations

OR

b. ☒ One adequate and well-controlled clinical investigation and confirmatory evidence[1,2,3]

OR

c. ☐ Evidence that supported SEE from a prior approval *(e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch)*[2]

3. Complete response, if applicable
   a. ☐ SEE was established
   b. ☐ SEE was not established *(if checked, omit item 2)*

[1] FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (2019)
[2] FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* (1998)
[3] Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence (2023)]

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

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

The application was not presented to the Oncologic Drug Advisory Committee or other external consultants, as it did not raise significant efficacy concerns or new safety concerns warranting

ODAC discussion.

10 Pediatrics

The Applicant's Position:

A full waiver was granted by the FDA for pediatric study in R/R DLBCL (Reference ID: 4727983).

The FDA's Assessment:
This Application is subject to PREA based on the new indication. An agreed iPSP with a plan to request a full waiver for pediatric assessments was included in the application. A full waiver for conducting pediatrics assessments will be granted based on the rationale that studies are impossible or highly impractical given the rarity of R/R LBCL in pediatrics and ongoing studies evaluating higher priority products in pediatric patients with R/R LBCL.

11 Labeling Recommendations

Data:

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
Section 1: Indications and Usage	(b) (4)	FDA revised the indication as follows to reflect the study populations: ADCETRIS in combination with lenalidomide and a rituximab product is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma, including DLBCL NOS, DLBCL arising from indolent lymphoma, or high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy who are not eligible for auto-HSCT or CAR T therapy.
Section 2: Dosage and Administration	Added recommended dosage, prophylactic medication and dosage modifications for adverse reaction.	FDA generally agreed with recommended dosage and prophylactic medications, but modified nomenclature used to

		align with the revised indication (i.e., LBCL, (b) (4)). FDA added a footnote to the recommended dosage table to note that starting with cycle 2, intravenous rituximab could be substituted with subcutaneous rituximab and hyaluronidase. FDA modified the dosage modifications for grade 2 sensory neuropathy to align with other recent labels for antibody-drug conjugates in Oncology.
Section 5: Warnings and Precautions	Added information characterizing peripheral neuropathy (e.g., time to onset, time to resolution) based on ECHELON-3.	FDA generally agreed but added a few more specifics including % of dose reductions, (b) (4) and permanent discontinuations due to peripheral neuropathy.
Section 6: Adverse Reactions	Added safety information based on ECHELON-3.	FDA modified this section to align with recent labels in oncology, including: • Pooling the most common AEs for BV monotherapy and in combination • Removing laboratory-based AE terms from the adverse reactions (AR) table and including the laboratory terms in the laboratory abnormalities table as appropriate • modifying the AR and laboratory abnormalities table columns to include All Grades and Grade 3 or 4 columns, noting any fatalities in footnotes to the table • replacing long lists of preferred terms in the AR table footnotes with "includes other related terms" • (b) (4)

Section 14: Clinical Studies	Added efficacy information based on ECHELON-3	FDA generally agreed with the efficacy results of OS, PFS, and ORR, but modified the section to for clarity and to streamline information; FDA removed results from the KM figures because they are already presented in the efficacy table.

The Applicant's Position:

Based on the data from the ECHELON-3 study, the Applicant is proposing the aforementioned changes in the ADCETRIS label.

The FDA's Assessment:

FDA's substantive modifications to the USPI are described in the table above. See the approval letter for final labeling.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

The clinical review team does not recommend a REMS. Based on the observed safety profile of brentuximab vedotin, safety issues can be adequately managed through appropriate labeling and routine post-marketing surveillance.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

No postmarketing requirements or commitments were issued.

14 Division Director (DHOT) (NME ONLY)

X

15 Division Director (OCP)

X

16 Division Director (OB)

X

17 Division Director (Clinical)

X _____

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X _____

19 Appendices

19.1. References

The Applicant's References:

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19.2. Financial Disclosure

The Applicant's Position:

Financial disclosures information for the ECHELON-3 study is described in Section 8.1.2.

Covered Clinical Study (Name and/or Number): ECHELON-3

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 884 * *There are 883 unique Investigators with no financial interests		
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: NA Significant payments of other sorts: NA Proprietary interest in the product tested held by investigator: NA Significant equity interest held by investigator in study: NA Sponsor of covered study: NA		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☒ No disclosable interests or arrangements; see m1.3.4 (Request details from Applicant)

Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 884* * There are 883 unique Investigators with no financial interests		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

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

The FDA's Assessment:

The Agency agrees with the Applicant. We note that the Applicant did not obtain certification and/or financial disclosure from 4 sub-investigators, but this is unlikely to have impacted the integrity of the trial.

19.3. Nonclinical Pharmacology/Toxicology

The Applicant's Position:

No new information is provided in the current submission.

The FDA's Assessment:

[FDA will complete this section.]

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Population PK Analysis

N/A

The FDA's Assessment:

No population PK analysis was conducted to support efficacy supplement 108.

19.4.2. Exposure-Response Analysis

19.4.2.1. ER (efficacy) Executive Summary

The FDA's Assessment:

No clear E-R associations were identified between observed Cycle 1 ADC Cmax and OS, PFS, or ORR in Study ECHELON-3 patients who received BV+Len+R. The E-R efficacy analysis did not identify any concerns regarding efficacy and generally supports efficacy of the proposed dosage.

19.4.2.2. ER (efficacy) Assessment Summary

The Applicant's Position:

ITT subjects who were randomized to and received at least one dose of BV were grouped by tertiles and their respective survival curves were compared. No relationships between Cycle 1 C_{trough} of ADC and efficacy endpoints were found. Subjects randomized to the BV+Len+R arm showed consistent OS and PFS benefits across all tertiles of BV exposure. The KM curves for OS and PFS did not rank by ADC exposure tertiles and were separated from the placebo+Len+R arm. These results support the consistent treatment benefit of BV across the range of exposures achieved in subjects with R/R DLBCL at the 1.2 mg/kg Q3W dosing regimen used in ECHELON-3.

General Information		
Goal of ER analysis		To confirm that 1.2 mg/kg Q3W BV provides positive benefit-risk to adult patients with R/R DLBCL who have received 2 or more lines of systemic therapies.
Study Included		ECHELON-3
Endpoint		Primary: OS Secondary: PFS
No. of Patients (total, and with individual PK)		Total =122 (ITT subjects randomized to receive at least one dose of BV) Patient had reportable individual PK = 97
Population Characteristics (m5.3.5.1, ECHELON-3 CSR, Table 14.2.1.1)	General	- Age median: 74.0 yr (range: 29-87 yr) - Weight median: 68.0 kg (range: 40.4-123 kg) - 60 (53.6%) male - 65 (58.0%) White; 28 (25.0%) Asian; 22 (17.0) Others/Unknown/Not reported
	Pediatrics (if any)	None
Dose(s) Included		1.2 mg/kg Q3W BV
Exposure Metrics Explored (range)		Cycle 1 C_{trough}
Covariates Evaluated		N/A

Final Model Parameters	**Summary**	**Acceptability [FDA's comments]**
Model Structure	N/A	The updated E-R efficacy analysis in 118 patients with available Cycle 1 ADC C_{EOI} and efficacy data is presented in **Figure 3**, **Figure 4**, and **Figure 5**. FDA determined that Cycle 1 ADC C_{EOI} is more likely to adequately identify E-R efficacy associations compared to Cycle 1 ADC Ctrough due to a significant number of
Model Parameter Estimates	N/A	
Model Evaluation	N/A	
Covariates and Clinical Relevance	N/A	
Simulation for Specific Population	N/A	
Visualization of E-R relationships	Figure 6 Kaplan-Meier Plots for Overall Survival (OS) by Tertiles of ADC Cycle 1 Trough Concentrations and Figure 7 Kaplan-Meier Plots for Progression Free Survival (PFS) by Tertiles of ADC Cycle 1 Trough Concentrations	

		patients with missing Ctrough data. The Applicant's analysis in **Figure 6** and **Figure** 7 may not adequately characterize E-R efficacy associations due to missing Cycle 1 Ctrough measurements in a significant number of patients (16/122 patients who received at least one dose of BV). The sample of patients with missing Cycle 1 Ctrough values tended to have worse OS and worse PFS compared to patients who received placebo+Len+R or patients with available ADC Ctrough measurements, which raises the concern that E-R analysis with Ctrough may fail to identify true E-R efficacy associations. The Applicant's analysis in **Figure 6** and **Figure** 7 also excluded 10 patients in the safety run-in with PK and efficacy data.
Overall Clinical Relevance for ER	No relationship between exposure and efficacy was found	No clear E-R efficacy associations were identified between observed ADC Cycle 1 C_{EOI} and OS, PFS, or ORR in ECHELON-3. The E-R analysis generally supports the efficacy of the proposed dosage for the proposed indication.
Labeling Language	**Description**	**Acceptability [FDA's comments]**

12.2 Pharmacodynamics	N/A	No changes to the labeling based on E-R efficacy were proposed. The current labeling language in 12.2 is acceptable.

The FDA's Assessment:

The FDA's E-R efficacy assessment determined that Cycle 1 ADC C_{EOI} (i.e., Cycle 1 ADC C_{max}) is more likely to adequately identify E-R efficacy associations compared to Cycle 1 ADC C_{trough} due to a significant number of patients with missing C_{trough} data. Observed Cycle 1 ADC C_{EOI} values were unavailable or missing in 4 patients (3.3%) while Cycle 1 ADC C_{trough} values were unavailable or missing in 16 patients (13%) out of 122 patients who received at least one dose of BV. The sample of patients with missing Cycle 1 C_{trough} values tended to have worse OS and worse PFS compared to patients who received placebo+Len+R and patients with available C_{trough} measurements, which raises the concern that E-R analysis with C_{trough} may fail to identify true E-R efficacy associations. The Applicant's analysis also excluded 10 patients in the safety run-in with available Cycle 1 ADC C_{trough} measurements, and so 26/122 (21%) of patients who received at least one BV dose were not included in the Applicant's E-R efficacy analysis for Cycle 1 ADC C_{trough}.

