NDA/sBLA 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-106
Priority or Standard	Priority
Submit Date(s)	May 14, 2022
Received Date(s)	May 16, 2022
PDUFA Goal Date	November 16, 2022
Division/Office	Division of Hematologic Malignancies II
Review Completion Date	November 9, 2022
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	1.8 mg/kg up to a maximum of 180 mg every 3 weeks for a maximum of 5 doses
Applicant Proposed Indication(s)/Population(s)	Pediatric patients 2 years and older with previously untreated high risk classical Hodgkin lymphoma (cHL), in combination with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide
Recommendation on Regulatory Action	Regular Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of pediatric patients 2 years and older with previously untreated high risk classical Hodgkin lymphoma (cHL), in combination with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide

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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

ABVE-PC	doxorubicin (Adriamycin), bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide
ADC	antibody drug conjugate
AE	adverse event
ALCL	anaplastic large cell lymphoma
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATA	antitherapeutic antibody
AUC	area under the concentration time curve
auto HSCT	autologous hematopoietic stem cell transplantation
AVEPC	doxorubicin (Adriamycin), vincristine, etoposide, prednisone, and cyclophosphamide
BLA	biologics license application
BV	brentuximab vedotin
CFR	Code of Federal Regulations
cHL	classical Hodgkin Lymphoma
CI	confidence interval
COG	Children's Oncology Group
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Event
CTEP AERS	Cancer Therapy and Evaluation Program Adverse Event Reporting System
DCTD	Division of Cancer Treatment and Diagnosis
ECG	electrocardiogram
eCTD	electronic common technical document
EFS	event free survival
E-R	exposure-response
ERR	early response rate
FDA	Food and Drug Administration
GCP	good clinical practice
G-CSF	granulocyte colony stimulating factor
HL	Hodgkin lymphoma
HR	hazard ratio
ICH	International Conference on Harmonization
ISS	integrated summary of safety

ISRT	involved site radiation
ITT	intent to treat
IV	intravenous
LMA	Large mediastinal adenopathy
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	monomethyl auristatin E
NCI	National Cancer Institute
NME	new molecular entity
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PN	peripheral neuropathy
PPK	population PK
PRO	patient reported outcome
PT	preferred term
REMS	risk evaluation and mitigation strategy
RRL	rapid responding lesion
RT	radiotherapy
RTR	radiotherapy rate
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SRL	slow responding lesion
TEAE	treatment emergent adverse event
ULN	upper limit of normal

1 Executive Summary

1.1. Product Introduction

Drug: ADCETRIS® (brentuximab vedotin)

Pharmacological Class: Brentuximab vedotin is a CD30-directed antibody-drug conjugate, comprised of a chimeric IgG1 directed against CD30 conjugated to the microtubule disrupting agent monomethyl auristatin (MMAE).

Current Indications: Adcetris received initial US approval in 2011. The current approved indications for Adcetris are for the treatment of adult patients with:

- Previously untreated Stage III or IV classical Hodgkin lymphoma (cHL), in combination with chemotherapy.
- Classical Hodgkin lymphoma (cHL) at high risk of relapse or progression as post-autologous hematopoietic stem cell transplantation (auto-HSCT) consolidation.
- 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.
- 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, in combination with cyclophosphamide, doxorubicin, and prednisone.
- Systemic anaplastic large cell lymphoma (sALCL) after failure of at least one prior multi- agent chemotherapy regimen.
- Primary cutaneous anaplastic large cell lymphoma (pcALCL) or CD30-expressing mycosis fungoides (MF) who have received prior systemic therapy.

Proposed Indication:
Treatment of pediatric patients 2 years and older with previously untreated high risk classical Hodgkin lymphoma (cHL), in combination with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide.

Dosing Regimen: 1.8 mg/kg up to a maximum of 180 mg every 3 weeks (Q3W) for a maximum of 5 doses

The review team recommends approval of ADCETRIS (brentuximab vedotin) for the following indication:

> *Treatment of pediatric patients 2 years and older with previously untreated high risk classical Hodgkin lymphoma (cHL), in combination with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide.*

Approval of brentuximab vedotin in the above indication is based on the totality of evidence from Study AHOD1331, which demonstrated a favorable benefit-risk profile for pediatric patients 2 years and older with previously untreated, high risk cHL.

Data from four additional studies were included in the application and were supportive:

- Study C25002: A Phase 1/2 dose escalation study of brentuximab vedotin in 36 pediatric patients aged 2 to <18 years with relapsed/refractory HL or systemic anaplastic large cell lymphoma (sALCL).
- Study AHOD1221: A Phase 1/2, single-arm, open-label non-randomized study of brentuximab vedotin in combination with gemcitabine in 46 pediatric and young adult patients aged >12 months to ≤30 years with relapsed/refractory cHL.
- Study ANHL12P1: A Phase 2, randomized, open-label study of brentuximab vedotin (N=68) or crizotinib (N=69) in combination with standard chemotherapy in pediatric patients aged <22 years with previously untreated, non-localized sALCL.
- Study HLHR13: A Phase 2, single-arm, non-randomized study of brentuximab vedotin substituting for vincristine in the OEPA/COPDac (vincristine, etoposide, prednisone, doxorubicin/cyclophosphamide, vincristine, prednisone, dacarbazine) regimen in 77 pediatric patients aged ≤18 years with previously untreated, high risk, CH30+ cHL.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The clinical benefit of brentuximab vedotin was established in AHOD1331, a phase 3, global, randomized study in children and young adults with previously untreated high risk cHL. Patients aged 2 to <22 years with previously untreated, pathologically confirmed high risk (defined as Ann Arbor Stage IIB with bulk, Stage IIIB, Stage IVA, or Stage IVB) cHL were enrolled. Patients were stratified by disease stage and were randomized 1:1 to receive either brentuximab vedotin plus the chemotherapy backbone of doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide (AVEPC) or the control arm of doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide (ABVE-PC). Patients in the brentuximab vedotin (BV) arm received BV at 1.8 mg/kg IV over 30 minutes on Day 1 of each 21-day cycle in addition to AVEPC chemotherapy. After two cycles, early response was assessed by positron emission tomography (PET) for all patients in both arms. All patients subsequently received three additional cycles, for a total of five treatment cycles in each arm.

Efficacy:

- The primary endpoint in AHOD1331 was event free survival (EFS), defined as the time from randomization to any of the following events: disease progression or relapse, second malignancy, or death, whichever comes first.
- Median EFS was not reached in either arm. In the BV-AVEPC arm, the estimated EFS rate was 92.5% (95% CI: 88.8, 95.0) at 2 years and 92.1% (95% CI: 88.4, 94.7) at 3 years, compared to 84.8% (95% CI: 80.1, 88.5) at 2 years and 82.3% (95% CI: 77.2, 86.3) at 3 years in the ABVE-PC control arm. The hazard ratio (HR) was 0.41 (95% CI: 0.25, 0.67), corresponding to a 59% reduction in the risk of an EFS event in the BV-AVEPC arm versus the ABVE-PC arm.
- Secondary efficacy endpoints were Early Response Rate (ERR) and Response-directed Radiation Therapy (RTR) rate.
- The Early Response Rate (ERR) was similar in the two treatment arms (BV-AVEPC: 79.3%; [95% CI: 74.3, 83.8]; ABVE-PC: 79%; [95% CI: 73.9, 83.5]).
- The Response-Directed Radiotherapy Rate (RTR) was similar in the two treatment arms (BV-AVEPC: 40%; [95% CI: 9.7, 17.7]; ABVE-PC: 43%; [95% CI: 10.6, 18.8]).

The Applicant proposed an indication in pediatric patients 2 years and older. The FDA notes that despite the AHOD1331 eligibility criteria including patients aged ≥2 to <22, the youngest patient enrolled in this study was 3 years old. Because cHL tends to be a disease of older children, and is rare in very young children, the FDA concluded that the patient population enrolled in AHOD1331 was representative of the normal distribution of cHL in pediatric patients, and was acceptable. The clinical course of newly diagnosed high risk cHL in 2 year olds is expected to be similar to that of 3 year olds, and in practice, these patients are expected to be treated with the same chemotherapy regimens as older children. Therefore, based on the data provided, the safety and efficacy of BV+AVEPC in 2 year olds with previously untreated high risk cHL should be similar to the safety and efficacy established in pediatric patients in Study AHOD1331. Further, the Applicant provided additional safety information from other studies in children less than 6 that demonstrated a similar safety profile to older children. Thus, the FDA determined that the proposed indication for use in patients 2 years and older was acceptable.

The efficacy results from Study AHOD1331 demonstrate substantial evidence of effectiveness for brentuximab vedotin in combination with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide for pediatric patients with newly diagnosed, high risk cHL.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

The benefit-risk assessment for brentuximab vedotin is primarily based on the results from the pivotal study, AHOD1331, a phase 3, randomized trial in children aged 2 to 21 with previously untreated, high risk classical Hodgkin lymphoma (cHL). A total of 600 patients were stratified by disease stage and were randomized 1:1 to receive either brentuximab vedotin plus doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide (AVEPC) chemotherapy (N=300) or the standard of care, doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide (ABVE-PC) chemotherapy (N=300). Patients in the brentuximab vedotin (BV) arm received BV at a dose of 1.8 mg/kg IV over 30 minutes on Day 1 of each 21-day cycle. Treatment continued for a total of five planned cycles of therapy. Data from four additional studies (C25002, AHOD1221, ANHL12P1, and HLHR13) were included in this application and were supportive.

Efficacy: The primary endpoint in AHOD1331 was event-free survival (EFS), defined as the time from randomization to any of the following events: disease progression or relapse, second malignancy, or death, whichever comes first. The median EFS was not reached in either arm. In the brentuximab vedotin plus AVEPC arm, the estimated EFS rate was 92.5% (95% CI: 88.8, 95.0) at 2 years and 92.1% (95% CI: 88.4, 94.7) at 3 years, compared to 84.8% (95% CI: 80.1, 88.5) at 2 years and 82.3% (95% CI: 77.2, 86.3) at 3 years in the ABVE-PC control arm. The hazard ratio (HR) was 0.41 (95% CI: 0.25, 0.67), corresponding to a 59% reduction in the risk of an EFS event in the BV-AVEPC arm versus the ABVE-PC arm.

Safety: The safety profile of brentuximab vedotin in pediatric patients with previously untreated, high risk cHL was established in Study AHOD1331. There were 296 patients treated with BV plus AVEPC and 297 patients treated with ABVE-PC, which comprised the safety population. More patients in the BV-AVEPC arm experienced a Grade ≥ 3 treatment-emergent adverse events (TEAE) at 74% compared to 68% in the control arm. Grade ≥3 TEAEs that occurred in ≥20% of patients with ≥5% higher incidence in the BV-AVEPC arm included the following: Grade 4 neutropenia (BV-AVEPC: 43%; ABVE-PC: 36%), Grade 4 thrombocytopenia (BV-AVEPC: 22%; ABVE-PC: 16%), and Grade 3 anemia (BV-AVEPC: 35%; ABVE-PC: 28%). In the BV-AVEPC arm, 64 patients (22%) experienced at least 1 TEAE serious adverse event (SAE). The most common SAEs included hypotension (N=10; 3%), febrile neutropenia (N=9; 3%), sepsis (N=7; 2%), colitis (N=7; 2%), and embolism (N=7; 2%). Peripheral neuropathy is specified as an adverse event of special interest with brentuximab vedotin and occurred in approximately 20% of patients in both treatment arms (81% sensory, 29% motor). In general, the overall safety profile of brentuximab vedotin in pediatric patients with newly diagnosed, high risk cHL in Study AHOD1331 was similar to the known safety profile of brentuximab vedotin. There were no new safety signals identified in the pediatric population.

Benefit/risk: The overall benefit/risk of brentuximab vedotin is favorable for the intended patient population and supports regular approval of brentuximab vedotin in combination with AVEPC chemotherapy for pediatric patients 2 years and older with previously untreated, high risk cHL.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Classical Hodgkin lymphoma (cHL) is a B-cell lymphoproliferative disorder, which represents approximately 6% of pediatric cancers. • High risk patients have a 5-year event-free survival (EFS) of <85%.	• Classical Hodgkin lymphoma (cHL) is a serious and life-threatening disease and is typically fatal if left untreated or uncured.
Current Treatment Options	• The standard of care for pediatric patients with high-risk cHL typically includes intensive, multi-drug chemotherapy regimens, including ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide), and OEPA/COPDac (vincristine, etoposide, prednisone, doxorubicin-cyclophosphamide, vincristine, prednisone, dacarbazine).	• There is an unmet medical need for new therapies for pediatric cHL. In general, the aim of new therapies is to improve overall efficacy while decreasing toxicity and optimizing long-term quality of life.
Benefit	• The primary clinical benefit of brentuximab vedotin in pediatric patients with newly diagnosed, high risk cHL was established by the efficacy results from Study AHOD1331. • The median EFS was not reached in either arm. In the BV-AVEPC arm, the estimated EFS rate was 92.5% (95% CI: 88.8, 95.0) at 2 years and 92.1% (95% CI: 88.4, 94.7) at 3 years, compared to 84.8% (95% CI: 80.1, 88.5) at 2 years and 82.3% (95% CI: 77.2, 86.3) at 3 years in the ABVE-PC control arm. • The hazard ratio (HR) was 0.41 (95% CI: 0.25, 0.67), corresponding to a 59% reduction in the risk of an EFS event in the BV-AVEPC arm versus the ABVE-PC arm.	• The statistically significant improvement in the primary endpoint of EFS provides substantial evidence of effectiveness to support the approval of brentuximab vedotin in combination with AVEPC chemotherapy in pediatric patients with newly diagnosed, high risk cHL.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The safety of brentuximab vedotin in pediatric patients with newly diagnosed, high risk cHL was evaluated in Study AHOD1331. • The most common adverse events in both treatment arms were neutropenia (BV-AVEPC: 50%; ABVE-PC: 40%), leukopenia (BV-AVEPC: 43%; ABVE-PC: 35%), anemia (BV-AVEPC: 37%; ABVE-PC: 31%), thrombocytopenia (BV-AVEPC: 32%; ABVE-PC: 27%), and febrile neutropenia (BV-AVEPC: 31%; ABVE-PC: 32%). • Grade ≥3 treatment-emergent adverse events that occurred in ≥20% of patients with ≥5% higher incidence in the BV-AVEPC arm included the following: Grade 4 neutropenia (BV-AVEPC: 43%; ABVE-PC: 36%), Grade 4 thrombocytopenia (BV-AVEPC: 22%; ABVE-PC: 16%), and Grade 3 anemia (BV-AVEPC: 35%; ABVE-PC: 28%).	• The overall safety profile of brentuximab vedotin in pediatric patients with newly diagnosed, high risk cHL in Study AHOD1331 was similar to the known safety profile of brentuximab vedotin. • There were no new safety signals identified in the pediatric population. • The label was updated to convey the risks of brentuximab vedotin in combination with AVEPC chemotherapy in pediatric patients with newly diagnosed, high risk cHL. • Brentuximab has an acceptable safety profile in pediatric patients with newly diagnosed high risk cHL.

1.4. Patient Experience Data

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

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

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

	☐ Patient-focused drug development or other stakeholder meeting summary reports	
	☐ Observational survey studies designed to capture patient experience data	
	☐ Natural history studies	
	☐ Patient preference studies (e.g., submitted studies or scientific publications)	
	☐ Other: (Please specify)	
☐	Patient experience data that was not submitted in the application, but was considered in this review.	

X _____

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

HL is a B-cell lymphoproliferative disorder which affects approximately 8500 new patients annually representing about 10% of all lymphomas in the US. HL is divided into 2 types, cHL, which accounts for 90% to 95% of all cases and nodular lymphocyte predominant HL which accounts for 5% to 10% of cases. Four histological subtypes of cHL are distinguished: nodular sclerosis cHL, mixed cellularity cHL, lymphocyte--depleted cHL, and lymphocyte-rich cHL (Ansell et al, 2020). cHL has a bimodal age incidence, with a peak incidence in adolescents and young adults between the ages of 15 and 30 years followed by a peak in adult patients aged 55 years or older (Ansell et al, 2020). cHL represents about 6% of all childhood cancers (Allen et al, 2015). In the pediatric population, the incidence rate is approximately 3.1 per 100,000 between the ages of 15 and 19, approximately 0.7 per 100,000 in children under 14 years of age, and approximately 0.1 per 100,000 in patients <5 years of age (Noone et al, 2017).