FDA requested an updated E-R efficacy analysis using the observed Cycle 1 ADC C_{EOI} in all patients who received at least one dose of BV. An updated version of the E-R efficacy dataset was submitted in response to the FDA's 19 September 2024 information request (seq no. 0409). The updated E-R efficacy analysis included data from 118 patients with Cycle 1 ADC C_{EOI} who received BV 1.2 mg/kg Q3W in combination with Len+R in ECHELON-3, including 9 patients in the safety run-in and 109 patients in the randomized BV+Len+R arm.

Table 39 summarizes observed Cycle 1 PK concentrations in patients who received at least one dose of BV in combination with Len+R.

Table 39: Summary of Exposure Metrics for Exposure-Response Analysis in ECHELON-3

	Statistic	Cycle 1 Concentration at EOI	Cycle 1 C_{trough}
	Number of subjects	118	106
ADC (ug/mL)	Geo Mean (CV%)	24.7 (98.2%)	0.303 (67.8%)
	Median	27.6	0.304
	5th to 95th percentile	15.15 - 39.015	0.103 - 0.71
	Min - Max	0.006 - 63.4	0.044 - 0.874
MMAE (ng/mL)	Geo Mean (CV%)	0.131 (116%)	0.1 (118%)
	Median	0.114	0.102
	5th to 95th percentile	0.044 - 0.883	0.013 - 0.436
	Min - Max	0.013 - 2.15	0.013 - 1.63

Total number of patients who received at least one dose of BV in ECHELON-3 = 122.
Concentrations below LLOQ were set to 1/2 * LLOQ value for descriptive statistics of exposure.
ADC LLOQ = 0.0125 ug/mL. MMAE LLOQ=0.025 ng/mL.
ADC = antibody-drug conjugate; Ctrough = trough concentration; CV = coefficient of variation; EOI = end of brentuximab vedotin infusion; LLOQ = lower limit of quantification; MMAE = monomethyl auristatin E.
Source: Reviewer's analysis of Applicant's updated E-R datasets submitted in response to 19Sept2024 information request (seqn 0409)

No clear differences in OS or PFS were observed across Cycle 1 ADC C_{EOI} tertiles, as shown in **Figure 3** and **Figure 4** in Section 6.3.1. The OS and PFS generally appeared better in all three Cycle 1 ADC C_{EOI} tertiles compared to patients who received placebo+Len+R, which supports the efficacy of the proposed dosage.

Additionally, no significant associations were observed between ORR and Cycle 1 ADC C_{EOI}. Logistic regression of ORR versus Cycle 1 ADC C_{EOI} is presented in **Figure 5**. The probability of OR generally appeared higher across the range of Cycle 1 ADC C_{EOI} in patients who received BV+Len+R compared to the ORR in patients who received placebo (Placebo+Len+R ORR = 49/118 [41.5%] as reported in Section 8.1.4).

The lack of clear E-R efficacy associations may be related to the relatively narrow exposure range in ECHELON-3 which only included one dosage of BV (i.e., 1.2 mg/kg Q3W). It is unclear efficacy may be associated with ADC exposure over a wider range of BV doses for the proposed indication.

Overall, the E-R efficacy analysis did not identify any concerns regarding efficacy with the proposed dosage. The E-R efficacy analysis with Cycle 1 ADC C_{EOI} generally supports the efficacy of the proposed BV dosage (i.e., 1.2 mg/kg Q3W).

19.4.2.3. ER (safety) Executive Summary

The FDA's Assessment:

The E-R safety analysis supports the proposed dosage for general patient population.

Higher observed Cycle 1 ADC C_{EOI} (i.e., Cycle 1 ADC maximum concentration) was associated with higher probability of TEAE leading to any dose modification of one or more treatment drug, TEAE leading to dose delay or interruption of one or more drug, Grade ≥3 infection, any grade peripheral neuropathy, and Grade ≥2 peripheral neuropathy in Study ECHELON-3 patients who received at least one dose of BV in combination with Len+R. Higher Cycle 1 ADC C_{EOI} was also associated with shorter time to onset of first TEAE leading to any dose modification of one or more treatment drug, TEAE leading to dose delay or interruption of one or more drug, and Grade ≥3 infection.

Neither MMAE C_{max} nor MMAE C_{avg} were evaluated in ECHELON-3, and so no E-R safety conclusions are available regarding MMAE exposure in ECHELON-3.

19.4.2.4. ER (safety) Assessment Summary

The Applicant's Position:

The relationships between observed incidence of safety endpoints of interest and Cycle 1 C_{trough} of ADC and MMAE were examined via tertile analysis. Overall, there was no indication of differential safety with exposure for the AEs evaluated. Increased ADC Cycle 1 C_{trough} were not associated with increased incidence of Grade 3 or higher TEAEs, Grade 3 or higher neutropenia, Grade 4 or higher neutropenia, Grade 3 or higher infections, and febrile neutropenia (Table 6 and Table 7). ADC exposure was found to be predictive of only Grade 2 or higher PN, while higher MMAE Cycle 1 C_{trough} was not a predictor of any of the safety endpoints evaluated.

General Information			
Goal of ER analysis		To confirm that 1.2 mg/kg Q3W BV provides positive benefit-risk to adult patients with R/R DLBCL who have received 2 or more lines of systemic therapies.	
Study Included		ECHELON-3	
Population Included		Adult patients with R/R DLBCL who have received 2 or more lines of systemic therapies.	
Endpoint		• Grade 3 or higher TEAE • Grade 3 or higher neutropenia • Grade 4 or higher neutropenia • Grade 3 or higher infections • Febrile neutropenia • Grade 2 or higher PN	
No. of Patients (total, and with individual PK)		Total =122 (ITT subjects randomized to receive at least one dose of BV) Patient had reportable individual PK = 97	
Population Characteristics (m5.3.5.1, ECHELON-3 CSR, Table 14.2.1.1)	General	- Age median: 74.0 yr (range: 29-87 yr) - Weight median: 68.0 kg (range: 40.4-123 kg) - 60 (53.6%) male - 65 (58.0%) White; 28 (25.0%) Asian; 19 (17.0%) Others/Unknown/Not reported	
	Organ impairment	N/A	
	Pediatrics (if any)	None	
	Geriatrics (if any)	79 (70.5%) subj ≥65 yr,48(43%) subj ≥75 yr)	
Dose(s) Included		1.2 mg/kg Q3W BV	
Exposure Metrics Explored (range)		Cycle 1 C_{trough}	
Covariates Evaluated		N/A	
Final Model Parameters		**Summary**	**Acceptability [FDA's comments]**
Model Structure		N/A	FDA requested an updated E-R safety analysis using the observed Cycle 1 ADC C_{EOI} which was available in a greater number of patients (n=118) compared to
Model Parameter Estimates		N/A	
Model Evaluation		N/A	
Covariates and Clinical Relevance		N/A	
Simulation for Specific Population		N/A	

		Ctrough (n=106). The updated E-R safety analysis also included data from the safety run-in arm of ECHELON-3 which was excluded from the Applicant's analyses described in **Table 6** and **Table 7**.
Visualization of E-R relationships	Visualization figure not generated	**Figure 15, Figure 16, Figure 17**, and **Figure 18**
Overall Clinical Relevance for ER	No indication of differential safety profile driven by exposure (Table 6 and Table 7)	Higher ADC Cycle 1 C_{EOI} was associated with higher risk of peripheral neuropathy (any grade and Grade ≥2), Grade ≥3 infection, TEAE leading to any dose modification of any treatment drug, and TEAE leading to any dose delay, interruption, hold, or skip of any treatment drug. MMAE Cmax and Cavg were not evaluated in ECHELON-3 and so no MMAE exposure was unable to be evaluated for E-R safety associations in ECHELON-3.
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	N/A	No changes to the labeling based on E-R safety were proposed. The current labeling language in 12.2 is acceptable.

The FDA's Assessment:

The FDA's E-R safety assessment determined that Cycle 1 ADC C_{EOI} is more likely to adequately identify E-R safety associations compared to Cycle 1 ADC C_{trough} due to a significant

number of patients with missing C_{trough} data. As described in Section 19.4.2.2, observed Cycle 1 ADC C_{EOI} values were unavailable or missing in 4 patients (3.3%) while Cycle 1 ADC C_{trough} values were unavailable or missing in 16 patients (13%) out of 122 patients who received at least one dose of BV. The Applicant's E-R analysis also excluded 10 patients in the safety run-in with available Cycle 1 ADC C_{trough} measurements, and so 26/122 (21%) of patients who received at least one BV dose were not included in the Applicant's E-R safety analysis for Cycle 1 ADC C_{trough}.

The FDA's assessment is based on the updated E-R safety analysis and dataset which were submitted by the Applicant in response to the FDA's 19September2024 information request (seq no. 0409). The updated E-R safety analysis included data from 118 patients with Cycle 1 ADC C_{EOI} who received BV 1.2 mg/kg Q3W in combination with Len+R in ECHELON-3, including 9 patients in the safety run-in and 109 patients in the randomized BV+Len+R arm. Observed ADC and MMAE concentrations are summarized in **Table 39**. The overall rates of TEAEs leading to dose modifications are summarized in **Table 40**.