A challenge in treating pediatric cHL is finding the optimal balance between achieving tumor free survival and minimizing treatment-related morbidity and mortality. While contemporary combined modality therapy in children and adolescents and young adults results in 5 to 10-year survival rates of more than 90% when patients of all stages are evaluated, there remain subgroups of patients with cHL, such as those with high-risk disease, for whom the cure rates are suboptimal. It is among these high-risk patients that intensification of treatment with current conventional agents is inadequate. Furthermore, death rates from treatment-associated morbidity escalate for decades following initial remission (Hudson et al, 1998; Donaldson et al, 1999; Bhatia et al, 2003; Castellino et al, 2011). Risk adapted treatment approaches lead to decrease in radiation fields and doses, and dose dense schedules with contemporary therapy allow overall reduced exposure to chemotherapy, yet the cumulative incidence of Second Malignant Neoplasms remains elevated.

High-risk subgroups of patients with cHL have 5-year EFS <85%, where escalation of chemotherapy does not improve outcomes further; additionally the need for optimizing long term quality of life, together indicate the need for novel therapy (Federico et al, 2009; Viviani et al, 2011; Gordon et al, 2013).

The FDA's Assessment:

The FDA agrees with the Applicant's description of Hodgkin lymphoma (HL), as well as the assessment of cHL in pediatric patients.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

Two dose-dense procarbazine-free chemotherapy regimens that have emerged as standard backbones to maximize intensity without exceeding safety thresholds are OEPA-COPDac

(vincristine, etoposide, prednisone, and doxorubicin-cyclophosphamide, vincristine, prednisone, and dacarbazine) and ABVE-PC.

The OEPA-COPP or COPDac regimen was studied in the randomized, open-label, non-inferiority Euro-Net PHL C1 trial, where children and adolescents with newly diagnosed intermediate or advanced stage cHL were treated based on a response adapted approach for administering radiotherapy. Median follow-up was 66.5 months (IQR 62.7 to 71.7). Of 1287 patients in the per-protocol group, after 2 cycles of OEPA, 514 (40%) had an adequate response to treatment and were not treated with radiotherapy and 773 patients (60%) with inadequate response were scheduled for radiotherapy. In patients who responded adequately, EFS rate at 5 years was 90.1% (95% CI: 87.5, 92.7%). EFS rates at 5 years in 892 patients who were randomly assigned to treatment with COPP vs COPDAC and analyzed per protocol were 89.9% (95% CI: 87.1, 92.8%) for COPP (n=444) versus 86.1% (95% CI: 82.9, 89.4%) for COPDAC (n=448).Overall the study showed for patients with high risk disease, radiation therapy could be omitted if adequate response was observed without compromising the EFS and OS benefit, and that consolidation with CPDAC showed less gonadotoxicity with maintained efficacy; rendering OEPA/CPDAC an acceptable regimen for pediatric patients with high risk cHL, with a 5-year EFS benefit of up to 90%.

The efficacy, tolerability, and safety of the ABVE-PC regimen have been well studied in 3 pediatric trials conducted by Children's Oncology Group (COG): P9425, AHOD0031, and AHOD0831. ABVE-PC is a preferred chemotherapy option as part of multimodal approach for intermediate and high-risk patients with cHL.

The P9425 study conducted in 1997, first described the dose dense ABVE-PC regimen use among patients with either intermediate-risk (IB, IIA/IIIA1 with large mediastinal adenopathy or IIIA2) or high-risk (IIB, IIIB, IV) cHL. Early responses were evaluated after 3 cycles of ABVE-PC. Those with rapid early response (RER) received involved field radiation, while subjects with slow early response (SER) received 2 additional cycles of ABVE-PC (total 5 cycles) followed with radiation. A total of 163 patients with high-risk cHL were enrolled and were evaluated for early response. Sixty-one percent of the high-risk patients (n=97) showed RER. The 5-year EFS was 85% (±3%).

The AHOD0031 study was a phase 3 trial that enrolled 1712 pediatric patients with intermediate risk cHL, defined as IA to IIA with bulk, IAE to IIAE, IB to IIB, IIIA, or IVA. Early response was assessed after 2 cycles of ABVE-PC regimen. Subjects with rapid early response (RER) received 2 additional cycles of ABVE-PC for consolidation and randomized either to observation or involved field radiation therapy (IFRT). Subjects with slow early response (SER) were randomized to receive augmented therapy with either 2 additional cycles of ABVE-PC + radiotherapy (RT) or 2 cycles of DECA (dexamethasone, etoposide, cisplatin, and cytarabine) followed by 2 ABVE-PC cycles and RT. Among 1712 eligible patients, 4-year EFS was 85.0%. This large phase 3 study showed the safety and tolerability of the dose dense ABVE-PC regimen in addition to effectiveness of a response-based approach in intermediate risk patients.

Most recently, AHOD0831, a prospective non-randomized, phase 3 multicenter study, tested a response-based approach in 165 pediatric subjects with high-risk (Stage IIIB/IVB) cHL. All subjects received 2 cycles of ABVE-PC, followed by early response assessment with functional imaging. Subjects with RER received consolidation with 2 additional cycles of ABVE-PC (total 4 cycles), followed by RT to sites of initial bulky involvement only. Subjects with SER received induction chemotherapy with 2 cycles of ifosfamide and vinorelbine every 21 days, followed by 2 more cycles of ABVE-PC (total 6 cycles) and involved field RT. After the initial 2 cycles, among the 164 evaluable subjects, 81 (50%) were RER and 80 (50%) were SER. The 3-year EFS was 81% (95% CI: 74, 86.3%) and the 5-year EFS was 79.1% (95% CI: 71.5, 84.8%). Results from this study for patients with Stage IIIB/IVB disease were generally similar to that observed in the P9425 study (81.7% [95% CI: 71.8, 88.3%], N=88).

Risk-adapted protocols with shorter-duration of treatment have emerged as the current standard of care. While the majority of studies of high-risk pediatric HL report EFS of 75% to 85%, certain high-risk patients, for example, those with Stage IVB disease, consistently have the poorest outcomes. The incorporation of brentuximab vedotin into the standard chemotherapy backbone (ABVE-PC) provides an opportunity to improve disease control while minimizing treatment burden in this group of high risk patients with an unmet need.

The FDA's Assessment:

The FDA agrees with the Applicant's analysis of the current treatment options for pediatric cHL. In general, risk-adapted treatment of cHL is determined by the stage of the disease. Patients with high-risk subgroups of HL have an EFS of 75-85%, with Stage IV patients having the worst outcomes. The standard of care for pediatric patients with high-risk cHL typically includes intensive, multi-drug chemotherapy regimens including ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide) and OEPA/COPDac (vincristine, etoposide, prednisone, doxorubicin-cyclophosphamide, vincristine, prednisone, dacarbazine). However, initial or salvage chemotherapy regimens that contain high doses of alkylating agents, anthracyclines, and radiation are associated with significant toxicities, including long-term sequelae such as second malignancies, cardiovascular disease, and pulmonary toxicity. Thus, there remains a need for novel therapies in this patient population. The principal goal for the treatment of pediatric cHL is to improve disease control while minimizing treatment and long-term toxicity.

Recent approvals for the treatment of adult patients with HL are displayed in Table 1. Older approvals for HL are displayed in Table 2.

Table 1: Recent Approvals for Hodgkin Lymphoma

Drug Year Approval type	Trial	Population	Endpoint	Duration
Brentuximab vedotin 2011 Accelerated approval	Open-label, single arm N=102	After failure of ASCT or after failure of two prior multi-agent chemotherapy regimens in patients not ASCT candidates.	ORR: 73% (CR: 32%, PR: 41%)	Median DOR of ORR: 6.7 months (CR median DOR 20.5 months; PR median DOR: 3.5 months)
Brentuximab vedotin 2015 Regular approval	Randomized, double-blind, placebo controlled, (brentuximab vedotin vs ASCT placebo)	As consolidation following ASCT for patients at high risk of relapse or progression	Primary endpoint: PFS determined by independent review facility. HR=0.57 (95% CI 0.40, 0.81)	
Nivolumab 2016 Accelerated approval	Two single arm trials N=95	Relapse or progressed after ASCT and post transplantation brentuximab Vedotin	Combined efficacy: ORR (per IWG 2007): 65% (62/95) CR: 7% (7/95) PR: 58% (55/95)	Median DOR: 8.7 months
Pembrolizumab 2017 Accelerated approval	Phase 2, single arm trial N=210	Adult and pediatric patients with refractory cHL or those who have relapsed after 2 or more prior lines of therapy	ORR (per Revised Response Criteria for Malignant Lymphoma): 69% (95% CI: 62, 75) CR: 22%, PR: 47%	Median DOR: 11.1 months

Pembrolizumab 2020 Regular approval	KEYNOTE-204: Randomized, open-label, phase 3 study of pembrolizumab vs. brentuximab KEYNOTE-051: single-arm study; N=22	KEYNOTE-204: Relapsed or refractory cHL after at least one multiagent regimen KEYNOTE-051: pediatric patients with solid tumors or lymphoma	KEYNOTE-204: Primary endpoint: PFS determined by independent review facility. HR=0.65 (95% CI 0.48, 0.88) KEYNOTE-051: ORR: 59% (95% CI: 36-79)	

ASCT: autologous stem cell transplantation; CI: confidence interval; CR: complete response; DOR: duration of response; HR: hazard ratio; PFS: progression free survival; PR: partial response; ORR: overall response rate
Source: FDA Analysis

Table 2: Older Approvals in Hodgkin lymphoma

Class	Drug	Year of Approval
Alkylating agents	Carmustine	1977
	Lomustine	1976
	Dacarbazine	1975
	Procarbazine	1969
	Cyclophosphamide	1959
	Chlorambucil	1957
	Mechlorethamine	1949
Antitumor antibiotics	Doxorubicin	1974
	Bleomycin	1973
Antimicrotubule agents	Vinblastine	1965
	Vincristine	1963

Source: FDA Analysis

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Brentuximab vedotin (ADCETRIS®) initial marketing approval was granted by the FDA in August 2011; since then ADCETRIS® has been approved in 76 countries/regions. Authorized indications in the US for treatment of adult patients include those with:

(1) previously untreated Stage III or IV cHL, in combination with doxorubicin, vinblastine, and dacarbazine

(2) cHL at high-risk of relapse or progression as post-autologous hematopoietic stem cell transplantation (auto-HSCT) consolidation

(3) cHL after failure of auto-HSCT or after failure of at least 2 prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates

(4) 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, in combination with cyclophosphamide, doxorubicin, and prednisone

(5) sALCL after failure of at least 1 prior multi-agent chemotherapy regimen

(6) primary cutaneous ALCL (pcALCL) or CD30 expressing mycosis fungoides (MF) who have received prior systemic therapy.

The FDA's Assessment:

The FDA agrees with the Applicant's description of the U.S. Regulatory Actions and marketing history of brentuximab vedotin.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Key interactions with the FDA for brentuximab vedotin development in the pediatric population are summarized in Table 3.

Table 3: Applicant – Key FDA Interactions and Correspondence for Brentuximab Vedotin Development in Pediatric Population

Date	FDA Interactions	Key Outcomes
28 June 2018	Initial submission of proposed pediatric study request (PPSR) (SN 1927), which included C25002 and AHOD1221 as proposed studies	Inadequate Study Request
29 March 2019	Revised PPSR submission (SN 1969)	Inadequate Study Request
23 January 2020	Revised PPSR submission (SN 2011)	Inadequate Study Request

Date	FDA Interactions	Key Outcomes
03 December 2020	Type C Meeting (Reference ID: 4712323)	Discussed the alternative approach of data extrapolation from adult patients with previously untreated Stage III and IV cHL to pediatric patients. The FDA reiterated the importance of including study AHOD1331 in the Written Request
26 February 2021	Submission of final PPSR (SN 2109), which included 5 pediatric studies: C25002, AHOD1221, ANHL12P1, HLHR13, and AHOD1331	PPSR was accepted by the FDA
12 July 2021	Written Request for pediatric studies for brentuximab vedotin (Reference ID:4824427)	FDA issued the Written Request requiring study reports and proposed labeling to be submitted on or before 30 April 2022
04 August 2021	Written Request Amendment 1 (Reference ID: 4859657)	Amended the submission timeline from 30 April 2022 to 19 May 2022
14 October 2021	Type B pre-sBLA Meeting (Reference ID: 4874306)	Discussed the proposed content and format of the sBLA intended to support the initially proposed indications of brentuximab vedotin for the treatment of pediatric patients (b) (4)
14 February 2022	Email communication of the planned submission of sBLA	Informed FDA that the sBLA to be submitted for fulfillment of the Written Request (b) (4) for the treatment of pediatric patients with previously untreated cHL based on pivotal study AHOD1331

The FDA's Assessment:

In general, the FDA agrees with the Applicant's summary of the Presubmission/submission regulatory activity. Additional details include the following:

- An initial proposed pediatric study request (PPSR) was submitted on June 28, 2018 with two proposed studies (C25002 and AHOD1221). This PPSR did not include evaluation of brentuximab in pediatric patients with previously untreated cHL. In addition, there was an inadequate number of patients (total patients and within each age group), inadequate PK data, and the Applicant failed to include all relevant studies. An inadequate PPSR letter was issued on September 14, 2018.
- A revised PPSR was submitted on March 26, 2019 with four proposed studies (C25002, AHOD1221, HLHR13, and ANHL12P1). This revised PPSR did not include the randomized study (AHOD1331), and the PK data included was inadequate. An inadequate PPSR letter was issued on July 23, 2019.
- A revised PPSR was submitted on January 22, 2020 with five proposed studies (C25002, AHOD1221, HLHR13, ANHL12P1, and (b) (4)), as well as PK data from Study AHOD1331. This revised PPSR did not include efficacy and safety data from Study AHOD1331 or an

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extrapolation from adult efficacy data in newly diagnosed cHL. Therefore, an inadequate PPSR letter was issued on March 25, 2020.

- A Type C meeting was held on December 3, 2020 to discuss the potential extrapolation of data from adult patients with previously untreated Stage III or IV cHL to pediatric patients. During this meeting, the Agency reiterated the importance of the AHOD1331 study and noted that the proposed extrapolation by itself would not be sufficient.
- A revised PPSR was submitted on February 26, 2021 with five proposed studies (C25002, AHOD1221, HLHR13, ANHL12P1, and AHOD1331).
- The original Written Request was issued on July 12, 2021.
- The Written Request underwent one amendment on September 21, 2021. In this amendment, the timeframe for submitting reports of the studies was revised from April 30, 2022 to May 19, 2022. All other terms stated in the original WR remained the same.

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

4.1. Office of Scientific Investigations (OSI)

The FDA's Assessment:
In support of BLA 125388, S-106, OSI conducted inspections at one domestic clinical site and the Children's Oncology Group (COG), who was the co-sponsor for the pivotal study, AHOD1331. OSI concluded that the study data derived from the clinical site is considered reliable and the study data submitted to the FDA for assessment appeared acceptable in support of the proposed indication. OSI is planning to conduct an inspection at a second clinical site, which is pending at the time of this review.

4.2. Product Quality

The FDA's Assessment:
There are no product quality issues with this supplement.

4.3. Clinical Microbiology

The FDA's Assessment:
Not applicable.

4.4. Devices and Companion Diagnostic Issues

The FDA's Assessment:
Not applicable.

5 Nonclinical Pharmacology/Toxicology

No new information is provided in the current submission.

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

Brentuximab vedotin (BV) is an antibody-drug conjugate (ADC) composed of a CD30-targeted chimeric monoclonal antibody (cAC10) covalently linked, via an enzyme-cleavable linker, to the microtubule-disrupting agent monomethyl auristatin E (MMAE). The overall average drug-to-antibody ratio is approximately 4. The proposed indication is for treatment of pediatric patients 2 years and older with previously untreated high risk classical Hodgkin lymphoma (cHL), in combination with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide (AVEPC). The proposed dosing regimen is 1.8 mg/kg up to a maximum of 180 mg every 3 weeks for a maximum of 5 doses via 30-min IV infusion.

The evidence of efficacy at the proposed dosing regimen is supported by the results of a Phase 3, randomized, open-label study (AHOD1331). A total of 300 pediatric and young adult patients aged 3 to 19 years, with previously untreated high risk cHL, were randomized to receive BV 1.8 mg/kg IV Q3W in combination with AVEPC. The rate of Event-Free Survival (EFS) events (primary endpoint) was 8% (23/300) in the BV-AVEPC arm compared to 17% (52/300) in the control arm (ABVE-PC) [Hazard Ratio (95% CI): 0.41 (0.25, 0.67)]. Zero of the 26 patients with pharmacokinetic (PK) data experienced an EFS event, but no clear associations were identified between EFS and body weight or age category. No clear differences in rates of early response, complete metabolic response, or response-directed radiation therapy were identified according to Cycle 1 ADC exposure (C_{trough}, AUC, and C_{max}), body weight, or age category. Although lower body weight was associated with lower exposure following 1.8 mg/kg IV Q3W, this difference in exposure did not appear to have a clinically relevant impact on efficacy.