Table 40: Incidence of TEAEs Leading to Dose Modifications in ECHELON-3 across Quartiles of Cycle 1 Day 1 ADC Concentration at End of Infusion

	BV+Len+R					
TEAE	ADC C_{EOI} Q1 (n=30)	ADC C_{EOI} Q2 (n=30)	ADC C_{EOI} Q3 (n=28)	ADC C_{EOI} Q4 (n=30)	**OVERALL (n=118)**	**Placebo+Len+R (n=115)**
TEAE leading to discontinuation of treatment	3 (10%)	7 (23.3%)	7 (25%)	5 (16.7%)	22 (18.6%)	10 (8.7%)
TEAE leading to discontinuation of one or more drugs	7 (23.3%)	9 (30%)	8 (28.6%)	9 (30%)	33 (28%)	12 (10.4%)
TEAE leading to discontinuation of BV/placebo	5 (16.7%)	7 (23.3%)	8 (28.6%)	7 (23.3%)	27 (22.9%)	11 (9.6%)
TEAE leading to discontinuation of lenalidomide	6 (20%)	9 (30%)	7 (25%)	7 (23.3%)	29 (24.6%)	11 (9.6%)
TEAE leading to discontinuation of rituximab	5 (16.7%)	7 (23.3%)	7 (25%)	5 (16.7%)	24 (20.3%)	11 (9.6%)
TEAE leading to delay, interruption, or elimination of one or more drugs	18 (60%)	21 (70%)	18 (64.3%)	27 (90%)	84 (71.2%)	47 (40.9%)
TEAE leading to delay, interruption, or elimination of BV/placebo	13 (43.3%)	18 (60%)	15 (53.6%)	18 (60%)	64 (54.2%)	33 (28.7%)
TEAE leading to delay, interruption, or elimination of lenalidomide	14 (46.7%)	14 (46.7%)	8 (28.6%)	22 (73.3%)	58 (49.2%)	33 (28.7%)
TEAE leading to delay, interruption, or elimination of rituximab	12 (40%)	17 (56.7%)	15 (53.6%)	20 (66.7%)	64 (54.2%)	28 (24.3%)

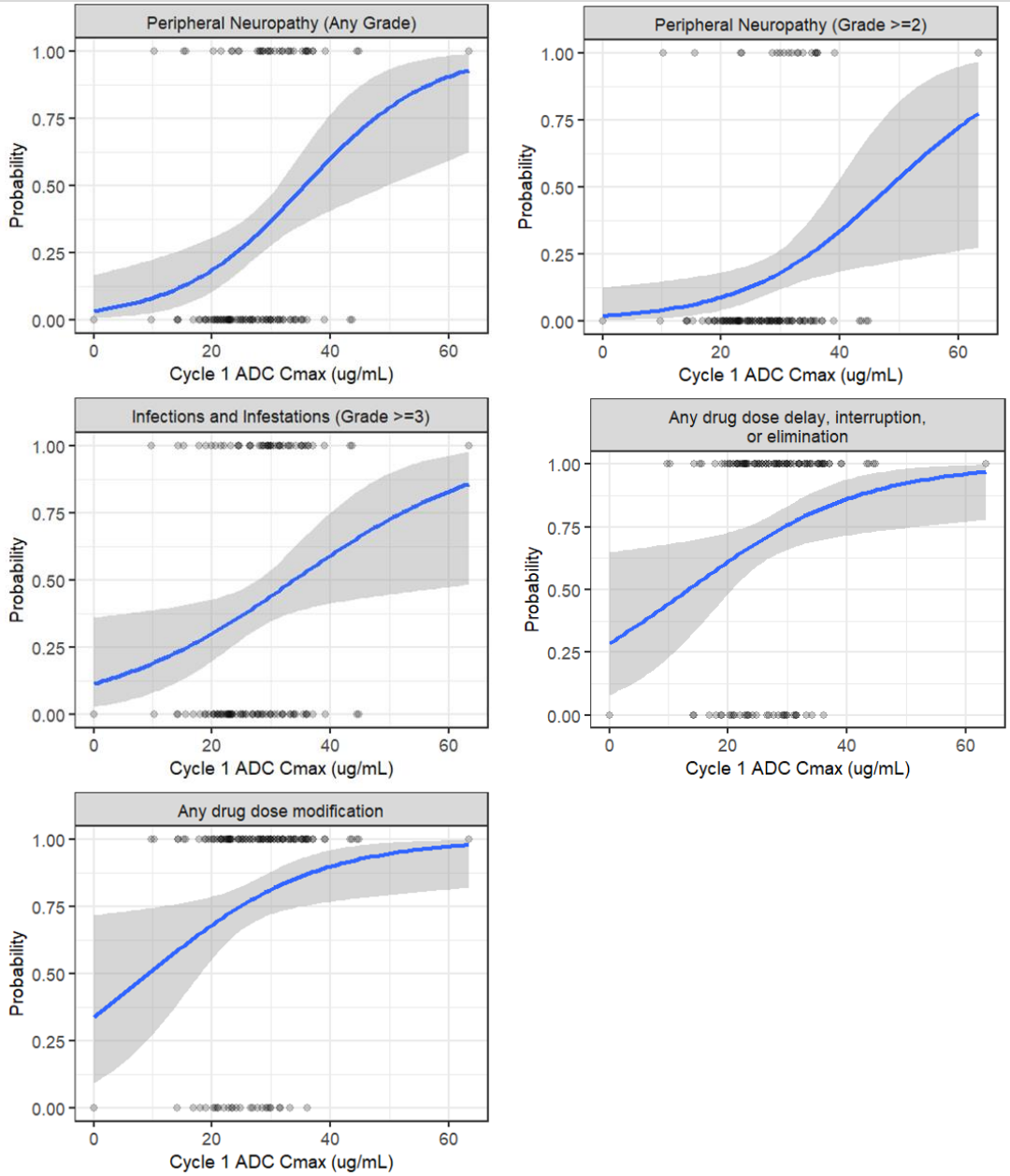
TEAE	BV+Len+R					Placebo+Len+R (n=115)
	ADC C_{EOI} Q1 (n=30)	ADC C_{EOI} Q2 (n=30)	ADC C_{EOI} Q3 (n=28)	ADC C_{EOI} Q4 (n=30)	**OVERALL (n=118)**	
TEAE leading to dose reduction of one or more drugs	18 (60%)	17 (56.7%)	16 (57.1%)	20 (66.7%)	71 (60.2%)	44 (38.3%)
TEAE leading to dose reduction of BV/placebo	1 (3.3%)	NA	3 (10.7%)	6 (20%)	10 (8.5%)	2 (1.7%)
TEAE leading to dose reduction of lenalidomide	17 (56.7%)	17 (56.7%)	16 (57.1%)	18 (60%)	68 (57.6%)	43 (37.4%)
Any modification of one or more drugs due to TEAE	20 (66.7%)	22 (73.3%)	21 (75%)	28 (93.3%)	91 (77.1%)	56 (48.7%)
Any modification of BV/placebo due to TEAE	14 (46.7%)	20 (66.7%)	19 (67.9%)	22 (73.3%)	75 (63.6%)	39 (33.9%)
Any modification of lenalidomide due to TEAE	19 (63.3%)	21 (70%)	18 (64.3%)	27 (90%)	85 (72%)	54 (47%)
Any modification of rituximab due to TEAE	13 (43.3%)	19 (63.3%)	18 (64.3%)	22 (73.3%)	72 (61%)	35 (30.4%)

Any modification refers to any discontinuation, dose reduction, delay, interruption, or elimination of a drug.
ADC = antibody drug conjugate; BV = brentuximab vedotin; C_{EOI} = concentration at the end of brentuximab vedotin infusion; Len+R = lenalidomide and rituximab; Q = quartile (e.g., Q1 = lowest exposure quartile);
TEAE = treatment emergent adverse event.
Source: Reviewer's analysis of clinical adverse event dataset (seqn 0387) and Applicant's updated E-R safety dataset "aemat-v2.csv" submitted in response to 19Sept2024 information request (seqn 0409)

Higher Cycle 1 ADC C_{EOI} was associated with increased incidence of the following safety events in 118 patients who received at least one dose of BV in combination with Len+R, as shown in **Figure 15**:

- Any grade peripheral neuropathy
- Grade ≥2 peripheral neuropathy
- Grade ≥3 infection
- TEAE leading to any dose modification (i.e., any discontinuation, dose reduction, delay, interruption, hold, or skip) of one or more treatment drug
- TEAE leading to any dose delay, interruption, or elimination of one or more treatment drug

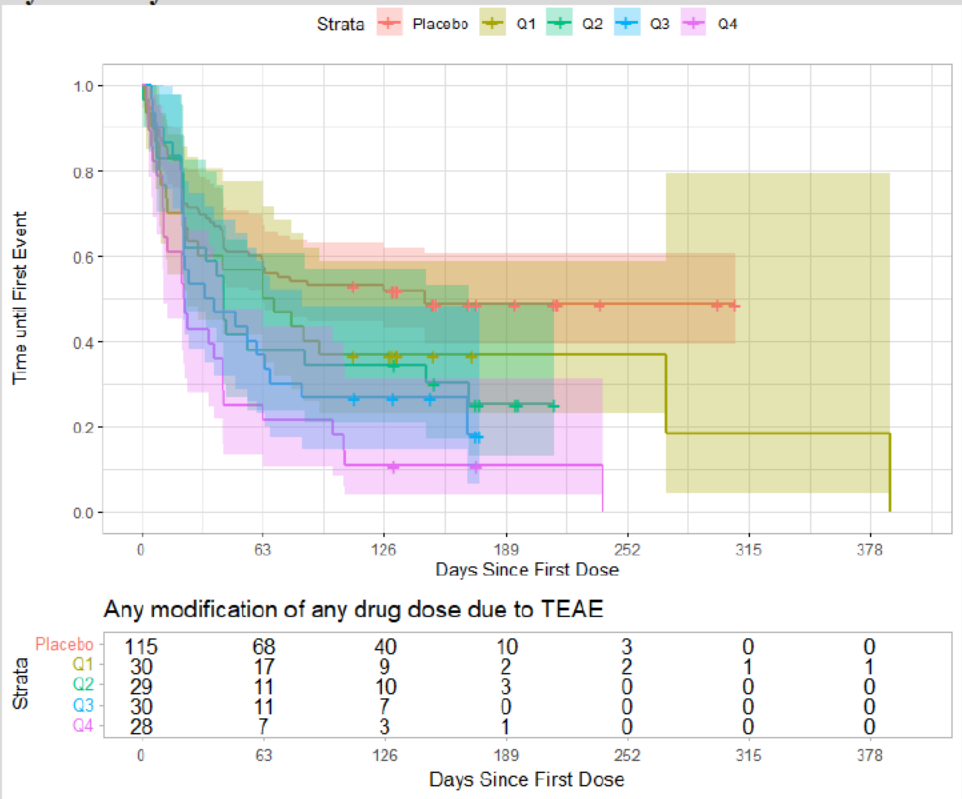
Figure 15: E-R Safety Logistic Regression of Safety Event Probability versus Cycle 1 Day 1 ADC Concentration at End of Infusion



Note that ADC concentration at the end of BV infusion on Cycle 1 Day 1 is equal to Cycle 1 ADC maximum concentration.
ADC = antibody drug conjugate; BV = brentuximab vedotin; Cmax = maximum concentration.
Source: Reviewer's analysis of clinical adverse event dataset (seqn 0387) and Applicant's updated E-R safety dataset "aemat-v2.csv" submitted in response to 19Sept2024 information request (seqn 0409)

FDA also compared time to first event across exposure quartiles to account for potential differences in TEAE onset and treatment duration. Kaplan-Meier plots show that higher ADC C_{EOI} was associated with higher incidence and shorter time to first TEAE leading to any dose modification of one or more treatment drug (**Figure 16**), TEAE leading to any dose delay, interruption, or elimination of one or more drug (**Figure 17**), and Grade ≥3 infection (**Figure 18**) in patients who received at least one dose of BV in ECHELON-3.

Figure 16: Time to First TEAE Leading to Any Drug Dose Modification versus Quartile of Cycle 1 Day 1 ADC Concentration at End of Infusion

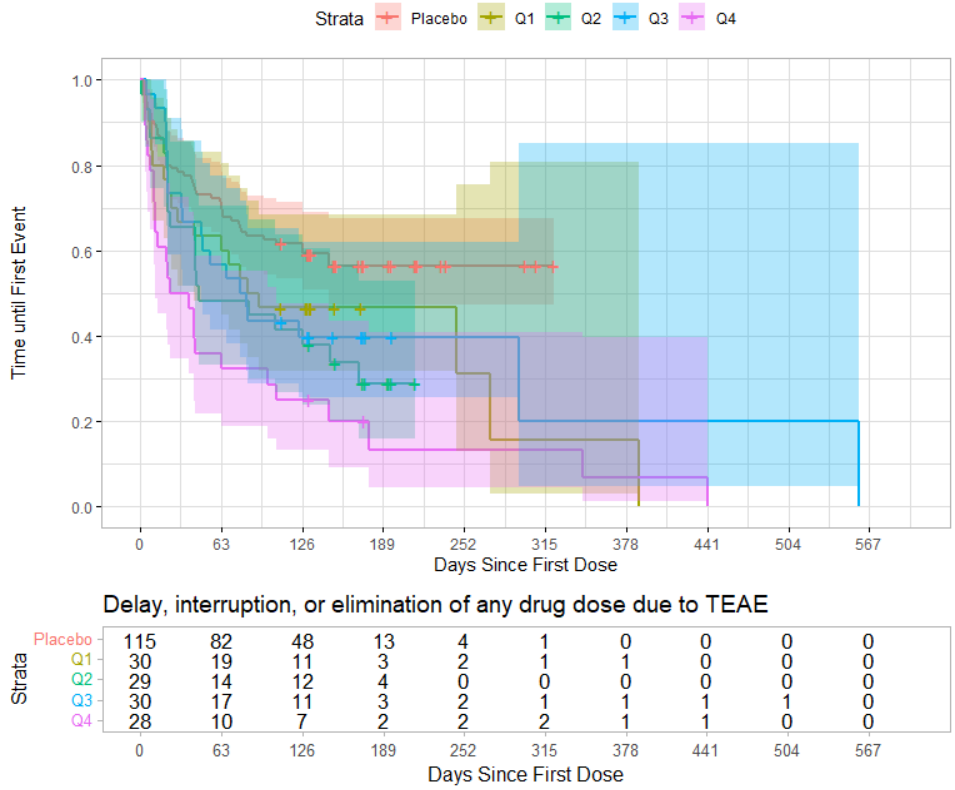


Note that ADC concentration at the end of BV infusion on Cycle 1 Day 1 is equal to Cycle 1 ADC maximum concentration. Dose modification includes any dose delay, interruption, elimination, reduction, or discontinuation of any drug.

ADC = antibody drug conjugate; E-R = exposure-response; Q = quartile (e.g., Q1 = lowest exposure quartile); TEAE = treatment emergent adverse event.

Source: Reviewer's analysis of Study ECHELON-3 adverse event dataset (seqn 0387) and E-R safety datasets submitted in Applicant's response to 19Sept2024 information request (seqn 0409)

Figure 17: Time to First TEAE Leading to Amy Drug Dose Delay versus Quartile of Cycle 1 Day 1 ADC Concentration at End of Infusion

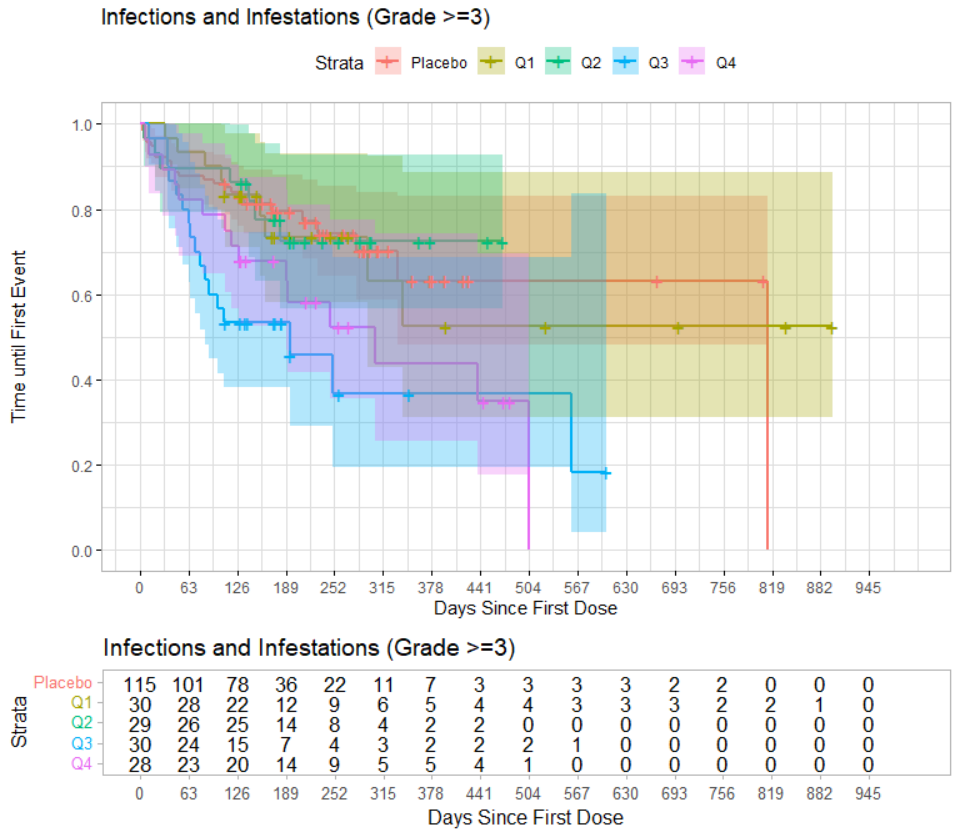


Note that ADC concentration at the end of BV infusion on Cycle 1 Day 1 is equal to Cycle 1 ADC maximum concentration. Dose delay includes delay, interruption, or elimination of any drug dose.

ADC = antibody drug conjugate; E-R = exposure-response; Q = quartile (e.g., Q1 = lowest exposure quartile); TEAE = treatment emergent adverse event.