The exposure-response (E-R) safety analysis did not identify any clear associations between steady state exposure (ADC C_{max}, ADC AUC, MMAE C_{max}, and MMAE AUC) and incidence of Grade ≥3 peripheral neuropathy, Grade ≥3 neutropenia, Grade ≥3 febrile neutropenia, BV dose modification, or any drug dose modification. Overall, the E-R efficacy and safety analyses support the proposed 1.8 mg/kg IV Q3W dosage in pediatric patients aged 2 years and older.

The Clinical Pharmacology section of this BLA supplement is supported by PK characterization, population PK (PPK) and E-R analyses, and immunogenicity assessment. The key review questions focused on the appropriateness of the proposed dosing regimen in pediatric patients 2 to <6 years and 6 to <12 years of age. Based on totality of the safety, efficacy, PK, and PD data, the proposed dosing regimen of BV 1.8 mg/kg (up to 180 mg) IV Q3W for pediatric patients aged 2 years and older appears acceptable from a clinical pharmacology perspective.

Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in the submitted efficacy supplement and it is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below.

Review Issues	Recommendations and Comments
Evidence of effectiveness	An ongoing phase 3, open-label, multicenter, randomized study (AHOD1331) in children and young adult patients with previously untreated high risk cHL. A total of 600 patients with previously untreated, pathologically confirmed Ann Arbor Stage IIB with bulk, Stage IIIB, Stage IVA, or Stage IVB cHL were 1:1 randomized to the active arm (BV-AVEPC) or the control arm (ABVE-PC).
General Dosing instructions	The recommended starting dose of BV in combination with chemotherapy (AVEPC) is 1.8 mg/kg up to a maximum of 180 mg every 3 weeks for a maximum of 5 doses via 30-min IV infusion.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Higher body weight was associated with higher ADC and MMAE exposures following 1.8 mg/kg IV every 3 weeks. For younger pediatric patients with lower body weight, the ADC and MMAE exposures are lower compared to those in older pediatric patients with higher body weight due to the smaller amount of total dose. No dose modification is needed for specific populations of sex or race. These factors were not found to be clinically significant covariates on brentuximab vedotin PK. The recommended dosage with renal and hepatic impairment in pediatric patients is based on the effects of renal and hepatic impairment on exposure in adults. The recommended starting dose for pediatric patients aged 2 and older with previously untreated cHL who have mild hepatic impairment (i.e., Child-Pugh A) is 1.2 mg/kg up to a maximum of 120 mg every 3 weeks for a maximum of 5 doses. Avoid use of BV in pediatric patients aged 2 and older with previously untreated cHL who have moderate hepatic impairment (Child-Pugh B), severe hepatic impairment (Child-Pugh C), or severe renal impairment (CrCL less than 30 mL/min).
Immunogenicity	Twenty-six pediatric patients with cHL were tested for antibodies to BV using a sensitive electrochemiluminescence immunoassay. None of the patients tested positive for anti-brentuximab vedotin antibodies.

There is 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 brentuximab vedotin in adults has been previously submitted (BLA125388, SN0218, m2.7.2). The new clinical pharmacology data presented in the current submission includes an evaluation of PK in pediatric subjects using data from studies C25002, HLHR13, and AHOD1331. Additionally, the exposure-response (E-R) (efficacy/safety) relationship was evaluated using data from AHOD1331. Key results are summarized below:

- The PK of brentuximab vedotin analytes ADC and MMAE in pediatric subjects were generally consistent with those of adult subjects.
- Body weight was identified as the only significant factor for the PK of brentuximab vedotin. Pediatric subjects with higher body weight were found to have higher CL and higher central volume of distribution for ADC and MMAE.
- After adjusting for body weight, factors including age, sex, race, disease indication, baseline albumin, immunogenicity, and concomitant administration of chemotherapy agents and prednisone had no impact on the PK of ADC and MMAE.
- Overall, weight-based dosing provides similar exposures in pediatric subjects aged 12 to <18 years compared to adult subjects, and numerically lower exposures in pediatric subjects aged 2 to <12 years due to their lower body weights.
- No apparent relationships between exposure and efficacy/safety endpoints were found.
    - While the ADC exposure was numerically lower in subjects aged 2 to <12 years, consistent EFS benefit was observed in subjects aged 2 to <12 and 12 to <18 years in the AHOD1331 study.
    - Within the pediatric subjects that were randomized and received the 1.8 mg/kg Q3W dose, there were no clear relationships between exposure and incidence rates of peripheral neuropathy, neutrophil count decrease or febrile neutropenia in pediatric population based on age and body weight subgroup analyses and exposure response analyses.

The Applicant's Position:

The PK of brentuximab vedotin is similar between pediatric subjects and adults. Body weight was the only clinically meaningful predictor for the PK of brentuximab vedotin. Weight-based dosing provides similar exposures in pediatric subjects aged 12 to <18 years compared to adult subjects, and numerically lower exposures in subjects aged 2 to <12 years. There was no indication of differential efficacy and safety with exposure or with age and body weight. Collectively, these results support the recommended 1.8 mg/kg Q3W brentuximab vedotin dose in combination with AVEPC for the proposed indication in pediatric subjects aged 2 years and older with previously untreated high-risk cHL.

The FDA's Assessment:
The FDA agrees with the Applicant that the proposed dosing regimen of BV 1.8 mg/kg Q3W for pediatric patients 2 years and older is acceptable from a clinical pharmacology perspective based on totality of the safety, efficacy, PK, and PD data. See Section 6.2.2 for details.

However, FDA disagrees with the Applicant's statement that the PK of brentuximab vedotin is similar between pediatric and adult patients. Higher body weight was associated with higher ADC and MMAE exposures following 1.8 mg/kg IV every 3 weeks. As such, ADC and MMAE exposures were lower in pediatric patients aged 2 to < 6 years (weight range 15.4 to 18.0 kg) and 6 to <12 years (weight range 18.2 to 62 kg) compared to pediatric patients aged 12 to <18 years of age (weight range 36.5 to 104 kg) and adult patients due to the smaller milligram amount of total dose in younger pediatric patients with lower weight. However, patients aged 12 to <18 years are predicted to have similar ADC and MMAE exposure compared to adults following 1.8 mg/kg IV Q3W.

Although ADC and MMAE exposures were predicted to be lower in pediatric patients with lower body weight following 1.8 mg/kg IV Q3W, this difference in exposure does not appear to have had a clinically relevant impact on efficacy based on E-R efficacy analysis. See Section 6.2.2.1 for details.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:
The PK of brentuximab vedotin in pediatric subjects was characterized via population PK analysis, including subjects from C25002 (N=36), AHOD1331 (N=26), and HLHR13 (N=16). Body weight was the only clinically meaningful predictor for the PK of brentuximab vedotin (Figure 1). The PK of ADC and MMAE in the pediatric population were consistent across disease indications and between monotherapy and in combination with chemotherapy agents (Section 6.2.2.2, Figure 3 and Figure 4). Using the recommended dose of 1.8 mg/kg Q3W (up to a maximum of 180 mg), the PK exposures of ADC and MMAE in pediatric subjects aged 12 to <18 years were generally comparable to those in adults, while exposures in subjects aged 2 to <12 years were numerically lower (Figure 2).

Figure 1: Applicant - Individual-predicted ADC (A) and MMAE (B) Clearance (L/day) Versus Body Weight (kg) in Pediatric Subjects

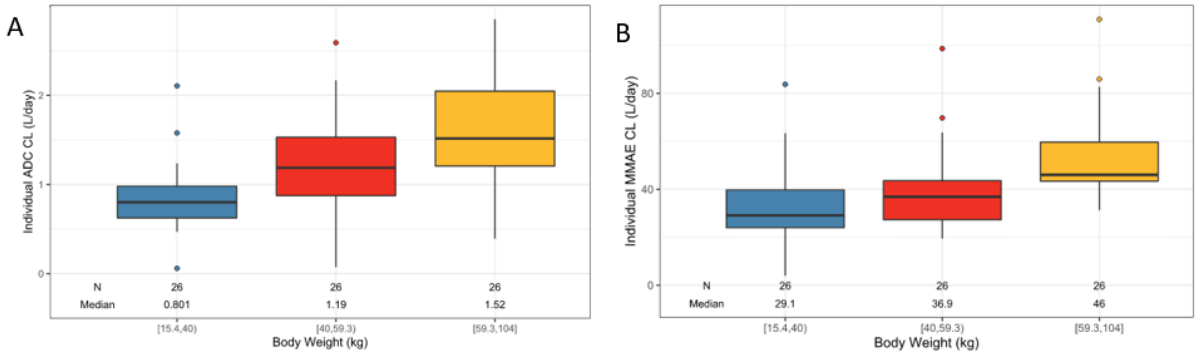
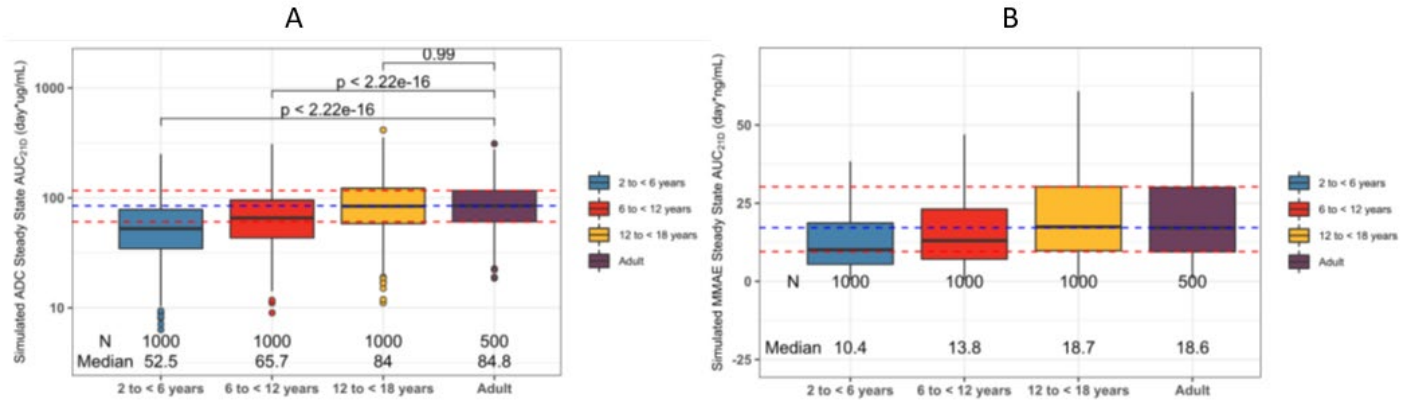


Figure 2: Applicant - Simulated Steady-State AUC_{21D} for ADC (A) and MMAE (B) in Virtual Pediatric Subjects by Age Group[1]



[1] The body weights of pediatric population were resampled from CDC growth charts[2].
Box plots represent: the median by the horizontal line, the 25th -75th percentiles by the box, and the 5th – 95th percentiles by the whiskers. Data points that are located outside the whiskers are outliers. Blue dashed line represents the median value in adult reference population, while the upper and lower red dashed lines represent the 25th and 75th percentiles of simulated adult exposures.
[2] CDC NCHS. Percent Data Files with LMS Values Weight-for-age charts, 2 to 20 years. https://www.cdc.gov/growthcharts/percentile_data_files htm. Accessed Apr 27, 2022.
Source: m2.7.2 Figure 14

E-R analyses for pediatric subjects focused on the clinical data from AHOD1331. In the experimental arm of the study, brentuximab vedotin was given at 1.8 mg/kg (maximum 180 mg) on Day 1 of every 21-day cycle in combination with appropriate dose of AVEPC. A total of 300 subjects were randomized to the experimental arm and 296 received at least 1 dose of BV-AVEPC treatment. As the PK population (N=26) was limited and primarily consisted of ages <13 years by design, an age subgroup analysis in the treated population was generated to supplement the E-R analysis.

Based on the exploratory E-R analysis, there was no indication of differential efficacy with exposure; subjects aged 2 to <12 years had lower exposure but there was no apparent impact

on EFS (Section 6.3.2.2, Figure 5). Additionally, exposures (Cycle 1 C_{ave}) were similar in subjects grouped by early response rates or requiring response-directed radiation therapy (Section 6.3.2.2, Figure 6). There was no apparent evidence of exposure driven safety in the pediatric population in the AEs evaluated; the incidence rates of Grade 2 and higher PN, Grade 3 and higher PN, Grade 3 and higher neutrophil count decrease, and Grade 3 and higher febrile neutropenia did not appear to trend with age or body weight (Section 6.3.2.2).

The Applicant's Position:

Weight-based dosing for brentuximab vedotin is approved for all 6 indications in adults. The recommended dose in pediatric subjects aged ≥2 years is 1.8 mg/kg brentuximab vedotin (up to a maximum of 180 mg) administered Q3W with each cycle of chemotherapy for a maximum of 5 doses. The recommended dose is supported by the positive benefit-risk profile from the randomized pivotal Phase 3 study AHOD1331, the generally similar range of PK exposures across pediatric age groups compared to adults, and the totality of E-R findings for both efficacy and safety endpoints.

The FDA's Assessment:

FDA generally agrees with the Applicant that the proposed dosing regimen of BV 1.8 mg/kg (up to 180 mg) IV Q3W for pediatric patients 2 years and older is acceptable from a clinical pharmacology perspective based on totality of the safety, efficacy, PK, and PD data.

1. Efficacy:

In Study AHOD1331, the rate of Event-Free Survival (primary endpoint), defined as the time from randomization to the earliest of disease progression or relapse, second malignancy, or death due to any cause, was better in the BV-AVEPC arm (23/300 [8%]) compared to the control ABVE-PC arm (52/300 [17%]) (HR 0.41 [95% CI: 0.25, 0.67]; 2-sided p=0.0002). No clear difference in EFS was observed in patients aged 2 to < 6 years (N=5), 6 to <12 years (N=47), and 12 to <18 years (N=222) in the BV-AVEPC arm (see Section 6.3.2).

Exposure-response analysis revealed no clear difference in secondary endpoints of early response, complete metabolic response, or response-directed radiation therapy according to Cycle 1 ADC exposure (C_{trough}, AUC, and C_{max}). However, the lack of E-R trends may have been due to the relatively small number of patients with PK data in AHOD1331 (n=26).

2. Safety:

The overall incidence of TEAEs in the BV-AVEPC arm (76%) was similar to ABVE-PC arm (73%), with Grade ≥ 3 TEAEs slightly higher in the BV-AVEPC arm (BV-AVEPC: 74% vs. ABVE-PC: 68%). The most common (≥20%) TEAEs in the BV-AVEPC arm were neutrophil count decreased (50%), white blood cell count decreased (43%), anemia (37%), platelet count decreased (32%), febrile neutropenia (31%), and lymphocyte count decreased (24%). The safety findings were consistent with the established safety profile of brentuximab for adults with cHL.

No clear relationships were identified between Cycle 1 exposure (ADC C_{max}, ADC C_{avg}, MMAE C_{max}, and MMAE C_{avg}) and incidence of Grade ≥2 peripheral neuropathy, Grade ≥3 neutrophil count decreased, Grade ≥3 febrile neutropenia, BV dose modification, and any drug dose modification. However, the lack of E-R safety trends may be due to the relatively small number of patients with PK data in AHOD1331 (n=26).

3. PK:

Higher body weight was associated with higher ADC and MMAE exposures following 1.8 mg/kg IV Q3W. A summary of age and body weight in patients with PK data is presented in Table 4. Predicted differences in steady state (i.e., Cycle 4) AUC (AUC_{ss}) according to age category are summarized in Table 5.

a. Pediatric patients 12 to < 18 years of age:

Following the BV dose of 1.8 mg/kg IV Q3W in patients 12 to <18 years of age (N=41), dose-normalized C_{avg} was similar to that observed in adult patients taking BV at 1.2 mg/kg Q2W. Combining with the overall efficacy and safety profile in Study AHOD1331, FDA agrees that the proposed BV dosage of 1.8 mg/kg (up to 180 mg) IV Q3W is acceptable for patients 12 to <18 years of age.

b. Pediatric patients 6 to < 12 years of age:

Following the BV dose of 1.8 mg/kg IV Q3W, patients aged 6 to <12 years are expected to have 22% lower median ADC AUC_{ss} and 25% lower median MMAE AUC_{ss} compared to patients aged 12 to <18 years.