Source: Reviewer's analysis of Study ECHELON-3 adverse event dataset (seqn 0387) and E-R safety datasets submitted in Applicant's response to 19Sept2024 information request (seqn 0409)

Figure 18: Time to First Grade 3 and Above Infection versus Quartile of Cycle 1 Day 1 ADC Concentration at End of Infusion



Note that ADC concentration at the end of BV infusion on Cycle 1 Day 1 is equal to Cycle 1 ADC maximum concentration.
ADC = antibody drug conjugate; E-R = exposure-response; Q = quartile (e.g., Q1 = lowest exposure quartile); TEAE = treatment emergent adverse event.
Source: Reviewer's analysis of Study ECHELON-3 adverse event dataset (seqn 0387) and E-R safety datasets submitted in Applicant's response to 19Sept2024 information request (seqn 0409)

No clear E-R safety associations were observed in the BV+Len+R arm between higher ADC C_{EOI} and increased rate of the following TEAEs:

- Grade ≥3 neutrophil count decrease (derived from laboratory dataset)
- Grade ≥3 hemoglobin decrease (derived from laboratory dataset)
- Grade ≥3 leukocyte count decrease (derived from laboratory dataset)
- Grade ≥3 lymphocyte count decrease (derived from laboratory dataset)
- Grade ≥3 platelet count decrease (derived from laboratory dataset)
- TEAE leading to any dose modification of BV/placebo
- TEAE leading to any dose delay/interruption/hold/skip of BV/placebo
- TEAE leading to dose reduction of any treatment drug
- TEAE leading to dose reduction of BV/placebo drug

- TEAE leading to discontinuation of any drug
- TEAE leading to discontinuation of BV/placebo

Potential E-R associations could not be evaluated for any grade febrile neutropenia, Grade ≥3 febrile neutropenia, or Grade ≥3 peripheral neuropathy due to relatively low incidence in ECHELON-3 (<10% of 118 patients with available Cycle 1 ADC C_{EOI}).

In ECHELON-3, MMAE concentrations were sampled at the end of BV infusion (C_{EOI}) and at the end of Cycle 1 (C_{trough}). E-R safety associations with MMAE exposure are much more likely for MMAE C_{max} and C_{avg} compared to MMAE C_{EOI} or C_{trough}, as MMAE is the active microtubule-disrupting payload of BV and the time to maximum MMAE concentration is 1 to 3 days after BV administration. However, ECHELON-3 did not evaluate C_{max} or C_{avg}. Due to the timing of the sparse MMAE samples, it is not unexpected that no E-R safety associations were identified with MMAE C_{EOI} or C_{trough}. The E-R safety assessment with MMAE C_{trough} was further limited by the significant number of patients with missing Cycle 1 C_{trough} data, as discussed above in this section. Therefore, no E-R safety conclusions are available regarding MMAE exposure in ECHELON-3. It should be noted that higher ADC exposure has no clear association with higher MMAE exposure and so E-R analysis of ADC exposure may not identify E-R safety associations with MMAE C_{max} or C_{avg}.

The E-R analysis did not identify any new major safety concerns with the proposed dosage in the general population. The risk of worse toxicity with higher MMAE exposure cannot be ruled out for the proposed dosage because MMAE exposure was unable to be evaluated for E-R safety associations in ECHELON-3. Patients with hepatic impairment and patients with severe renal impairment are expected to have higher MMAE exposure than patients without organ impairment. Therefore, a dose reduction in patients with mild hepatic impairment is appropriate from a clinical pharmacology perspective. Clinical pharmacology assessment also supports recommendations to avoid use in patients with moderate hepatic impairment, severe hepatic impairment, or severe renal impairment. See Section 6 for additional details regarding organ impairment and dosing recommendations.

19.4.2.5. Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position:

Patients with progressive disease (PD) after ≥2 prior lines of systemic therapy are unlikely to derive additional benefit from currently available systemic therapy options. Patients with R/R DLBCL who have exhausted options such as CAR T-cell therapy and bispecific antibodies face a significant challenge. Currently there is no standard treatment regimen for this patient population, representing a critically unmet need for these patients.

1.2 mg/kg Q3W BV in combination with lenalidomide and rituximab demonstrated a statistically significant and clinically meaningful improvement in OS and PFS compared to the placebo plus lenalidomide and rituximab control arm. Importantly, consistent treatment benefits were seen within the entire clinical exposures of BV achieved in ECHELON-3, as evidenced by the lack of ER relationships between ADC exposure and OS/PFS. The combination of BV+Len+R was well

tolerated with a manageable safety profile consistent with each drug individually. There were no new safety signals identified in ECHELON-3. Further, there were generally no relationships between exposure and incidence rates of safety endpoints evaluated (Grade 3 or higher TEAEs, neutropenia, Grade 3 or higher infections, febrile neutropenia, and PN) based on results of ER analyses using both ADC and MMAE exposures. Only ADC exposure was identified as a predictor for Grade 2 or higher PN, consistent with the dose modifications implemented in ECHELON-3. Collectively, these results support a favorable benefit-risk profile in this population of R/R DLBCL that currently have few treatment options.

The FDA's Assessment:

FDA agrees that patients who received BV+Len+R experienced better OS and PFS compared to patients who received Placebo+Len+R in ECHELON-3. No E-R efficacy associations were identified with ADC Cycle 1 C_{EOI} and OS, PFS, or ORR. The E-R efficacy assessment generally supports the proposed dosage.

FDA does not agree with the Applicant's Section 19.4.2.5 statement that "*there were generally no relationships between exposure and incidence rates of safety endpoints evaluated (Grade 3 or higher TEAEs, neutropenia, Grade 3 or higher infections, febrile neutropenia, and PN).*" As described in Section 19.4.2.4, higher observed Cycle 1 ADC C_{EOI} was associated with higher risk of TEAE leading to any drug dose modification; TEAE leading to any drug dose delay, interruption, or elimination; Grade ≥3 infection; any grade peripheral neuropathy; and Grade ≥2 peripheral neuropathy in Study ECHELON-3 patients who received at least one dose of BV in combination with Len+R.

E-R analysis generally supports a positive benefit-risk evaluation with the proposed dosage in the general patient population. However, MMAE exposure in ECHELON-3 was unable to be evaluated for potential associations with safety events and so the risk of worse toxicity without any improvement in efficacy at higher MMAE exposures is a concern. Patients with hepatic impairment and patients with severe renal impairment are expected to have higher MMAE exposure than patients without organ impairment. Therefore, FDA's clinical pharmacology assessment supports a dose reduction in patients with mild hepatic impairment to maintain a positive benefit-risk ratio. The assessment also supports avoiding use of brentuximab vedotin in patients with moderate hepatic impairment, severe hepatic impairment, or severe renal impairment.

Refer to Section 19.4.2.2 for the detailed E-R efficacy assessment and Section 19.4.2.4 for the detailed E-R safety assessment.

19.5. FDA Grouping of Preferred Terms for Safety Analysis

The FDA's Assessment:

The following grouping of terms was adopted for the primary safety analyses for Study ECHELON-3.

Table 41: Grouping of Preferred Terms for FDA Safety Analysis

FDA Grouped PT for Echelon-3	Included in Grouping	Not Included
Abdominal pain	All PTs containing "abdominal pain", Abdominal discomfort, Epigastric discomfort. Gastrointestinal pain	Abdominal distension, [Abdominal rigidity]
Alopecia	Alopecia, Alopecia areata, alopecia totalis, alopecia general	
Altered taste	Dysgeusia, Taste disorder, Ageusia	
Anemia	All PTs containing "anaemia", haemoglobin decreased	
Arthralgia	Arthralgia, periarthritis	
Atrial fibrillation or flutter	Atrial fibrillation, Atrial flutter	
Bruising	All PTs containing "bruise," "contusion," or "ecchymosis"	Petechiae, Purpura
Cardiac arrhythmias	High-level group term, "Cardiac arrhythmias", "arrythmia"	Sinus arrythmia
Cardiac failure	All PTs containing "cardiac failure", Cardiomyopathy, ischaemic, Cardiomyopathy, hypertensive cardiomyopathy, left ventricular dysfunction, acute left ventricular failure, ejection fraction decreased.	
Cellulitis	Cellulitis, All PTs containing "skin infection"	
Chest pain	Chest discomfort, Angina pectoris, chest pain	Non-cardiac chest pain
Colitis (excluding infectious)	Colitis, enterocolitis	Necrotizing colitis, neutropenic colitis, Enteritis, enterocolitis viral, Campylobacter colitis Clostridium difficile colitis Cytomegalovirus colitis
Cough	All PTs containing "Cough", upper-airway cough syndrome	Allergic cough
Cytomegalovirus infection	Cytomegalovirus infection reactivation, Cytomegalovirus infection,	
Diarrhea	All PTs including Diarrhea except mentioned	Diarrhoea infectious, colitis

FDA Grouped PT for Echelon-3	Included in Grouping	Not Included
Dyspnea	All PTs containing "Dyspnoea"	Acute respiratory failure, [Respiratory failure, Respiratory rate increased, Tachypnea, Bronchospasm, Wheezing]
Dizziness	All PTs containing "Dizziness" or "Vertigo"	
Edema	Edema, Edema peripheral, Fluid overload, Fluid retention, Face edema, Peripheral swelling, Pulmonary edema, , peripheral swelling, swelling, swelling face	Localized sites of edema (e.g. Localized edema, Lip edema, Nasal edema, Periorbital edema, eyelid edema, eye edema, gingival edema, Eye swelling, etc.), Angioedema
Fatigue or asthenia	Asthenia, Fatigue	Lethargy, muscle fatigue
Febrile neutropenia	Febrile neutropenia, Neutropenic sepsis, Febrile bone marrow aplasia, Neutropenic infection * Note: Neutropenic sepsis is counted under both the "febrile neutropenia" and "sepsis" PTs	
Gastroenteritis	Gastroenteritis and specific types (e.g. campylobacter, viral, candidiasis), Enteritis,	Gastritis, Duodenitis,
Gastrointestinal hemorrhage	All PTs containing "Gastrointestinal hemorrhage", anal haemorrhage, , Hematochezia, Hematemesis, Large intestinal hemorrhage, Melena, Hemorrhoidal hemorrhage, Rectal hemorrhage, Upper gastrointestinal haemorrhage	
Hemorrhage	All PTs containing "hemorrhage", "hemorrhagic", or "hematoma", all PTs contained in FDA's "Gastrointestinal hemorrhage" grouping, hematochezia, hematemesis, Hemarthrosis, Hemoptysis, Hematuria, hemoptysis, hemothorax, Epistaxis, intermenstrual bleeding.	Petechiae, Purpura, FDA's grouping for "Bruising"
Headache	All PTs containing "headache", Migraine, Ophthalmic migraine	
Hepatitis	All PTs containing "hepatitis", hepatitis toxic, Hepatotoxicity, Drug-induced liver injury, Liver injury.	FDA's "Transaminase elevation" grouping, PTs containing "Hepatic failure", Hepatic encephalopathy, NASH.

FDA Grouped PT for Echelon-3	Included in Grouping	Not Included
Transaminase elevation	Alanine aminotransferase increased, Aspartate aminotransferase increased, hepatic enzyme abnormal, transaminase increased, Hepatic enzyme increased, liver function test increased, transaminase increased	PTs under FDA's "Hepatitis" grouping, PTs containing "hepatic failure", Hepatic function abnormal
Hepatic function abnormal	AST increase, ALT increase, Hepatic enzyme increased, Transaminases increased, Hepatocellular injury, Hepatic failure, Blood alkaline phosphatase increased, Drug-induced liver injury, Gamma-glutamyl transferase increased [Liver function test abnormal, Hepatotoxicity, Hepatic enzyme abnormal, Hypertransaminemia, Hypertransaminemia]	[Hepatic encephalopathy, Hepatitis, Hepatitis acute]
Herpes virus infection	High-level group term, "Herpes viral infection", terms containing "herpes" and "varicella", Epstein-Barr viraemia, herpes dermatitis	
Hyperglycemia	SMQ: Hyperglycemia, Blood glucose increased, glucose tolerance impaired, Diabetes mellitus, Type 2 diabetes mellitus	
Interstitial lung disease	SMQ (Pneumonitis, Acute respiratory distress syndrome, Interstitial lung disease)	Radiation pneumonitis
Leukopenia	Leukopenia, White blood cell count decrease	
Lower respiratory tract infection	All PTs containing "bronchitis" or "lower respiratory tract infection", Bronchiolitis, Tracheitis,	
Lymphopenia	Lymphopenia, lymphocyte count decreased	
Mucositis or stomatitis	Aphthous ulcer, Oral mucosal blistering, Stomatitis, Mucosal inflammation, mucosal infection, , mucosal ulceration, Mouth ulceration, Oral pain, Oropharyngeal pain, Odynophagia, , Tongue ulceration, tongue blistering, Oral discomfort]	
Musculoskeletal pain	Musculoskeletal chest pain, Musculoskeletal pain, Musculoskeletal discomfort Back pain, Non-cardiac chest pain, , Musculoskeletal discomfort, Neck pain, Pain in extremity, Myalgia, Spinal pain, Bone pain	arthralgia
Myocardial ischemia or infarction	Acute myocardial infarction, Myocardial ischemia, Angina unstable, Troponin increased, Acute coronary syndrome,	Angina pectoris

FDA Grouped PT for Echelon-3	Included in Grouping	Not Included
Nausea	Nausea, Retching	
Neuropathy peripheral	Broad SMQ for peripheral neuropathy excluding muscle weakness and gait disturbance. polyneuropathy, peripheral sensory neuropathy, neuropathy peripheral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, neuralgia (intercostal, trigeminal), dysaesthesia, oral dysaesthesia, Paraesthesia (oral), Hypoaesthesia (oral too), Peroneal nerve palsy, areflexia, Paraesthesia, Hyperaesthesia,	burning sensation, neurological symptoms, Post herpetic neuralgia, ileus paralytic, Vocal cord paralysis
Neutropenia	Neutropenia, Neutrophil count decreased	Pancytopenia, Aplasia
Pneumonia	All PTs containing "pneumonia", including within another word (e.g. bronchopneumonia), Bronchopulmonary aspergillosis, Lung infiltration, Lung consolidation Included AEs of COVID-19 pneumonia which were also included in the COVID-19 grouping.	
Pruritus	Pruritus, Pruritis generalized, [Pruritus allergic, Prurigo, Excoriation]	Aquagenic pruritus, Localized sites of pruritus (Eye pruritus, anal pruritus, pruritus genital, nasal pruritus)
Rash	All PTs containing "rash", all PTs containing "dermatitis" except as noted, Drug eruption, Erythema (catheter site, genital, gingival, infusion site, pharyngeal), Erythema multiforme, palmar erythema, plantar erythema, Skin reaction, Skin toxicity, dermatitis acneiform neutrophilic dermatosis	All PTs containing "Eczema ", seborrheic dermatitis, Actinic keratosis, Folliculitis, Urticaria, Herpes dermatitis, contact dermatitis, stasis dermatitis, Erythema nodosum, Erythema annulare, Dermatitis infected or bullous, urticaria,
Renal insufficiency	All PTs containing "renal failure" or "nephropathy", Acute kidney injury, Blood creatinine increase, Creatinine renal clearance decreased, Glomerular filtration rate decreased, Renal impairment, Hypercreatinemia, Chronic kidney disease. Renal injury	
Respiratory tract infection	Respiratory tract infection (unspecified) + specific types (e.g. metapneumovirus infection, Parainfluenza virus infection, Respiratory syncytial virus infection), Influenza, H1N1 influenza, Influenza like illness, Respiratory syncytial virus infection	Upper respiratory tract infection, Lower respiratory tract infection

FDA Grouped PT for Echelon-3	Included in Grouping	Not Included
Second primary malignancy	PTs including "cancer, "carcinoma, neoplasm", melanoma, leukemia, lymphoma, MDS, myeloma, Bowen's disease, neoplasm malignant, Bone marrow tumour cell infiltration, pituitary tumour	
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**	Device related infection
Thrombocytopenia	Thrombocytopenia, Platelet count decreased	Pancytopenia, immune thrombocytopenia
Thrombosis or thromboembolism	All PTs containing "thrombosis" except as noted, Pulmonary embolism, device related thrombosis	Superficial thrombosis, Embolic stroke
Upper respiratory tract infection	All PTs containing "upper respiratory tract infection," "sinusitis," "laryngitis," "tonsillitis," or "pharyngitis," including within another word (e.g. nasopharyngitis, pharyngotonsilitis), all PTs containing "rhinitis" except as noted, Rhinovirus infection, Human rhinovirus test positive	Rhinitis allergic Allergic pharyngitis Allergic sinusitis, Reflux laryngitis, Epiglottitis
Urinary tract infection	All PTs containing "cystitis" or "urinary tract infection", Pyelonephritis, Kidney infection	Cystitis non infective cystitis, cystitis radiation
Ventricular arrhythmia	High-level term, "Ventricular arrhythmias and cardiac arrest", ventricular fibrillation,	

Source: FDA analysis

[a] Grouping for other lab-related AEs is similar, e.g., hyperglycemia = hyperglycemia + blood glucose increased, lymphopenia = lymphopenia + lymphocyte count decreased

[b] This grouping defines respiratory tract infection (RTI) of unspecified localization. Where designated, FDA also evaluated all "RTI" including the "Upper RTI" and "Lower RTI" grouping.

BLA 125388/S-108				

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Christopher Jay, PhD, MS	OCP/DCPI	Sections: 6, 19.4	Select one: ☑ Authored ☐ Approved
	Signature: Christopher E. Jay -S			Digitally signed by Christopher E. Jay -S Date: 2025.01.17 15:57:35 -05'00'
Clinical Pharmacology Team Leader	Ankit Shah, PhD	OCP/DCPI	Sections: 6, 19.4	Select one: ☑ Authored ☑ Approved
	Signature: Ankit B. Shah -S			Digitally signed by Ankit B. Shah -S Date: 2025.01.17 16:01:56 -05'00'
Clinical Pharmacology Division Director	Brian Booth, PhD	OCP/DCPI	Sections: 6, 15, 19.4	Select one: ☐ Authored ☑ Approved
	Signature: Brian P. Booth -S			Digitally signed by Brian P. Booth -S Date: 2025.01.21 15:50:24 -05'00'
Pharmacometrics Reviewer	Robyn Konicki, PharmD	OCP/DPM	Sections: 6, 19.4	Select one: ☑ Authored ☐ Approved
	Signature: Robyn E. Konicki -S			Digitally signed by Robyn E. Konicki -S Date: 2025.01.21 16:13:12 -05'00'
Pharmacometrics Associate Director	Jiang Liu, PhD	OCP/DPM	Sections: 6, 19.4	Select one: ☑ Authored ☑ Approved
	Signature: Jiang Liu -S			Digitally signed by Jiang Liu -S Date: 2025.01.21 17:39:17 -05'00'
Associate Director for Labeling	Elizabeth Everhart, MSN, RN, ACNP	OOD	Sections: 11	Select one: ☑ Authored ☑ Approved
	Signature: Elizabeth E. Everhart -S			Digitally signed by Elizabeth E. Everhart -S Date: 2025.01.22 13:45:26 -05'00'
Clinical Reviewer	Maryam SarrafYazdy, MD	OOD/DHM II	Sections: All	Select one: ☑ Authored ☐ Approved
	Signature: Maryam Sarraf Yazdy -S			Digitally signed by Maryam Sarraf Yazdy -S Date: 2025.01.22 14:08:43 -05'00'
Clinical Team Leader	Margret Merino, MD	OOD/DHM II	Sections: All	Select one: ☑ Authored ☑ Approved
	Signature: Margret Merino -S			Digitally signed by Margret Merino -S Date: 2025.01.22 15:24:07 -05'00'