The lower exposure in patients aged 6 to <12 years did not have a clinically relevant impact on efficacy endpoints for treatment of previously untreated high risk cHL (see Section 19.4.2.2). No clear differences in efficacy endpoints were identified according to age or body weight subgroup in pediatric patients with previously untreated high risk cHL (n=26). Therefore, current data supports the proposed BV dosage of 1.8 mg/kg IV Q3W in patients 6 to <12 years of age from a clinical pharmacology perspective.

c. Pediatric patients 2 to < 6 years of age:

The median (range, n) body weight in pediatric patients aged 2 to <6 years was 16.1 kg (15.4 to 18 kg, n=3). Following the BV dose of 1.8 mg/kg IV Q3W, patients aged 3 to <6 years are expected to have 37% lower median ADC AUC_{ss} and 41% lower median MMAE AUC_{ss} compared to patients aged 12 to <17 years.

The lower exposure in patients aged 2 to <6 years did not have a clinically relevant impact on efficacy endpoints for treatment of previously untreated high risk cHL (see Section 19.4.2.2), although the number of patients aged 2 to <6 years with PK data was very limited (n=3 with age range of 3 to 5 years). No clear differences in efficacy endpoints were identified according to

age or body weight subgroup in pediatric patients with high risk cHL (n=26). Although PK data is only available in patients aged 3 and older, patients aged 2 years are expected to have similar PK and exposure as patients aged 3 years. Therefore, current data supports the proposed BV dosage of 1.8 mg/kg IV Q3W in patients 2 to <6 years of age from a clinical pharmacology perspective.

d. Pediatric patients <2 years of age:

It should be noted that pediatric patients younger than 2 years may have ontogeny-related or developmental differences in PK that are not characterized in the current PPK analysis. As such, efficacy, safety, and PK have not been established in pediatric patients younger than 2 years with previously untreated high risk cHL.

Table 4: Summary of Baseline Weight according to Age Category in Patients with PK Data

Covariate	Statistic	2 to <6 years (n = 3)	6 to <12 years (n=30)	12 to <18 years (n=41)	18 to <22 years (n=4)
Age (years)	Mean (SD)	3.7 (1.2)	9.5 (1.7)	14.9 (1.9)	18.4 (0.5)
	Median	3	10	15	18.25
	Min - Max	3 - 5	6 - 11	12 - 17.9	18 - 19
Baseline Weight (kg)	Mean (SD)	16.5 (1.3)	35.9 (11.7)	61.1 (13.8)	59.9 (9.7)
	Median	16.1	35.1	59.6	59.65
	Min - Max	15.4 - 18	18.2 - 62	36.5 - 103.8	51.2 - 69

PK = pharmacokinetic; SD = standard deviation.
Source: FDA Analysis of Applicant's Population Pharmacokinetic PK Dataset

Table 5: Summary of Predicted ADC and MMAE Exposures at Steady State in Virtual Pediatric Patients following BV dosage of 1.8 mg/kg IV Q3W

Exposure	Statistic	3 to <6 years (N=768)	6 to <12 years (N=1000)	12 to <17 years (N=837)
ADC AUCss (day·µg/mL)	Mean (CV%)	60.7 (57.8%)	75.1 (57.9%)	97.3 (60%)
	Median	52.8	65.7	84.1
	Min, Max	8, 250.7	9, 308.5	11.1, 354
	Change in Median AUCss from 12 to <17 years (%)	37%	22%	N/A
MMAE AUCss (day·ng/mL)	Mean (CV%)	17.0 (115.9%)	21.9 (118.7%)	27.5 (108.4%)
	Median	10.8	13.8	18.4
	Min, Max	0.5, 182	0.6, 285.7	0.7, 301.7
	Change in Median AUCss from 12 to <17 years (%)	41%	25%	N/A

Virtual pediatric population contained 3000 virtual patients aged 2 to 18 years with patient demographics resampled from the CDC weight chart by age and sex with equal proportions of male and female patients. Steady

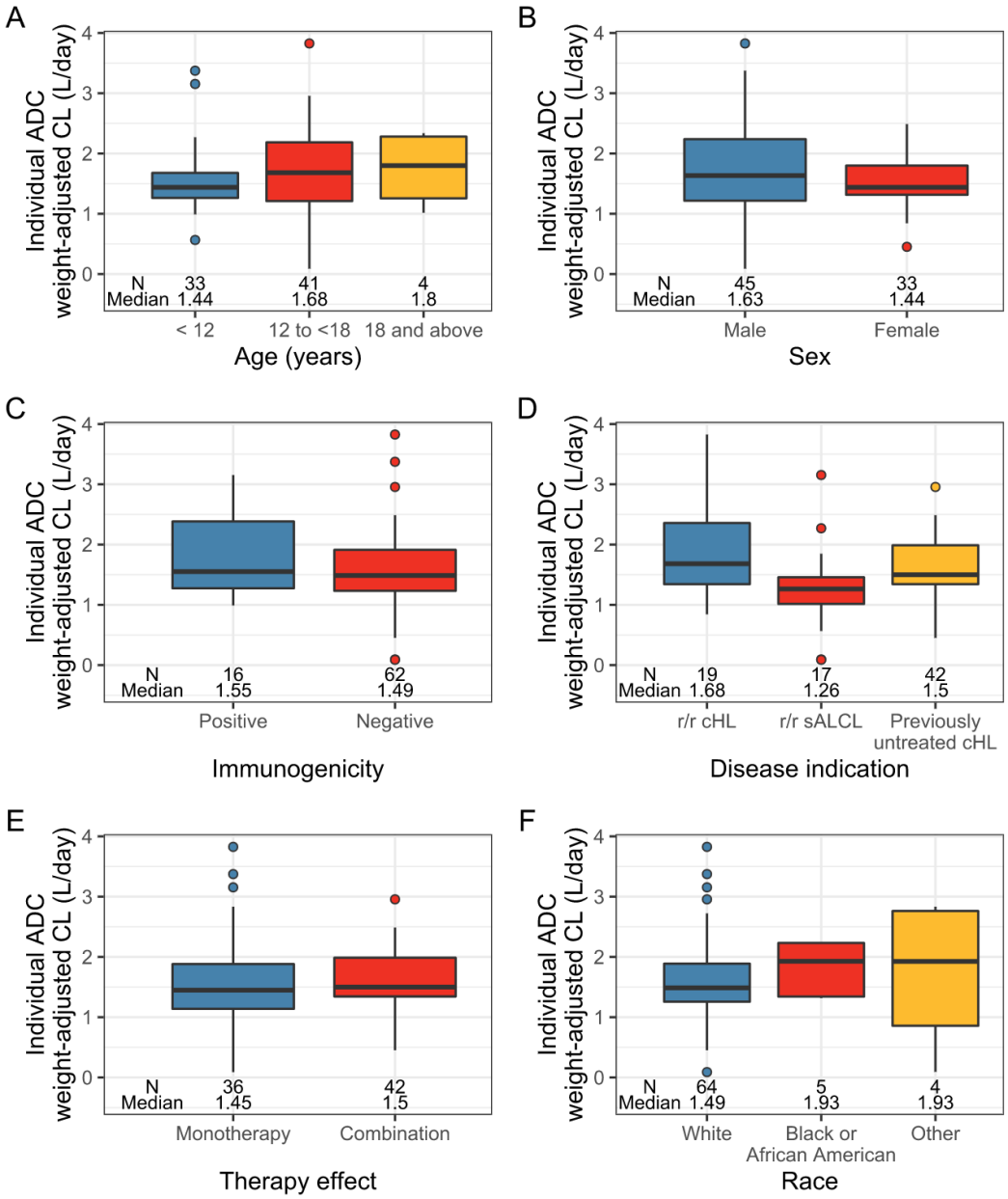
state exposure = exposure during Cycle 4 following 1.8 mg/kg (up to 180 mg) IV every 3 weeks; 1 cycle = 21 days.
ADC=antibody-drug conjugate; AUC=area under the concentration-time curve; BV=brentuximab vedotin;
CV = coefficient of variation; IV = intravenously; MMAE=monomethyl auristatin E; N/A = not applicable;
Q3W = every 3 weeks; SS = steady state.
Source: Applicant's "exposure-new-age-group-table.pdf" submitted to FDA on 14 October 2022.

6.2.2.2. Therapeutic Individualization

Data:

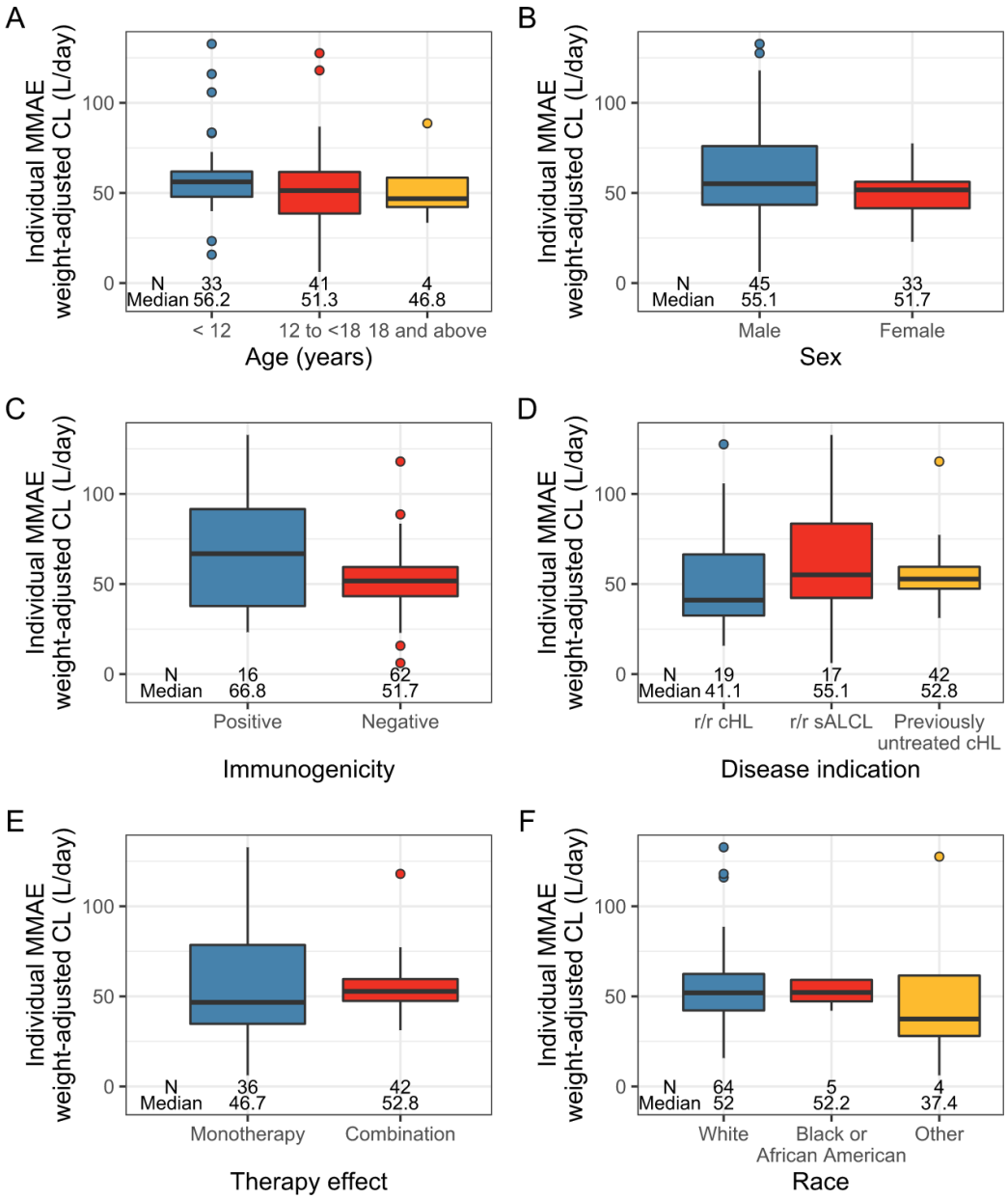
Intrinsic/Extrinsic Factors: Population PK modeling results showed that body weight was the only clinically significant predictor for the PK of ADC in pediatric subjects, consistent with findings in adults. After adjusting for body weight, CL values of brentuximab vedotin ADC and MMAE were similar across age groups and disease indication, between ATA positive and negative subjects, and between male and female pediatric subjects. ADC CL when brentuximab vedotin was administered as monotherapy (C25002) was similar to ADC CL when brentuximab vedotin was co-administered with various chemotherapy agents (AHOD1331 and HLHR13) (Figure 3). The same observation held for MMAE CL (Figure 4). Baseline albumin was not found to be a predictor of PK for ADC or MMAE. While the effect of race could not be formally evaluated during PPK covariate testing as the PK subjects were predominantly white (82.1%), based on descriptive analysis, the CL was comparable between white, black, and other racial groups for both ADC and MMAE.

Figure 3: Applicant - Individual ADC Weight Adjusted Clearance (L/Day) in Pediatric Subjects Grouped by Intrinsic/Extrinsic Factors



Individual ADC CL was normalized to 75 kg for comparisons.
Box plots represent: the median by the horizontal line, the 25th -75th percentiles by the box, and the 5th – 95th percentiles by the whiskers. Data points that are located outside the whiskers are outliers.
Source: m2.7.2 Figure 11

Figure 4: Applicant - Individual MMAE Weight Adjusted Clearance (L/Day) in Pediatric Subjects Grouped by Intrinsic/Extrinsic Factors



Individual MMAE CL was normalized to 75 kg for comparisons
Box plots represent: the median by the horizontal line, the 25th -75th percentiles by the box, and the 5th – 95th percentiles by the whiskers.
Source: m2.7.2 Figure 13

Special populations: Hepatic function biomarkers such as ALT, AST, and total bilirubin, and serum creatinine were not available from AHOD1331 and hence could not be formally evaluated as covariates; however, no apparent trends of these covariates were observed in the subpopulation analysis of C25002 and HLHR13 (m2.7.2).

The Applicant's Position:
Body weight was identified as the only clinically significant factor for the PK of brentuximab vedotin. After adjusting for body weight, other factors including age, sex, race, disease indication, baseline albumin, and immunogenicity had no impact on the PK of ADC and MMAE. Overall, weight-based dosing provides similar exposures in pediatric subjects aged 12 to <18 years compared to adult subjects, and numerically lower exposures in pediatric subjects aged 2 to <12 years due to their lower body weights. Importantly, no apparent impact of lower exposures on efficacy was noted in subjects aged 2 to <12 years in AHOD1331 compared to pediatric subjects aged 12 to <18 years and young adults. Therefore, no dose adjustment is required for the intrinsic/extrinsic factors evaluated.

The FDA's Assessment:
Following the proposed dosage of 1.8 mg/kg IV Q3W in pediatric patients aged 2 years and older with previously untreated high risk cHL, patients with lower body weight had lower ADC and MMAE exposures compared to patients with higher body weight. Younger patients had lower body weight, and thus lower exposures, compared to older patients. Given that no clear difference in EFS was observed in patients aged 2 to <6 years, 6 to <12 years, and 12 to <18 years in the BV-AVEPC arm and no apparent relationships between exposure and efficacy endpoints were identified, the lower exposure in young pediatric patients does not appear to be clinically relevant (see Section 19.4.2.2).

FDA disagrees with the Applicant that no dose adjustment is required for intrinsic factors such as organ impairment. Given limited data in pediatric patients, the recommended dosage with renal and hepatic impairment in pediatric patients is based on the effects of renal and hepatic impairment on exposure in adults. The recommended starting dose for pediatric patients aged 2 years and older with previously untreated high risk cHL who have mild hepatic impairment (i.e., Child-Pugh A) is 1.2 mg/kg up to a maximum of 120 mg every 3 weeks for a maximum of 5 doses. Avoid use of BV in pediatric patients aged 2 and older with previously untreated cHL who have moderate hepatic impairment (Child-Pugh B), severe hepatic impairment (Child-Pugh C), or severe renal impairment (CrCL less than 30 mL/min).

FDA generally agrees with the Applicant that race, sex, disease indication, and baseline albumin had no impact on the PK of ADC and MMAE. Given insufficient data in pediatric patients positive for ADA, the impact of immunogenicity on PK is unknown.