Statistical Reviewer	Jingyan Wang, PhD	OB/DBIX	Sections: 8	**Select one:** ☑ Authored ☐ Approved
	Signature: Jingyan Wang -S Digitally signed by Jingyan Wang -S Date: 2025.01.22 15:09:20 -06'00'			
Statistical Team Leader	Zhiheng Xu, PhD	OB/DBIX	Sections: 8	**Select one:** ☑ Authored ☑ Approved
	Signature: ZHIHENG XU -S Digitally signed by ZHIHENG XU -S Date: 2025.01.23 08:04:31 -05'00'			
Supervisory Mathematical Statistician	Jonathon Vallejo, PhD	OB/DBIX	Sections: All	**Select one:** ☐ Authored ☑ Approved
	Signature: Jonathon J. Vallejo -S Digitally signed by Jonathon J. Vallejo -S Date: 2025.01.24 10:10:27 -05'00'			
Cross-Disciplinary Team Leader (CDTL)	Margret Merino, MD	OOD/DHM II	Sections: All	**Select one:** ☑ Authored ☑ Approved
	Signature: Margret Merino -S Digitally signed by Margret Merino -S Date: 2025.01.22 15:24:41 -05'00'			
Deputy Division Director (Clinical)	Nicholas Richardson, DO, MPH	OOD/DHM II	Sections: All	**Select one:** ☐ Authored ☑ Approved
	Signature: Nicholas C. Richardson -S Digitally signed by Nicholas C. Richardson -S Date: 2025.01.24 15:33:13 -05'00'			

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MARGRET E MERINO
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NICHOLAS C RICHARDSON
02/11/2025 06:47:10 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125388Orig1s108

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: January 8, 2025

To: David Bak, PharmD, BCNSP, Senior Regulatory Project Manager
Division of Hematological Malignancies II (DHM2)

From: Louiza Bako, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, PharmD, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for ADCETRIS® (brentuximab vedotin) for injection, for intravenous use

BLA: 125388, S-108

Background:
In response to DHM2's consult request dated July 24, 2024, OPDP has reviewed the proposed Prescribing Information (PI), supplement S-108 for ADCETRIS® (brentuximab vedotin) for injection, for intravenous use. This supplement proposes a new indication for ADCETRIS in combination with lenalidomide and a rituximab product for the treatment of adult patients with relapsed or refractory LBCL, including diffuse large B-cell lymphoma (DLBCL) NOS, DLBCL arising from indolent lymphoma, or high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy who are not eligible for auto-HSCT or chimeric antigen receptor (CAR) T-cell therapy.

PI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on December 23, 2024, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Louiza Bako at (301)796-3970 or Louiza.Bako@fda.hhs.gov.

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

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LOUIZA N BAKO
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CLINICAL INSPECTION SUMMARY

Date	12/4/2024
From	Lydia Kim, M.D., Physician Min Lu, M.D., M.P.H., Team Leader Jenn Sellers, M.D., Ph.D., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	David Bak, Regulatory Project Manager Maryam SarrafYazdy, M.D., Clinical Reviewer Margret Merino, M.D., Team Leader Nicole Gormley, M.D., Division Director Division of Hematologic Malignancies 2 (DHM2) Office of Oncologic Diseases (OOD)
sBLA #	125388/S-108
Applicant	Seagen Inc. (acquired by Pfizer Inc. Dec 2023)
Drug	Brentuximab vedotin intravenous injection
NME	No
Review Priority	Standard
Proposed Indication	(b) (4)
Consultation Request Date	7/16/2024
Summary Goal Date	12/13/2024
Action Goal Date	1/28/2025
PDUFA Date	3/21/2025

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study SGN35-031 (ECHELON-3) were submitted to the Agency in support of this supplemental Biologics License Application (sBLA) for brentuximab (b) (4)

(b) (4)

(b) (4)

The study sponsor, Seagen Inc., was acquired by Pfizer Inc. on 12/14/2023 and is now a wholly owned subsidiary of the Pfizer Corporation. Pfizer was inspected for oversight and monitoring of Study SGN35-031.

Based on the inspection results of Pfizer Inc., it appears that the sponsor's trial management and oversight of Study SGN35-031 were adequate, and the data submitted by the Sponsor appear acceptable in support of the respective indication.

II. BACKGROUND

Brentuximab vedotin (hereafter called "brentuximab") is an antibody-drug conjugate (ADC) composed of an anti-CD30 monoclonal antibody conjugated by a protease-cleavable linker to the microtubule-disrupting drug monomethyl auristatin E (MMAE). Earlier studies in patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) have shown activity with brentuximab monotherapy, brentuximab in combination with lenalidomide, and brentuximab in combination with rituximab. The combination of brentuximab, lenalidomide, and rituximab (BV+Len+R) potentially may show improvement of the combination of lenalidomide and rituximab in R/R DLBCL. Brentuximab is proposed for the treatment of (b) (4) (b) (4) (b) (4) The clinical data from Study SGN35-031 were submitted to support the proposed indication.

Study SGN35-031 (ECHELON-3)

Study SGN35-031 was a phase 3, randomized, double-blind, placebo-controlled, active-comparator, multicenter study. There was a safety run-in period prior to the randomized portion of the study. Subjects must have had R/R DLBCL after at least 2 prior lines of therapy and must have been ineligible for HSCT or CAR T-cell therapy.

Subjects were randomized in a 1:1 manner to either the BV+Len+R arm or the placebo+Len+R arm. Randomization was stratified by CD30 expression (positive, ≥1% versus negative, <1%), cell of origin (germinal center type B-cell [GCB] or non-GCB), prior treatment with CAR T-cell (received or not received), and prior HSCT (includes allogenic or autologous HSCT) therapy (received or not received).

A total of 230 subjects (112 to the BV+Len+R arm and 118 to the placebo+Len+R arm) were randomized in this study; all but 2 randomized subjects (both in the placebo+Len+R arm) received ≥1 dose of study treatment.

Subjects in the BV+Len+R arm received brentuximab at 1.2 mg/kg via intravenous (IV) infusion on Day 1 of every 21-day cycle, rituximab 375 mg/m^2 as an IV infusion on Day 1 of

every 21-day cycle, and lenalidomide 20 mg orally daily. Subjects in the placebo+Len+R arm received placebo replacement for brentuximab administered via IV on Day 1 of every 21-day cycle. For subjects that tolerated rituximab IV infusion on Day 1 of Cycle 1, rituximab was administered at 1400 mg via subcutaneous injection (SQ) on Day 1 of every 21-day cycle for subsequent cycles. Either IV or SQ route of administration was permitted starting from Cycle 2 Day 1. Brentuximab was administered in until unacceptable toxicity or disease progression.

Efficacy of brentuximab in subjects with R/R DLBCL was assessed by overall survival (OS) to compare OS between the 2 treatment arms in the intent-to-treat (ITT) population. An interim analysis (IA) of OS for both efficacy and futility was performed at 134 OS events (78.8% information fraction).
A safety monitoring committee (SMC) including 3 external members reviewed data from the first 6 subjects who received open label BV+Len+R. The safety data for the subjects from this run-in period were evaluated after these subjects completed the first cycle of treatment. The SMC did not identify any new safety signals or concerns, and the SMC approved proceeding with the randomized portion of the study.

The trial was conducted in 172 sites in 16 countries. Study subjects first enrolled on August 20, 2020. Data cut-off calendar date for this application submission was January 22, 2024.

III. RESULTS

Pfizer, Inc.
2500 223rd St SE Bothwell, WA 98021

Inspection Dates: 10/28/2024-11/1/2024

The Seagen Inc., was acquired by Pfizer Inc. on 12/14/2023 and is now a wholly owned subsidiary of the Pfizer Corporation.

This inspection covered the Sponsor's study conduct and oversight related to Study SGN35-031.

Records reviewed during the inspection included:

- Sponsor electronic Trial Master File (eTMF)
- Investigator agreements or 1572s
- Financial disclosures
- Training records
- Protocol compliance
- Adverse events and serious adverse events including reporting
- Electronic systems used
- Transfer of regulatory obligations and oversight
- Monitoring of clinical study sites
- Written procedures relevant to the conduct of the trial
- Drug safety reporting

- Overall record(s) maintenance, adequacy, and retention

The Sponsor's criteria for selection of clinical investigator sites included a feasibility assessment, a completed investigator qualification questionnaire, and a successful Pre-Study Visit (PSV). There were 98 clinical sites that screened and/or randomized subjects in 14 countries, and 83 sites did not conduct the study under the IND. While there were no clinical investigators whose participation was terminated, Site 82011 in the Republic of Korea was placed on an enrollment pause on 10/18/2023 for inability to resolve open queries and issues in a timely fashion due to high enrollment. Enrollment was not reinstated at this site, as global enrollment was completed shortly thereafter on 11/23/2023.

The Clinical Research Organization (CRO), (b) (4) was responsible for monitor selection and training. Monitors' qualifications for the selected sites were reviewed. No issues with qualifications were identified. For the sites reviewed, there were no instances in which unblinded engaged in or conducted any of the blinded monitoring activities. The Sponsor's written business and operational procedures related to monitoring activities were reviewed. The Sponsor's most recent version (v05 dated 4/17/2024) of the clinical monitoring plan (CMP) for the SGN35-031 study was reviewed. The CRO's most current CMPs for blinded and unblinded monitoring activities were reviewed. Pre-trial, site initiation, and interim monitoring visits within the eTMF for selected sites were reviewed. During the inspection, it was noted, per the Sponsor's CMP (v02 dated 4/2/2021), the first interim monitoring visit should be completed "approximately 2 weeks after the first subject receives that first dose of study drug." At Sites 33018 and 42001, the first monitoring visit was conducted 22 days and 24 days, respectively, after the first subject was dosed with the investigational drug. For Site 33018, it was noted that the first monitoring visit was delayed for the first subject due to COVID-19. No other deviations or concerns with monitoring activities were noted.