6.2.2.3. Outstanding Issues

Data:
N/A

The Applicant's Position:
N/A

The FDA's Assessment:
FDA agrees that there are no outstanding issues for Clinical Pharmacology in this submission.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:
General pharmacology and PK characteristics of brentuximab vedotin in adults were previously submitted in BLA125388 and are summarized in ADCETRIS USPI. The general clinical pharmacology and PK information in pediatric subjects are summarized in Table 6. The population PK analysis included a total of 78 subjects from Studies C25002, AHOD1331, and HLHR13. Of these subjects, 3 were <6 years of age, 30 were 6 to <12 years of age, 41 were 12 to <18 years of age, and 4 were above 18 years of age. The exposure-response relationship was primarily evaluated in the randomized pivotal AHOD1331 study. As the PK population (N=26) primarily consisted of ages <13 years by design, age-specific analyses in the treated population (n=296) were generated to supplement exposure-response analysis for both efficacy and safety (sBLA m2.7.2 Section 3.5.1 and Section 3.5.2).

Table 6: Applicant – General Pharmacology and PK Characteristics of Brentuximab Vedotin in Pediatric Population

PK Features		
PK linearity	Consistent with the dose-linearity observed in adult population, the pediatric PK is dose-proportional from 1.4 mg/kg to 1.8 mg/kg.	
Accumulation at steady-state	After repeated dosing, ADC accumulation was minimal and MMAE exposures decreased over time. Population PK analysis predicted a median decline of MMAE area under the concentration curve from time 0 to 21 days postdose (AUC_{21D}) at Cycle 4 from Cycle 1 was ~ 57%, similar to the reported up to 50% reduction in MMAE exposures in adults.	
Absorption	**Absolute/Relative Bioavailability**	Not applicable.
	T_{max}	Maximum concentrations of ADC were observed near the end of infusion. Maximum concentrations of MMAE were observed approximately 1 to 3 days after end of infusion.
Distribution	**Volume of distribution**	For pediatric subjects aged 2 to <12 years and 12 to <18 years, the typical central volume of distribution values of ADC were 1.61 L/d and 3.21 L/d, respectively, based on median body weights of 21 kg and 54 kg sampled from CDC growth chart.
	% bound	In vitro, the binding of MMAE to human plasma proteins ranged from 68% to 82%.

PK Features		
Elimination	**Clearance (CL)**	For pediatric subjects aged 2 to <12 years and 12 to <18 years, the typical ADC CL values were 0.65 L/d and 1.17 L/d, respectively, based on median body weights of 21 kg and 54 kg sampled from CDC growth chart.
Immunogenicity /ATA Status	**Monotherapy**	In Study C25002, the ATA rate of brentuximab vedotin was 38% and was comparable to those observed in adult subjects with r/r cHL and sALCL or other monotherapy regimens.
	Combination	In Studies AHOD1331 and HLHR13, much lower ATA rates were observed when brentuximab vedotin was co-administered with chemotherapy drugs, consistent with adult data.
Intrinsic Factors	**Age**	Not clinically significant
	Sex	Not clinically significant
	Race	Could not be formally evaluated; comparable PK across racial groups based on descriptive analysis
	Disease indication	Not clinically significant
	Baseline albumin	Not clinically significant
	Immunogenicity	Not clinically significant
	Hepatic and Renal Impairment	Could not be formally evaluated; no apparent trends of liver function tests (AST, ALT, and total bilirubin) and eGFR (based on original Schwartz's equation) were detected.
Extrinsic Factors	**Drug interactions**	Drug interaction assessments in pediatric subjects have not been conducted with brentuximab vedotin.
	Meal Effects	Not applicable
Population PK Analysis	The final population PK models included body weight, the only clinically significant predictor for the PK of brentuximab vedotin.	
Pharmacodynamic Features		
Exposure-Response Analyses	**Efficacy**	In AHOD 1331: • Similar EFS rates were observed between pediatric subjects aged 2 to <12 and 12 to <18 years despite lower ADC exposure in subjects aged 2 to <12 years. • No apparent relationships between exposure and secondary endpoints of early response rate and rate of response-directed radiation therapy.
	Safety	In AHOD 1331, no apparent relationships between exposure and safety parameters were found. There were no clear relationships between exposure and incidences rates of PN, neutrophil count decrease or febrile neutropenia in pediatric population based on age and body weight subgroup analyses and exploratory E-R analyses.

The Applicant's Position:

The above summarized general pharmacology and PK characteristics of brentuximab vedotin in pediatric population confirmed the PK of ADC and MMAE in pediatric subjects aged 2 to <18 years were generally consistent with those of adults. Body weight was the only clinically meaningful predictor for the PK of brentuximab vedotin. The presence of anti-brentuximab vedotin antibodies did not show any impact on the PK of brentuximab vedotin and there was no evidence of its effect on safety and efficacy in children aged 2 to <18 years with previously

untreated high-risk cHL (m2.7.2). Collectively, the positive benefit-risk profile from pivotal study AHOD1331, the generally similar range of PK exposures across pediatric age groups compared to adults, and the totality of brentuximab vedotin exposure-response findings for both efficacy and safety endpoints support the recommended dosing regimen of 1.8 mg/kg brentuximab vedotin Q3W in combination with AVEPC.

The FDA's Assessment:

FDA generally agrees with the Applicant that the general clinical pharmacology and PK profile of BV is characterized in pediatric patients aged 2 to < 18 years. The proposed dosing regimen of 1.8 mg/kg IV brentuximab vedotin Q3W in combination with AVEPC is generally supported by totality of clinical efficacy, safety, PK, and PD data. Predicted ADC and MMAE exposure is summarized in Table 7, which demonstrates that higher body weight (i.e., consistent with that seen in patients aged 12 to <18 years) is associated with higher exposure compared to lower body weight (i.e., consistent with that observed in patients aged 2 to <6 years). The median AUC and C_{max} of ADC appeared slightly higher at steady state (i.e., Cycle 4) compared to Cycle 1. Exposure of MMAE during Cycle 1 was higher than exposure of MMAE at steady state, which is explained by the time-dependent rate of MMAE formation from ADC described in the MMAE PPK model (refer to Section 19.4.1.2).

FDA agrees with the Applicant that body weight is the only clinically meaningful factor for the PK of BV. Given limited data in pediatric patients positive for ADA, the effect of immunogenicity on PK is unknown.

FDA disagrees with the Applicant's statement that the PK of brentuximab vedotin is consistent between pediatric and adult patients. Higher body weight was associated with higher ADC and MMAE exposures following 1.8 mg/kg IV every 3 weeks. Patients aged 2 to <6 years and patients aged 6 to <12 years are predicted to have lower ADC and MMAE exposure compared to patients aged 12 to <18 years and adults following 1.8 mg/kg IV Q3W.

Due to the limited number of patients aged 2 to <12 (n=52), no meaningful conclusions can be drawn from the comparison of EFS rates in patients aged 2 to <6 years, 6 to <12 years, and 12 to <18 years (see Section 8.1.2). However, the lower exposure in patients with lower body weights did not appear to have a clinically relevant impact on efficacy endpoints (see Section 19.4.2.2). The E-R efficacy and safety analyses generally support the proposed dosage of 1.8 mg/kg IV Q3W in pediatric patients aged 2 years and older.

Table 7: Predicted ADC and MMAE Exposure following Brentuximab Vedotin 1.8 mg/kg IV Q3W According to Age Category

		Virtual Population (n=3500)			
Exposure Metric	**Statistic**	**2 to <6 years (N=1000)**	**6 to <12 years (N=1000)**	**12 to <18 years (N=1000)**	**≥18 years (N=500)**
ADC Cycle 1 AUC (day*ug/mL)	Mean (CV%)	44.1 (40.2%)	60.1 (43.6%)	82.1 (45.9%)	75.2 (38.3%)
	Median	42.9	57.0	76.3	71.5
	Min, Max	6.29, 121	8.97,167	11.1, 249	17.9, 182
	25^{th}, 75^{th} pct	30.7, 56.0	39.8, 75.4	55.2, 103	54.5, 92.1
ADC AUCss (day*ug/mL)	Mean (CV%)	59.8 (57.5%)	75.1 (57.9%)	97.7 (59.5%)	92.8 (48.5%)
	Median	52.5	65.7	84.0	84.8
	Min, Max	6.33, 251	9.01, 309	11.1, 414	18.6, 312
	25^{th}, 75^{th} pct	34.6, 78.3	43.3, 95.4	58.3, 122	60.6, 117
MMAE Cycle 1 AUC (day*ng/mL)	Mean (CV%)	17.6 (65.4%)	24.4 (65.4%)	32.3 (59.6%)	33.7 (74.8%)
	Median	14.8	20.1	27.6	25.5
	Min, Max	2.49, 88.0	3.04, 129	3.29, 128	2.75, 150
	25^{th}, 75^{th} pct	9.47, 22.6	13.4, 30.9	18.9,40.7	17.3, 42.3
MMAE AUCss (day*ng/mL)	Mean (CV%)	16.5 (119%)	21.9 (119%)	27.8 (106%)	26.8 (95.2%)
	Median	10.4	13.8	18.7	18.6
	Min, Max	0.520, 219	0.584, 286	0.732, 302	0.713, 226
	25^{th}, 75^{th} pct	5.59, 19.9	7.42, 24.9	10.2, 35.8	10.0, 35.0

Virtual pediatric population contained 3000 virtual patients aged 2 to 18 years with patient demographics resampled from the CDC weight chart by age and sex with equal proportions of male and female patients. Virtual adult population contained 500 patients aged ≥18 years with body weight resampled from two Phase 2 studies (SG035-0003 and SG035-0004). Steady state exposure = exposure during Cycle 4 following 1.8 mg/kg (up to 180 mg) IV Q3W; 1 cycle = 21 days.
ADC=antibody-drug conjugate; AUC=area under the concentration-time curve; CV = coefficient of variation; IV = intravenously; MMAE=monomethyl auristatin E; pct = percentile; Q3W = every 3 weeks; SS = steady state.
Source: Table 12 and Table 13 in the Applicant's Population PK Report

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 brentuximab vedotin effectiveness.

Data:
Evidence of effectiveness was obtained from randomized pivotal Study AHOD1331 comprising 296 subjects treated in the experimental arm (BV-AVEPC) and 297 in the control arm (ABVE-PC). Treatment on the BV-AVEPC arm resulted in a statistically significant and clinically meaningful 59% reduction in the risk of disease progression or relapse, second malignancy, or death compared to the ABVE-PC arm (HR 0.41 [95% CI: 0.25, 0.67]; 2-sided p=0.0002). In the BV-AVEPC arm, the estimated EFS rate was 92.5% (95% CI: 88.8, 95.0%) at 2 years and 92.1% (95% CI: 88.4, 94.7%) at 3 years, compared to 84.8% (95% CI: 80.1, 88.5%) at 2 years and 82.3% (95% CI: 77.2%, 86.3%) at 3 years in the ABVE-PC arm.

To support the clinical efficacy observed with brentuximab vedotin at 1.8 mg/kg on Day 1 of each 21-day cycle, up to 5 cycles, exposure-efficacy relationship was evaluated in subjects who were randomized and treated with BV-AVEPC regimen. While E-R analyses were limited (N=26), no apparent relationships between exposure and efficacy endpoints were found. Importantly, similar EFS rates were observed between pediatric subjects aged 2 to <12 and 12 to <18 years despite numerically lower ADC exposure in subjects aged 2 to <12 years (Section 6.3.2.2).

The Applicant's Position:
The relationships between brentuximab vedotin exposure and efficacy endpoints along with the age-subgroup analyses showed that treatment with 1.8 mg/kg brentuximab vedotin Q3W was associated with clinically meaningful efficacy across the entire range of exposures in pediatric subjects aged 2 years and older with previously untreated high risk cHL.

The FDA's Assessment:
FDA generally agrees the Applicant that the proposed dosing regimen of BV 1.8 mg/kg IV Q3W for pediatric patients aged 2 years and older is acceptable from a clinical pharmacology perspective based on totality of the safety, efficacy, PK, and PD data.

The E-R analysis of efficacy is limited by the relatively small numbers of patients and events. ADC exposure decreased with lower body weight, but the numbers of patients with low body weight were relatively limited. E-R efficacy data were only available in 4 patients weighing 15 to <20 kg and 1 patient weighing 20 to <30 kg, and the minimum body weight was 15.4 kg in the E-R efficacy analysis. For reference, the CDC growth charts indicate that the median weight is approximately 12 to 13 kg for a 24-month-old child and 14 kg for a 36-month-old child. Overall, the E-R efficacy analysis did not identify any clear trends between secondary efficacy endpoints and ADC exposure. See Section 19.4.2.1 for details. No EFS events occurred in patients with E-R efficacy data (n=26). Therefore, the relationship between EFS and ADC exposure is inconclusive.

Overall, the relationships between efficacy and ADC exposure are inconclusive in pediatric patients aged 2 years and older with previously untreated high risk cHL. Relationships between efficacy and body weight or age are also inconclusive in pediatric patients aged 2 years and older with previously untreated high risk cHL. The E-R analysis of efficacy supports the proposed dosage regimen.

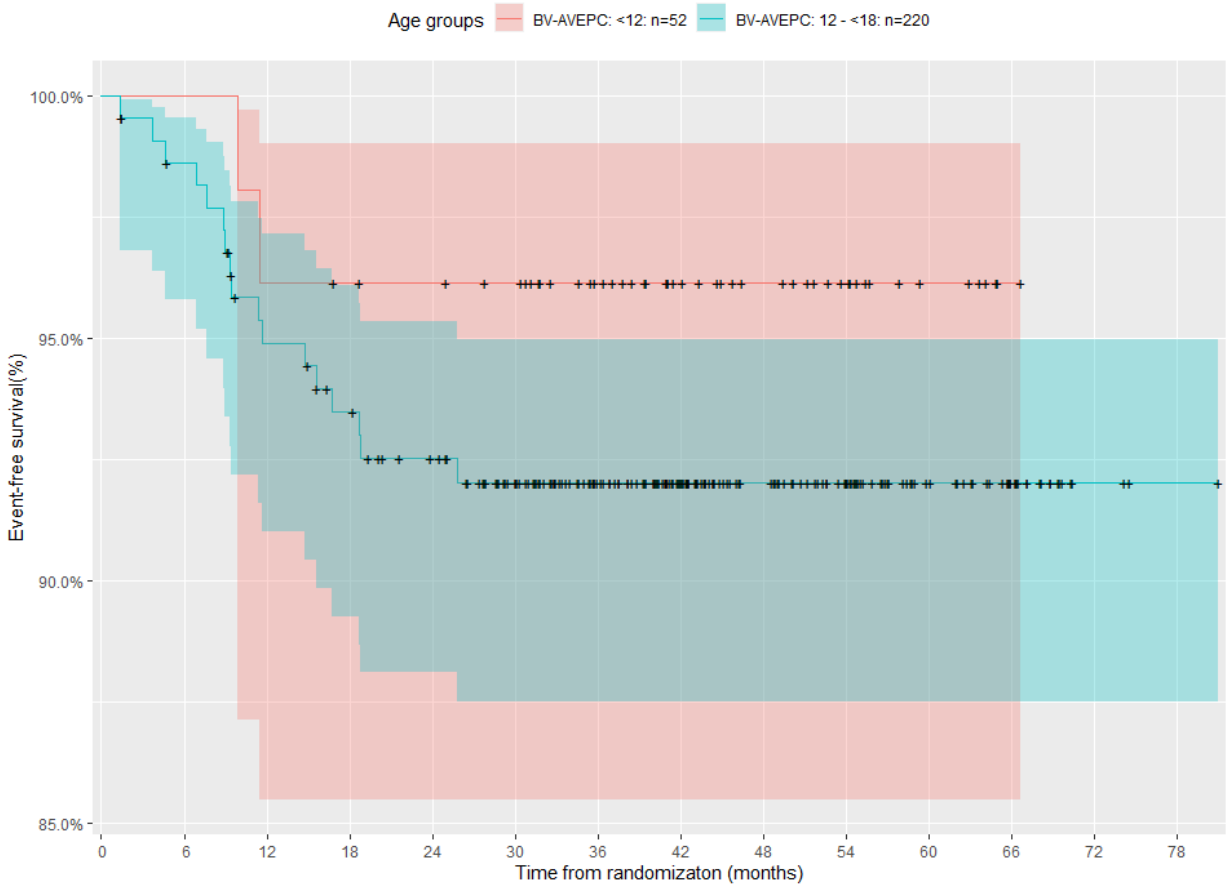
6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, 1.8 mg/kg brentuximab vedotin (up to a maximum of 180 mg) administered Q3W with each cycle of chemotherapy for a maximum of 5 doses is appropriate for pediatric subjects aged 2 years and older with previously untreated high-risk cHL. This dose recommendation was based on the totality of the PK, efficacy, and safety data.

Data:

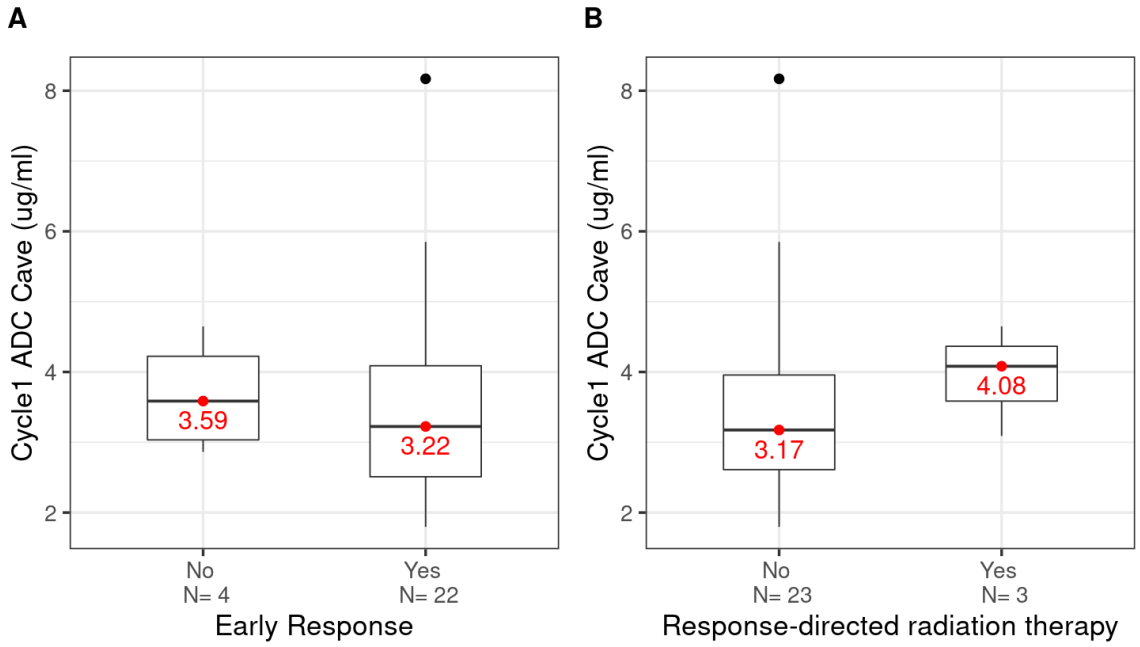
The age subgroup analysis for the primary endpoint, EFS, and exposure response analyses for secondary endpoints including ERR and RTR suggested the lack of apparent relationships between brentuximab vedotin ADC exposure and efficacy for pediatric subjects aged 2 years and older with previously untreated high-risk cHL in AHOD1331. Age subgroup analysis of EFS was conducted due to limited PK population along with low number of EFS events in AHOD1331. While the PPK model predicts lower ADC exposure in subjects aged 2 to <12 years, there was no apparent difference in EFS by age group. In pediatric subjects randomized to the BV-AVEPC arm, the estimated EFS rates at 36 months were comparable between pediatric subjects aged 2 to <12 years (96.2% [95% CI: 91.1%, 100%]) and 12 to <18 years (92.0% [95% CI: 88.5%, 95.7%]) (Figure 5). The exposure-efficacy analysis showed similar median ADC C_{ave} with overlapping ranges of exposure between response groups. In the limited sample size, there was no trend of lower exposure in PK subjects without early response or who required response-directed RT (Figure 6).

Figure 5: Applicant - Kaplan-Meier Curves for EFS with 95% CIs by Age Group (2 to <12 and 12 to ≤18)



Only subjects who were randomized and received treatment were included in this analysis. Shaded bands indicate 95% confidence intervals computed as exp[log(p)±1.96se(log(p))] where p = S(t) is the survival probability.
Source: sBLA m2.7.2 Figure 18

Figure 6: Applicant -Cycle 1 C_{ave} of ADC Grouped by (A) Early Response or (B) Rate of Response-Directed RT

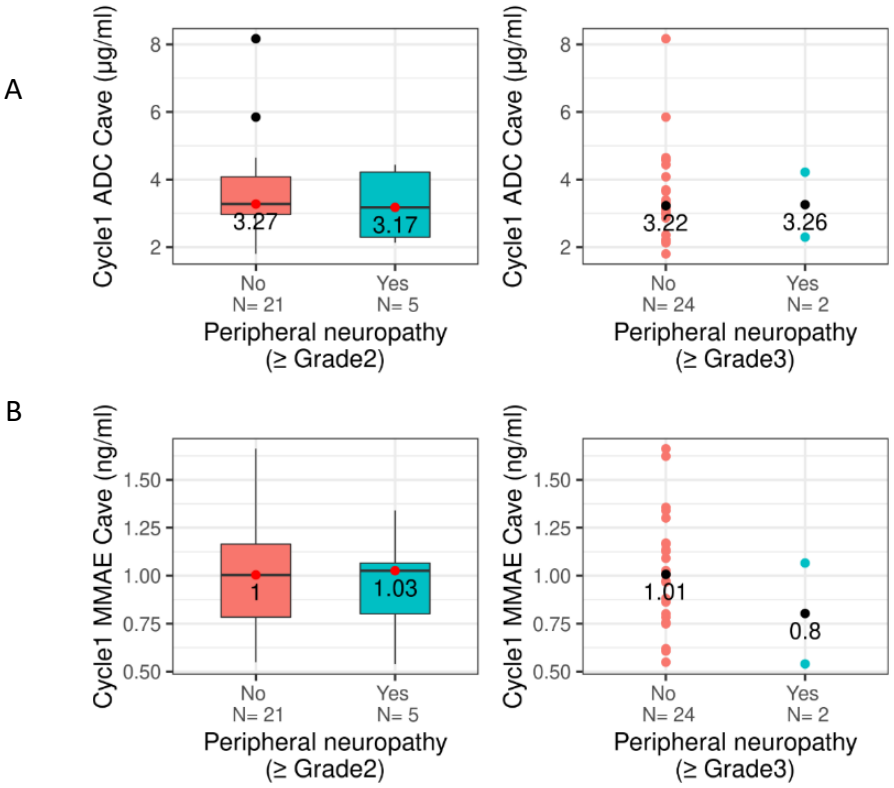


Source: m2.7.2 Figure 19

Of the 296 subjects treated with BV-AVEPC in AHOD1331, a median of 5.0 cycles of study treatment (range: 1 to 5 cycles) was received over a median duration of 15.0 weeks (range: 3 to 24 weeks). The majority of subjects (97%) completed all 5 cycles of BV-AVEPC. A total of 24 subjects (8%) had at least 1 dose modification of brentuximab vedotin.

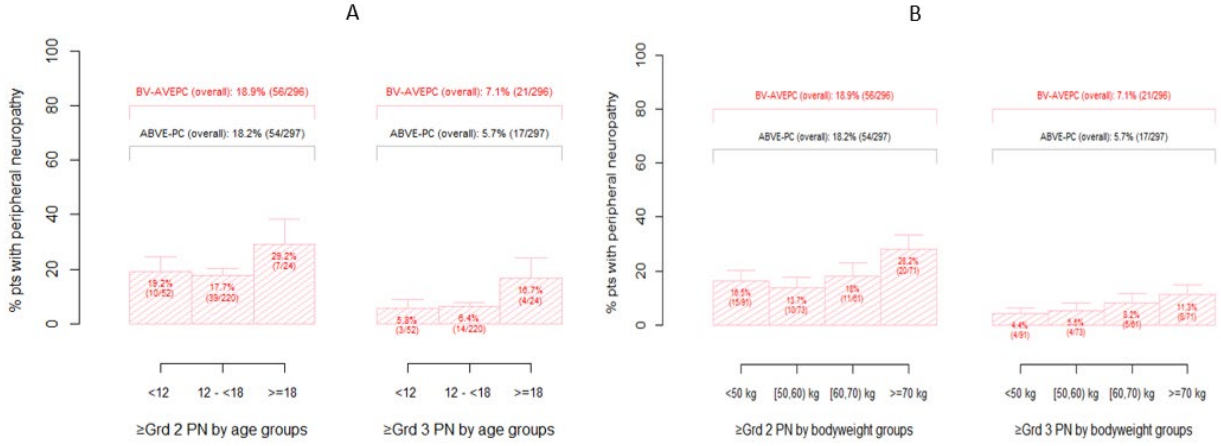
No new safety signals were identified in AHOD1331 and the overall safety findings were consistent with the established safety profile of the individual treatment components. Brentuximab vedotin exposure and safety relationships were evaluated in the PK population (N=26). Among the most frequently reported AEs in the randomized AHOD1331 study, safety parameters including peripheral neuropathy and neutropenia were evaluated as correlative relationships and had previously been reported in adults that received brentuximab vedotin (Suri 2018; m2.7.2, BLA125388, SN0218). Among pediatric subjects who were randomized and received the 1.8 mg/kg Q3W brentuximab vedotin dose, additional age and body weight subgroup analyses were conducted to delineate the relationships between exposure and safety parameters. As shown below, there were no clear relationships between exposure and incidence rates of Grade ≥2 PN and Grade ≥3 PN, neutrophil count decrease or Grade ≥3 febrile neutropenia in the pediatric population based on age and body weight subgroup analyses and E-R analyses (sBLA m2.7.2 Section 3.5.2).

Figure 7: Applicant - Comparisons of Cycle 1 Average ADC (A) and MMAE (B) Exposure Grouped by Subjects with Grade ≥2 or ≥3 PN and Subjects Without Grade ≥2 or ≥3 PN



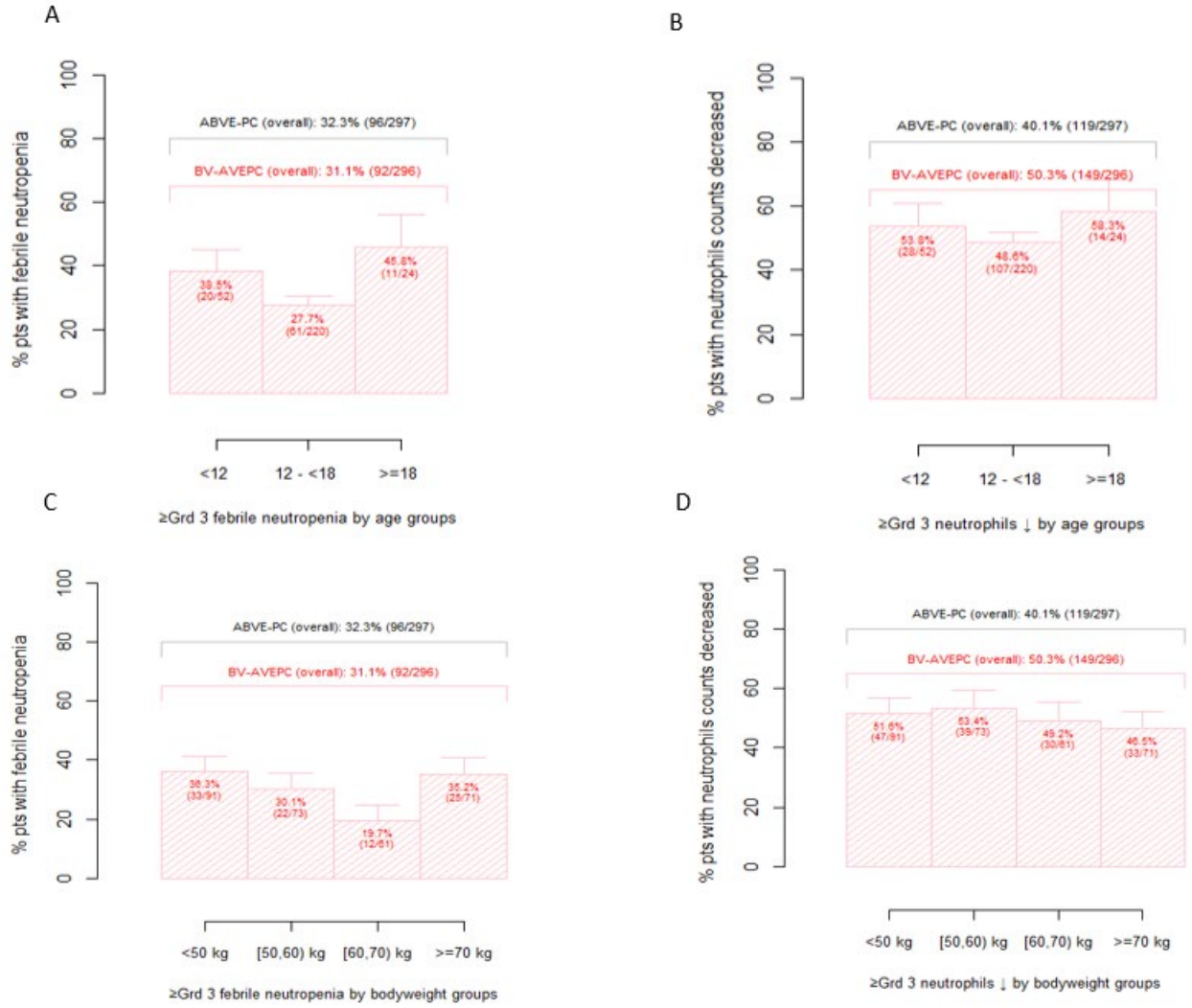
Source: m2.7.2 Figure 21

Figure 8: Applicant - Observed Incidence of Grade ≥2 PN and Grade ≥3 PN by Age Group (A) or by Body Weight Group (B) in BV-AVEPC Arm of AHOD1331



*Error bars represent standard deviations of incidence rates.
Source: m2.7.2 Figure 20

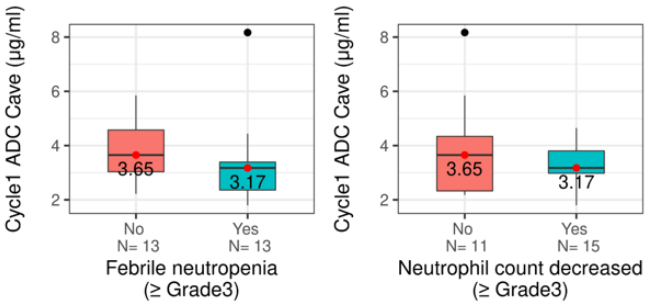
Figure 9: Applicant - Observed Incidence of Grade ≥3 Febrile Neutropenia and Neutrophil Count Decreased by Age Group (A,B) and by Body Weight Group (C,D) in BV-AVEPC Arm



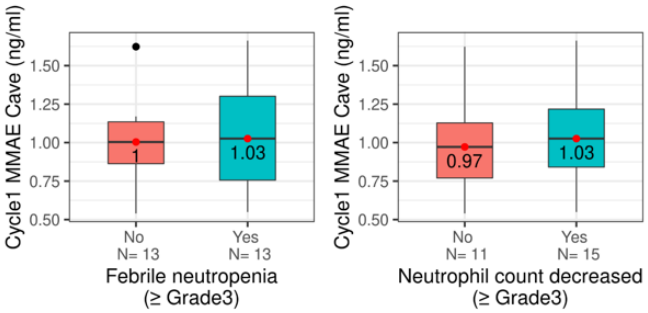
Error bars represent standard deviations of the incidence rates.
Source: m2.7.2 Figure 22 and 23]

Figure 10: Applicant - Comparisons of Cycle 1 Average ADC (A) and MMAE (B) Exposure Between Subjects with AEs and Subjects Without AEs

A



B



Source: m2.7.2 Figure 24

The Applicant's Position:

Brentuximab vedotin administered at 1.8 mg/kg (up to a maximum of 180 mg) on Day 1 of each 21-day cycle for up to 5 cycles in combination with AVEPC demonstrates a favorable benefit-risk profile for subjects 2 years and older with previously untreated high-risk cHL.

The FDA's Assessment:

As described in Section 6.3.2.1, the E-R efficacy analysis is supportive of the proposed dosage in pediatric patients aged 2 years and older with previously untreated high risk cHL.

E-R analysis of safety events did not identify any associations between exposure (ADC C_{max}, ADC AUC, MMAE C_{max}, and MMAE AUC) and incidence of Grade ≥2 peripheral neuropathy, Grade ≥3 neutrophil count decrease, Grade ≥3 febrile neutropenia, BV dose modification, and any drug dose modification in pediatric patients aged 2 years and older with previously untreated high risk cHL. However, the lack of identified E-R safety associations may be due to the limited number of patients in the E-R safety analysis (n=26). See Section 19.4.2.4.