Reviewer's comment: The delays in conducting the first monitoring visit due to COVID-19 at Sites 33018 and 42001 did not follow the clinical monitoring plan which did not appear to impact study efficacy or safety results.

For safety and adverse event reporting, procedures related to the processing of safety information in the safety database, receipt of product safety-related information, and notification to Global Safety Risk Management and safety signal management were reviewed. There was no underreporting of adverse events identified.

The written procedures and work instructions relating to clinical data management, data flow and integrity, and the implementation process for clinical studies in support of ongoing data review and cleaning were reviewed; no deficiencies or deviations were noted.

Electronic systems including Medidata Rave for eCRF and ARGUS for safety, electronic signatures, and related audit trails were reviewed; no issues were identified.

Overall, Study SGN35-031 appears to have been conducted adequately.

{See appended electronic signature page}

Lydia Kim, M.D. Physician
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

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Jenn Sellers, M.D., Ph.D. Branch Chief
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Office of Scientific Investigations

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/s/

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JENN W SELLERS
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	November 5, 2024
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	BLA 125388/S-108
Product Name, Dosage Form, and Strength:	Adcetris (brentuximab vedotin) for Injection, 50 mg/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Seagen Inc.
FDA Received Date:	May 21, 2024
TTT ID #:	2024-10246
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 INTRODUCTION

Seagen Inc. submitted an Efficacy Supplement for Adcetris (brentuximab vedotin) for Injection to propose a new indication (b) (4) (b) (4) (b) (4) We reviewed the proposed Adcetris Prescribing Information (PI) for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

Adcetris was approved on August 19, 2011 for the treatment of patients with Hodgkin lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates and for the treatment of patients with systemic anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen. It is supplied as a 50 mg vial for injection.

2 MATERIALS REVIEWED

This section lists the materials considered for our review of BLA 125388/S-108.

Table 1. Materials Considered for this Label and Labeling Review	
Materials Reviewed	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Previous DMEPA Reviews	C

3 CONCLUSION

The proposed Adcetris Prescribing Information (PI) may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Hematologic Malignancies 2 (DHM 2) in Section 4.

4 RECOMMENDATIONS FOR THE DIVISION OF HEMATOLOGIC MALIGNANCIES 2 (DHM 2)

A. Prescribing Information

1. Section 2 Dosage and Administration
    a. As currently presented in Table 2, the maximum dosage for Grade 3 Dosage Modification for Adcetris in combination with lenalidomide and rituximab lacks adequate spacing between the numerical dose and unit of measure. Lack of adequate spacing may impact readability and might result in wrong dosage errors. For example (e.g., the “m” in mg can sometimes be mistaken as a zero or two zeros). We recommend placing

adequate space between the numerical dose and unit of measure (e.g., 90 mg instead of 90mg) to improve readability.

b. In Section 2.6, *Instructions for Preparation and Administration*, under *Reconstitution*, the storage instructions for the reconstituted solution can be revised for clarity. Not including a "refrigerated" statement may result in the risk of the storage information being overlooked and lead to deteriorated drug medication errors. Additionally, the unit of measure does not follow each numeric value of temperature (e.g., "2° to 8°C"). This may lead to confusion and potential risk of preparation error. We recommend including the unit of measure after each numeric value of temperature. Revise to "If not diluted immediately, store the solution refrigerated at 2°C to 8°C (36°F to 46°F) and use within 24 hours of reconstitution.".

c. In Section 2.6, *Instructions for Preparation and Administration*, under *Dilution*, the storage instructions for the diluted solution can be revised for clarity. Not including a "refrigerated" statement may result in the risk of the storage information being overlooked and lead to deteriorated drug medication errors. Additionally, the unit of measure does not follow each numeric value of temperature (e.g., "2° to 8°C"). This may lead to confusion and potential risk of preparation error. We recommend including the unit of measure after each numeric value of temperature. Revise to "If not used immediately, store the solution refrigerated at 2°C to 8°C (36°F to 46°F) and use within 24 hours of reconstitution.".

2. Section 16 How Supplied/Storage and Handling

a. The unit of measure does not follow each numeric value of temperature (e.g., "2° to 8°C") and the storage instructions can be revised for clarity. Unclear storage information may lead to confusion and potential risk of deteriorated drug medication errors. We recommend adding the unit of measure after each numerical degree. Revise to "Store vial refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light.".

APPENDICES: METHODS AND RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Adcetris received on May 21, 2024 from Seagen Inc.

Table 2. Relevant Product Information for Adcetris	
Initial Approval Date	August 11, 2011
Proper Name	brentuximab vedotin

Table 2. Relevant Product Information for Adcetris	
Indication	• Previously Untreated Stage III or IV Classical Hodgkin Lymphoma (cHL), in Combination with Chemotherapy: for the treatment of adult patients with previously untreated Sage III or IV cHL, in combination with doxorubicin, vinblastine, and dacarbazine. • Previously Untreated High Risk Classical Hodgkin Lymphoma (cHL), in Combination with Chemotherapy: for the treatment of pediatric patients 2 years and older with previously untreated high risk cHL, in combination with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide. • Classical Hodgkin Lymphoma (cHL) Consolidation: for the treatment of adult patients with cHL at high risk of relapse or progression as post-autologous hematopoietic stem cell transplantation (auto-HSCT) consolidation. • Relapsed Classical Hodgkin Lymphoma (cHL): for the treatment of adult patients with cHL after failure of auto-HSCT or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates. • Previously Untreated Systemic Anaplastic Large Cell Lymphoma (sALCL) or Other CD30-Expressing Peripheral T-cell Lymphomas (PTCL), in Combination with Chemotherapy: for the treatment of adult patients with previously untreated sALCL or other CD30-expressing PTCL, including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified, in combination with cyclophosphamide, doxorubicin, and prednisone. • Relapsed Systemic Anaplastic Large Cell Lymphoma (sALCL): for the treatment of adult patients with sALCL after failure of at least one prior multi-agent chemotherapy regimen. • Relapsed Primary Cutaneous Anaplastic Large Cell Lymphoma (pcALCL) or CD30-Expressing Mycosis Fungoides (MF): for the treatment of adult patients with pcALCL or CD30-expressing MF who have received prior systemic therapy. • (b) (4)
Dosage Form	for Injection

Table 2. Relevant Product Information for Adcetris	
Strength	50 mg/vial
Route of Administration	Intravenous Infusion

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Table 2. Relevant Product Information for Adcetris			
Dose and Frequency	Indication	Recommended Dose*	Frequency and Duration
	Adult patients with previously untreated Stage III or IV classical Hodgkin lymphoma	1.2 mg/kg up to a maximum of 120 mg in combination with chemotherapy	Administer every 2 weeks until a maximum of 12 doses, disease progression, or unacceptable toxicity
	Pediatric patients with previously untreated high risk classical Hodgkin lymphoma	1.8 mg/kg up to a maximum of 180 mg in combination with chemotherapy	Administer every 3 weeks with each cycle of chemotherapy for a maximum of 5 doses
	Adult patients with classical Hodgkin lymphoma consolidation	1.8 mg/kg up to a maximum of 180 mg	Initiate treatment within 4-6 weeks post-auto-HSCT or upon recovery from auto-HSCT. Administer every 3 weeks until a maximum of 16 cycles, disease progression, or unacceptable toxicity
	Adult patients with relapsed classical Hodgkin lymphoma	1.8 mg/kg up to a maximum of 180 mg	Administer every 3 weeks until disease progression or unacceptable toxicity
	Adult patients with previously untreated systemic ALCL or other CD30-expressing peripheral T-cell lymphomas	1.8 mg/kg up to a maximum of 180 mg in combination with chemotherapy	Administer every 3 weeks with each cycle of chemotherapy for 6 to 8 doses
	Adult patients with relapsed Systemic ALCL	1.8 mg/kg up to a maximum of 180 mg	Administer every 3 weeks until disease progression or unacceptable toxicity
	Adult patients with relapsed primary cutaneous ALCL or	1.8 mg/kg up to a maximum of 180 mg	Administer every 3 weeks until a maximum of 16 cycles, disease

Table 2. Relevant Product Information for Adcetris		
	CD30-expressing mycosis Fungoides		progression, or unacceptable toxicity
	Adult patients with relapsed or refractory DLBCL [proposed]	1.2 mg/kg up to a maximum of 120 mg in combination with lenalidomide and rituximab	Administer every 3 weeks until disease progression, or unacceptable toxicity
	*The dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg.		
How Supplied	ADCETRIS (brentuximab vedotin) for Injection is supplied as a sterile, white to off-white preservative-free lyophilized cake or powder in individually-boxed single-dose vials: • NDC (51144-050-01), 50 mg brentuximab vedotin		
Storage	Store vial at 2° to 8°C (36° to 46°F) in the original carton to protect from light.		
Container Closure	30 mL clear glass vial with grey (b) (4) rubber stopper and 20 mm push-off seal (dark green).		

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Adcetris labels and labeling submitted by Seagen Inc..

- Prescribing Information received on May 21, 2024, available from \\CDSESUB1\EVSPROD\bla125388\0387\m1\us\114-labeling\draft\annotated\sgn35-031-draft-annot-label-text.pdf

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[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

APPENDIX C. PREVIOUS DMEPA REVIEWS

On August 29, 2024, we searched for previous DMEPA reviews relevant to this current review using the terms, '125388', 'Adcetris', and 'brentuximab'. Our search identified 1 previous review[b] since the date of our last search on September 26, 2022, and we considered our previous recommendations to see if they are applicable for this current review.

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[b] Iverson, N. Label and Labeling Review for Adcetris (BLA 125388/S-106). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 OCT 03. TTT ID No.: 2022-1707.

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