Overall, no differences in efficacy or safety were identified according to ADC or MMAE exposure in pediatric patients aged 2 years and older with previously untreated high risk cHL. The proposed dose of 1.8 mg/kg (up to a maximum dose of 180 mg) IV Q3W for up to 5 cycles is supported from a clinical pharmacology perspective.

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, 1.8 mg/kg brentuximab vedotin (up to a maximum of 180 mg) administered Q3W with each cycle of chemotherapy for a maximum of 5 doses is appropriate for subpopulations based on intrinsic patient factors.

Data:
The effects of age, sex, race, body weight, albumin, immunogenicity, and disease indication on the PK of brentuximab vedotin ADC and MMAE were evaluated by population PK modeling and posthoc descriptive analyses. Results indicated body weight was the only significant covariate for the PK of brentuximab vedotin in pediatric subjects. After adjusting for body weight, other intrinsic factors including age, sex, race, disease indication, baseline albumin and immunogenicity had no impact on the PK of ADC and MMAE (Section 6.2.2.2). Hepatic function biomarkers such as ALT, AST, and total bilirubin, and serum creatinine were not available from the AHOD1331 study and hence could not be formally evaluated as covariates; however, no apparent trends of these covariates were observed in the subpopulation analysis of C25002 and HLHR13. Population PK modeling and simulation analyses determined high body weight is associated with higher CL for ADC and MMAE. Therefore, overall, weight-based dosing provided similar exposures in pediatric subjects aged 12 to <18 years compared to adult subjects, and numerically lower exposures in pediatric subjects aged 2 to <12 years due to their lower body weights. Importantly, the safety and efficacy were comparable between age groups, and hence, dose adjustments based on age are not necessary.

The Applicant's Position:
Brentuximab vedotin administered at 1.8 mg/kg (up to a maximum dose of 180 mg) Q3W with each cycle of chemotherapy for a maximum of 5 doses is appropriate for subpopulations based on intrinsic patient factors. No alternative dosing regimen or management strategy is required for this patient population.

The FDA's Assessment:
No alternative dosing regimens are recommended according to sex, race, or ethnicity. However, the comparison of exposure according to race was limited because the majority of patients with PK data identified as White (n=64 [82%]), while 5 patients identified as Black or African American (6.4%), 2 patients identified as Asian (2.6%), 2 patients identified as other race (2.6%), and 5 patients had race not reported or unknown (6.4%).

As described in Section 6.3.2.1, relationships are inconclusive between efficacy and exposure, efficacy and body weight, and efficacy and age in pediatric patients aged 2 years and older with previously untreated high risk cHL. Based on current data, no alternative dosing regimens are recommended according to age or weight other than the proposed dose of 1.8 mg/kg (up to 180 mg) IV Q3W.

The impacts of renal and hepatic impairment on exposure and clinical outcomes could not be

evaluated in Study AHOD1331. However, based on the known effects of renal and hepatic impairment on exposure in adults, the recommended starting dose for pediatric patients aged 2 years and older with previously untreated cHL who have mild hepatic impairment (i.e., Child-Pugh A) is 1.2 mg/kg up to a maximum of 120 mg IV every 3 weeks for a maximum of 5 doses. No alternative dosing regimen is recommended in pediatric patients with mild (i.e., estimated creatinine clearance [CrCL] by Cockcroft-Gault equation: 60 to 89 mL/min) or moderate (i.e., estimated CrCL: 30 to 59 mL/min) renal impairment. Avoid use of BV in pediatric patients aged 2 years and older with previously untreated cHL who have moderate hepatic impairment (Child-Pugh B), severe hepatic impairment (Child-Pugh C), or severe renal impairment (CrCL less than 30 mL/min).

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

The Applicant's Position:
No. Drug-drug interactions data were previously submitted in BLA125388, SN0218 m2.7.2 and there is no new information. See also the current Adcetris USPI. Brentuximab vedotin 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 that support efficacy and safety of brentuximab vedotin in pediatric subjects with cHL.

Table 8: Applicant - Clinical Studies Supporting the Efficacy and Safety of Brentuximab Vedotin

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of subjects enrolled[a]	Study Population	No. of Centers and Countries
Studies to Support Efficacy and Safety								
AHOD1331	NCT02166463	Randomized, controlled	1.8 mg/kg BV Q3W + AVEPC or ABVE-PC Intravenous	Primary • EFS Secondary • ERR • RTR • Type, incidence, and severity of AEs. The proportion of subjects experiencing Grade ≥3 PN (assessed by modified Balis scale). Exploratory PK concentration time-profile data of BV ADC and MMAE ATA incidence rate.	5 x 21-day cycles	600	Previously untreated High-risk cHL	153 sites; 2 countries
HLHR13	NCT01920932	Open-label, Single-arm	AEPA (1.2 mg/kg BV) on days 1, 8, and 15 of each 28-day cycle; CAPDac (1.2 mg/kg BV) on days 1 and 8 of each 21-day cycle. Intravenous	Primary CR rate after 2 cycles of AEPA EFS after treatment with AEPA/CAPDAC Secondary Type, incidence, and severity of AEs PK and immunogenicity summary statistics	AEPA (1.2 mg/kg BV) - 2 cycles; CAPDac (1.2 mg/kg BV) - 4 cycles	77	Previously untreated High-risk cHL	6 sites, 1 country
AHOD1221	NCT01780662	Open-label, Single-arm	1.8 mg/kg Q3W+gemcitabine Intravenous	Primary CR rate after 4 cycles of BV + gemcitabine Descriptive summary of all toxicities; individual toxicity counts, and incidence rates Secondary	Up to 16 cycles	46	r/r cHL	37 sites; 2 countries

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of subjects enrolled[a]	Study Population	No. of Centers and Countries
				ORR				
C25002	NCT01492088	Open-label, single-arm, dose-escalation	1.4 or 1.8 mg/kg Q3W Intravenous	Primary endpoints Phase 1 and Secondary endpoints Phase 2 AEs, SAEs, clinical lab values, vital sign measurements Serum concentrations of BV (ADC), TAb; plasma concentrations of MMAE Primary endpoint Phase 2 and secondary endpoint Phase 1 ORR Secondary endpoint Phase 1 and Phase 2 ATA, nATA status, and ATA titer TTP, TTR, DoR, EFS, PFS, and OS	16 cycles	36	r/r cHL or r/r sALCL	12 sites; 8 countries
ANHL12P1	NCT01979536	Open-label, Randomized	1.8 mg/kg Q3W+standard chemo (6 cycles) or CZ + standard chemo Intravenous	Primary EFS Types, incidence, and severity of AEs	BV + standard chemo - 6 cycles CZ + standard chemo - 6 cycles	68*	sALCL	85 sites; 1 country

*Seagen Inc. reported the N as 63 in the PPSR; the final progress report indicates the number is 68 (number of subjects randomized to BV arm).

The Applicant's Position:

The clinical development of brentuximab vedotin in the pediatric population was conducted primarily as investigator-sponsored studies. Five pediatric studies are included in this sBLA. Three of these studies (AHOD1331, AHOD1221, ANHL12P1) were sponsored by the Division of Cancer Treatment and Diagnosis (DCTD) of NCI and conducted by the COG, 1 was sponsored by St Jude Children's Research Hospital (HLHR13), and 1 was sponsored by Takeda (Millennium Pharmaceutical Ltd) (C25002). Seagen Inc. supplied the investigational product brentuximab vedotin for the 4 investigator-sponsored studies; and Takeda conducted C25002 independently.

The FDA's Assessment:

The FDA agrees with the Applicant's description of the five clinical studies that were included in support of this Application. The pivotal study to support the proposed pediatric indication, and the focus of FDA's review, was AHOD1331. Studies HLHR13, C25002, AHOD1221, and ANHL12P1 were considered supportive.

- Study HLHR13: A single-arm, nonrandomized phase 2 study aimed to evaluate the treatment efficacy and safety of brentuximab vedotin substituting vincristine in the OEPA/COPDac regimen with or without radiation therapy. Patients aged ≤18 years with histologically confirmed, previously untreated high-risk CD30+ cHL (Stage IIB, IIIB, and IV) were included. The primary efficacy endpoints were early complete response after 2 cycles of AEPA and EFS compared to historical controls.
- Study AHOD1221: Phase 1/2, single-arm, open-label, nonrandomized study designed to identify the optimal dose of brentuximab vedotin for use in combination with gemcitabine and characterize the efficacy and safety of the brentuximab vedotin + gemcitabine combination in pediatric and young adult patients with r/r cHL. This study enrolled patients aged >12 months to ≤30 years. The study was conducted in two phases: RP2D finding phase (Part A), followed by safety and efficacy at the RP2D (Part B). During Part A, two dose levels of brentuximab vedotin were investigated (1.4 mg/kg and 1.8 mg/kg) in combination with gemcitabine, and 1.8 mg/kg was determined to the RP2D.
- Study C25002: Phase 1/2 multicenter dose-escalation study of brentuximab vedotin in pediatric patients with relapsed or refractory (r/r) Hodgkin lymphoma (HL) or systemic anaplastic large cell lymphoma (sALCL). This study enrolled patients aged 2 to <18 years with r/r sALCL and 5 to <18 years with r/r cHL. The primary objectives were to assess the safety and PK, determine the MTD and/or RP2D, and evaluate the antitumor activity of brentuximab vedotin in eligible pediatric patients. The study was conducted in 2 phases: a nonrandomized dose-finding phase that evaluated 2 planned dose cohorts: 1.4 mg/kg and 1.8 mg/kg once every 21 days, followed by the phase 2 portion of the study that was conducted at the RP2D of 1.8 mg/kg once every 21 days.
- Study ANHL12P1: A phase 2, randomized, open-label study aimed to evaluate the feasibility of the addition of brentuximab vedotin or crizotinib to standard chemotherapy in pediatric patients age <22 years with previously untreated non-localized sALCL. Patients were randomized 1:1 to either the brentuximab arm or the crizotinib arm. The primary endpoint was EFS.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study AHOD1331

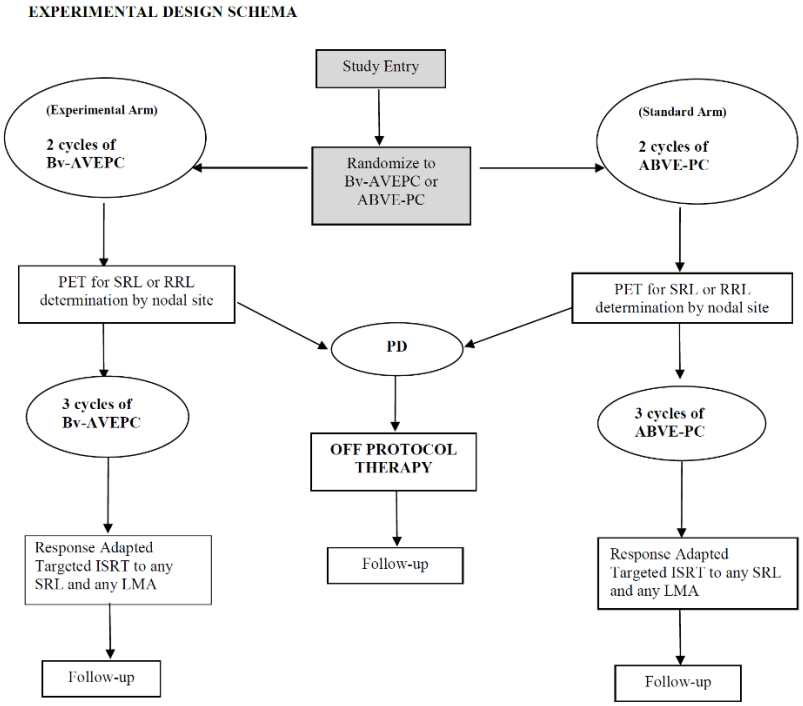
Trial Design

The Applicant's Description:

This is a randomized study conducted by NCI/COG that aims to examine the efficacy of brentuximab vedotin in pediatric subjects with high risk cHL. The primary outcome was EFS, where events included disease relapse/progression, second malignancy, or death. Eligible subjects for the study were those between the age of 2 to 21 years with newly diagnosed high risk cHL. Subjects were randomized 1:1 at the time of enrollment to 1 of 2 treatment arms: the control arm of doxorubicin (Adriamycin), bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide (ABVE-PC) or the experimental arm of brentuximab vedotin, doxorubicin (Adriamycin), vincristine, etoposide, prednisone, and cyclophosphamide (BV-AVEPC). Subjects in the BV-AVEPC arm received brentuximab vedotin at a dose of 1.8 mg/kg (max dose of 180 mg) IV over 30 mins on Day 1 of each cycle. Therapy consisted of 5 cycles of ABVE-PC or BV-AVEPC. Each cycle was 21 days.

At the completion of Cycle 2 (between Days 18 and 22 of Cycle 2), functional imaging was performed to determine response. At the end of 5 cycles of chemotherapy, subjects with slow responding lesion (SRL) at the post Cycle 2 received involved site radiation (ISRT) to SRL, and all subjects with large mediastinal mass (LMA) at initial diagnosis received ISRT to LMA. Subjects were followed closely off therapy for evidence of recurrent disease and subjects who were off protocol therapy were to be followed until they met the off study criteria.

Figure 11: Applicant - Schematic of Study Design



The FDA's Assessment:
The FDA agrees with the Applicant's description of the study design for the pivotal study, AHOD1331. AHOD1331 was conducted at 142 sites in the United States and 11 sites in Canada. Additional details for Study AHOD1331 include the following:

- ClinicalTrials.gov identifier: NCT02166463
- First patient enrolled: March 19, 2015
- Clinical cut-off date for this submission: December 31, 2021

Eligibility Criteria

The Applicant's Description:
Subjects were 2 to <22 years of age at the time of enrollment with newly diagnosed, pathologically confirmed cHL meeting 1 of the Ann Arbor stages (Stage IIB with bulk, IIIB, IVA, or IVB). Subjects must also have had adequate renal, liver, cardiac, and pulmonary function, as defined in the AHOD1331 protocol. Subjects with nodular lymphocyte-predominant cHL, immunodeficiency, previous chemotherapy or radiation therapy were excluded from enrollment.

The FDA's Assessment:
The FDA agrees with the Applicant's summary of the eligibility criteria for AHOD1331. Additional eligibility criteria include the following:

- All patients and/or their parents or legal guardians must sign a written informed consent
- All institutional, FDA, and NCI requirements for human studies must be met
- Adequate renal function defined as:
- Creatinine clearance or radioisotope GFR ≥70 mL/min/1.73 m^2 or
- A serum creatinine based on age/gender, as per Table 9 below:

Table 9: AHOD1331: Baseline Serum Creatinine Cutoff

Age (Years)	Maximum Serum Creatinine (mg/dL)	
	Male	Female
2 to <6	0.8	0.8
6 to <10	1	1
10 to <13	1.2	1.2
13 to <16	1.5	1.4
≥16	1.7	1.4

Source: AHOD1331 Clinical Protocol

- Adequate liver function defined as:
- Total bilirubin ≤1.5x ULN for age, and
- SGOT (AST) or AGPT (ALT) <2.5x ULN for age
- Adequate cardiac function defined as:
- Shortening fraction of ≥27% by echocardiogram, or
- Ejection fraction of ≥50% by radionuclide angiogram
- Adequate pulmonary function defined as:
- FEV_1/FVC>60% by pulmonary function test (PFT), unless due to large mediastinal mass from HL
- For children who are unable to cooperate for PFTs, the criteria are: no evidence of dyspnea at rest, no exercise intolerance, and a pulse oximetry reading of >92% on room air.

Additional Exclusion Criteria:

- Pregnant or lactating
- Sexually active patients of reproductive potential who have not agreed to use an effective contraceptive method for the duration of their study participation and for 30 days after the last dose of chemotherapy
- Patients who are HIV+
- Patients who received systemic corticosteroids within 28 days of enrollment

Study Endpoints

The Applicant's Description:

The primary endpoint was EFS, defined as the time from randomization to any of the following events: disease progression or relapse, second malignancy, or death due to any cause, whichever comes first. Secondary efficacy endpoints were early response rate (ERR), defined as

the proportion of subjects with early response after 2 cycles of chemotherapy (BV-AVEPC or ABVE-PC) as determined by central review, and RT rate (RTR), defined as the proportion of subjects needing response directed radiotherapy. Safety endpoints were type, incidence, and severity of AEs and proportion of subjects experiencing Grade ≥3 peripheral neuropathy (assessed by modified Balis scale). PK and immunogenicity endpoints included PK concentration time profile data of brentuximab vedotin ADC and MMAE, and ATA incidence rate.

The FDA's Assessment:
The FDA agrees with the Applicant's description of the efficacy endpoints. For the endpoint ERR, early response was defined as no slow responding lesions (SRL) or progressive disease at all sites (including large mediastinal mass), as determined by FDG-PET after two cycles of chemotherapy.

Statistical Analysis Plan and Amendments

The Applicant's Description:
Sample size determination: The study was designed (by DCTD/NCI) assuming a 3-year EFS rate of 82% for standard arm and was to have approximately 86% power to detect an 8% improvement in 3-year EFS rate in the BV-AVEPC arm using the log rank test when the EFS curves follow cure model. Power estimation is based on 290 eligible patients per arm and 1-sided log rank test with alpha level of 0.05. The study was to accrue 580 eligible patients, with a maximum accrual of 600 patients, accounting for an approximately 2% ineligibility rate.

Interim analyses: Interim efficacy and interim futility analyses were conducted by COG. Interim futility analysis was to be performed after approximately 25%, 50%, and 75% of the expected events, ie, after 20, 39, and 58 events. The stopping boundaries depended on the actual number of events observed at the time of the analyses.

The SAP was developed by the Applicant specifically to address objectives in the FDA Written Request (Reference ID: 4859657), including:

- To assess the EFS of BV-AVEPC in newly diagnosed high-risk cHL compared to those treated with ABVE-PC
- To determine whether children/young adults with high-risk cHL treated with BV-AVEPC have a higher ERR and a reduction in RTR compared to those treated with ABVE-PC.
- To compare safety, including the rate of neuropathy (>Grade 3), among patients treated on the BV-AVEPC to patients treated on the ABVE-PC.
- To characterize the pharmacokinetics of brentuximab vedotin in children.

The original version of the SAP was finalized on 20-Jan-2022 after the database extract and prior to DCTD/NCI sharing of the study results with the Applicant (21-Jan-2022). The SAP was revised to align with the FDA written request. The current version of the SAP, version 2.1, was finalized on 22-Mar-2022 before the analyses were conducted by the Applicant.

Analysis populations:

- The **ITT analysis set** included all randomized subjects. Subjects were analyzed according

to the treatment group assigned at randomization regardless of any actual dose treatment received.

- The **safety analysis set** included all subjects who received any amount of treatment. Subjects were analyzed according to the actual dose regimen received regardless of the randomization treatment assignment.
- The **PK analysis set** included all subjects who received any amount of treatment and from whom at least 1 blood sample was collected and assayed for ADC and MMAE.

Efficacy analyses: These were performed using the ITT analysis set. The log-rank test stratified by disease stage (recorded at randomization) was used in primary evaluation of EFS difference between BV-AVEPC and ABVE-PC arm. A stratified Cox proportional hazard model was used to estimate the hazard ratio of BV-AVEPC to ABVE-PC for EFS. Kaplan-Meier curves depicting EFS in the 2 arms were generated. The 2-sided 95% CIs for EFS rates were calculated using the complementary log transformation method (Collett 1994). ERR and RTR were summarized by arm and their exact 95% CIs were calculated using Clopper-Pearson method. Subjects without response assessment after Cycle 2 were counted as no early response and needing response-directed RT.

Subgroup analyses: Subgroup analyses were performed for the primary endpoint of EFS in subjects aged <12, 12-<18, and ≥18 years.

The FDA's Assessment:
The FDA generally agrees with the description of the statistical analysis plan and the amendments.

The FDA conducted the primary efficacy analysis (EFS) on the ITT analysis set. The ITT analysis set defined in the SAP included all randomized patients. All randomized patients included all patients older than 18 years old.

In addition, at least 77 events were required for the final analysis for detecting an 8% improvement in 3-year EFS in the BV-AVEPC arm (90%), compared to the standard treatment arm, assuming 3-year EFS rate of 82%.

There was no alpha allocation proposed in the interim analysis. There was no interim analysis conducted.

The final efficacy (EFS) analysis was planned to be conducted after a total of approximately 77 EFS events or 3-year follow-up from last enrollment, whichever occurred first. The data snapshot for final analysis was planned to be 12/31/2021. The primary efficacy analysis has an allocated of alpha of 1-sided 0.05 rather than the typical 0.025 for a 1-sided test.

Protocol Amendments

The Applicant's Description:

The original version of the protocol was approved on 16 Mar 2015. The protocol was amended 6 times during the course of the study. Table 10 describes the key changes made with each protocol amendment.

Table 10: Applicant – Summary of Protocol Amendments – AHOD1331

Version	Date	Key changes
Original	16-Mar-2015	---
Amendment 1	16-Nov-2015	Revised Comprehensive Adverse Event and Potential Risks (CAEPR) (Version 2.3, 2-Oct-2015) for SGN-35
Amendment 2B	14-Jun-2017	Increased age of eligibility from 18 to 21 Addition of PK studies Revisions in order to study the prognostic significance of Deauville 3 lesions in RRL subjects. Revisions for emphasis and clarity regarding requirement for timely submission of imaging for central review by IROC Updated instructions for use of antiemetics Permitted filgrastim biosimilars updated for both arms Updated for clarification of bone marrow biopsy requirement in adults vs. children Added Mucositis to Grade 3 GI toxicities not requiring expedited reporting. Updated radiotherapy (RT) instructions. Updated CYP3A4 Inducers and Inhibitors lists and instructions
Amendment 3	19-Apr-2018	Revisions to Dose Modifications for alignment with the update from CTCAE v4.0 to v5.0. The minimum timing of the final analysis was lowered from 5 to 3 years post closure to accrual Updated lists of CYP3A4 substrates, Inducers, Inhibitors and associated footnotes/instructions.
Amendment 4	25-Jun-2018	Revised CAEPR for SGN-35 (Version 2.4, 31-Jan-2018).
Amendment 5	19-Apr-2019	Revised CAEPR for brentuximab vedotin (Version 2.5, 13-Feb-2019).
Amendment 6	22-Jun-2020	Expanded the window to complete follow-up assessments

The FDA's Assessment:

The FDA agrees with the Applicant's description of the protocol amendments for AHOD1331.

8.1.2. Study Results

Compliance with Good Clinical Practices

Data:
N/A

The Applicant's Position:
The protocol for this study was designed in accordance with the general ethical principles outlined in the Declaration of Helsinki (Brazil 2015). 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 Harmonisation Good Clinical Practices, and applicable regional regulations/guidelines.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment that Study AHOD1331 was conducted in accordance with Good Clinical Practices. AHOD1331 included the following language in the CSR:

"This study was conducted in accordance with applicable regulations/guidelines set forth by the Food and Drug Administration (FDA) in 21 CFR Parts 11, 50, 54, 56, and 312; the European Union (EU) Directive 2001/20/EC and 2005/28/EC; and with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines. Essential documents are retained in accordance with ICH CGP."

Financial Disclosure

Data:

Study AHOD1331 was sponsored by the Division of Cancer Treatment and Diagnosis (DCTD) of National Cancer Institute (NCI). Financial Disclosure Forms (FDFs) collected by DCTD/NCI were considered confidential information; DCTD/NCI can provide them to the FDA directly upon request. Per information provided by DCTD/NCI, investigators' financial disclosure for AHOD1331 is summarized as follows:

- Financial arrangements: no investigators had disclosed significant financial arrangements with Seagen, as defined in 21 CFR 54.2(a).
- Equity interests: no investigators had disclosed having significant equity interests in Seagen, as defined in 21 CFR 54.2(b).
- Proprietary interests: no investigators had disclosed any proprietary interests in brentuximab vedotin.
- Employment with Sponsor: none of the principal investigators for AHOD1331 were prior or current employees of Seagen during the conduct of the study.
- Significant payments of other sorts (SPOOS): one sub-investigator, (b) (6) disclosed receiving SPOOS from Seagen that have a monetary value of more than $25,000. Seagen performed an internal audit of Finance, HR, and Compliance systems to investigate potential

payments, transfers of value and interest affiliations in relation to the disclosure of SPOOS by (b) (6). Seagen did not identify any SPOOS made to this investigator that exceeds the value of $25,000, the threshold defined in 21 CFR 54.2(f).

The Applicant's Position:
The only financial disclosure made in study AHOD1331 was SPOOS by investigator (b) (6) for which, Seagen's internal audit of Finance, HR, and Compliance systems could not corroborate. Any potential impact of financial interests by an individual investigator is minimized by the randomized design of AHOD1331, which was conducted by DCTD/NCI across 153 sites in the US and 11 sites in Canada.

The FDA's Assessment:
The FDA agrees that the Financial Disclosure information for AHOD1331 was submitted with this application. The financial disclosure information submitted is acceptable. See Section 19.2 for additional information regarding financial disclosures.

Patient Disposition

Data:
Six hundred subjects were enrolled and randomized 1:1 to either the control arm (ABVE-PC) or experimental arm (BV-AVEPC). Of the 593 treated subjects, 296 were treated in the BV-AVEPC arm and 297 were treated in the ABVE-PC arm. One subject was randomized to BV-AVEPC but received ABVE-PC (Table 11). The median duration of follow up in AHOD1331 was 42.23 months (range: 0.1 to 81.0) in the BV-AVEPC arm and 40.90 months (range: 0.0 to 78.0) in the control ABVE-PC arm (m5.3.5.1, AHOD1331 CSR, Table 14.1.2).

Table 11: Applicant – Summary of Subject Disposition (ITT Analysis Set) – AHOD1331

	BV-AVEPC (N=300) n (%)	ABVE-PC (N=300) n (%)	Total (N=600) n (%)
Subjects randomized	300 (100)	300 (100)	600 (100)
Subjects who received at least one dose of study treatment [a]	297 (99)	296 (99)	593 (99)
Reason randomized but not treated			
Physician decision	1 (<1)	0	1 (<1)
Repeat eligibility studies are outside the parameters required for eligibility	2 (1)	2 (1)	4 (1)
Missing	0	2 (1)	2 (<1)
Subjects on treatment	0	0	0
Subjects off treatment [b]	297 (99)	296 (99)	593 (99)
Subjects entered follow-up [c]	296 (99)	287 (96)	583 (97)
Reason for treatment discontinuation			
Completion of planned therapy	273 (91)	264 (88)	537 (90)
Physician determines it is in patient's best interest	9 (3)	10 (3)	19 (3)
Progressive disease	6 (2)	9 (3)	15 (3)
Refusal of further protocol therapy by patient/parent/guardian	6 (2)	5 (2)	11 (2)

	BV-AVEPC (N=300) n (%)	ABVE-PC (N=300) n (%)	Total (N=600) n (%)
Repeat eligibility studies are outside the parameters required for eligibility	0	2 (1)	2 (<1)
Missing	3 (1)	6 (2)	9 (2)
Subjects on study	257 (86)	249 (83)	506 (84)
Subjects off study [b]	43 (14)	51 (17)	94 (16)
Reason for study discontinuation			
Lost to follow-up	32 (11)	31 (10)	63 (11)
Withdrawal of consent	5 (2)	6 (2)	11 (2)
Death	2 (1)	4 (1)	6 (1)
Patient enrollment onto another COG study with tumor therapeutic intent	1 (<1)	3 (1)	4 (1)
Missing	3 (1)	7 (2)	10 (2)

a. Subject (b) (6) was randomized to BV-AVEPC but received ABVE-PC regimen.
b. Treatment includes protocol defined radiation therapy. Subjects who didn't complete any Follow-Up page and deemed ineligible by the study chair are considered as off treatment and off study.
c. Subjects who completed at least 1 follow-up.
Source: Module 5.3.5.1, AHOD1331 CSR, Table 14.1.1

The Applicant's Position:

As of the data snapshot date of 31-Dec-2021, all subjects in both arms were off study treatment, with 91% in the BV-AVEPC arm and 88% in the ABVE-PC arm having completed the planned therapy. 14% in the BV-AVEPC arm and 17% in the ABVE-PC arm had discontinued the study; the most common reason for discontinuation from the study was lost due to follow-up (11% and 10%, respectively). Median duration of follow up was similar between the 2 treatment arms,

The FDA's Assessment:

The FDA agrees with the Applicant's assessment of the patient disposition in Study AHOD1331. At the time of data cutoff, all patients in both treatment arms were off treatment. The majority of patients in both treatment arms completed the planned 5 cycles of therapy (BV-AVEPC: 91%; ABVE-PC: 88%). The FDA notes that, "completion of planned therapy" refers to completion of both chemotherapy and radiotherapy, when required. There were no significant differences in the treatment arms with regards to the reasons for treatment discontinuation or the reasons for study discontinuation. The FDA notes that "Adverse Event" was not listed as a reason for treatment discontinuation. The FDA sent an Information Request to the Applicant to obtain additional information regarding the treatment discontinuations due to adverse events. Per the Applicant, "Adverse Event" was not listed as a reason for discontinuation of treatment in the CRF. Therefore, treatment discontinuations could not be linked to specific adverse events. See Section 8.2.4 for additional discussion of treatment discontinuations and the limitations in the safety data available for Study AHOD1331.

Protocol Violations/Deviations

Data:
Protocol deficiencies were provided by audit reports performed by DCTD/NCI and the impact was categorized per the NCI audit guidelines (https://ctep.cancer.gov/branches/ctmb/clinicaltrials/docs/ctmb_audit_guidelines.pdf) as critical, major, and lesser deficiencies.

The Applicant's Position:
Per the NCI audits, no critical deficiencies were identified on the AHOD1331 study. Only deficiencies classified as major by audit and linked to subject ID are presented in the CSR.

The FDA's Assessment:
The FDA notes that protocol deviation information is not available for Study AHOD1331. Protocol deficiencies were provided by audit reports performed by DCTD/NCI and the impact was categorized per the NCI audit guidelines. A summary of the major protocol deficiencies identified by audit reports is provided in Table 12 below. The FDA agrees with the Applicant's statement that per the NCI audits, no critical deficiencies were identified on the AHOD1331 study.

Table 12: AHOD1331- Overview of Major Protocol Deficiencies

Category	Number of Protocol Deficiencies
General data management/quality details	10
Adverse event details	7
Treatment details	6
Informed consent details	5
Eligibility details	3
Disease outcome/response details	2

Source: FDA Reviewer's Analysis, Adapted from AHOD1331 CSR, Table 16.2.2

Table of Demographic Characteristics

Data:
Demographics in AHOD1331 are summarized in Table 13.

Table 13: Applicant – Summary of Demographics and Subject Characteristics (ITT Analysis Set) – AHOD1331

	BV-AVEPC (N=300)	ABVE-PC (N=300)	Total (N=600)
Age (yr)			
N	300	300	600
Mean (STD)	14.3 (3.1)	14.8 (3.0)	14.5 (3.1)
Median	15.0	15.0	15.0
Min, Max	3, 21	4, 21	3, 21
Age Category, n (%)			
< 6 years	5 (2)	4 (1)	9 (2)
6 - <12 years	47 (16)	34 (11)	81 (14)

	BV-AVEPC (N=300)	ABVE-PC (N=300)	Total (N=600)
12 - <18 years	222 (74)	226 (75)	448 (75)
≥18 years	26 (9)	36 (12)	62 (10)
Race, n (%)			
Black or African American	34 (11)	33 (11)	67 (11)
White	224 (75)	221 (74)	445 (74)
Asian	7 (2)	9 (3)	16 (3)
American Indian or Alaska Native	1 (<1)	0	1 (<1)
Native Hawaiian or Other Pacific Islander	2 (1)	3 (1)	5 (1)
Multiple Races	5 (2)	0	5 (1)
Unknown	19 (6)	14 (5)	33 (6)
Not Reported	8 (3)	20 (7)	28 (5)
Ethnicity, n (%)			
Hispanic or Latino	63 (21)	57 (19)	120 (20)
Not Hispanic or Latino	220 (73)	228 (76)	448 (75)
Unknown	9 (3)	7 (2)	16 (3)
Not Reported	8 (3)	8 (3)	16 (3)
Sex, n (%)			
Male	161 (54)	158 (53)	319 (53)
Female	139 (46)	142 (47)	281 (47)
BSA (m^2)			
N	101	89	190
Mean (STD)	1.6 (0.3)	1.6 (0.4)	1.6 (0.3)
Median	1.7	1.6	1.6
Min, Max	1, 2	1, 3	1, 3

Source: m5.3.5.1, AHOD1331 CSR, Table 14.2.1

The Applicant's Position:

Overall, the study included a roughly equal number of male (53%) and female (47%) subjects. The majority of subjects were White (74%) and not Hispanic or Latino (75%). Demographic characteristics were similar between the 2 treatment arms.

The FDA's Assessment:

The FDA agrees with the Applicant's description of the baseline demographics for study AHOD1331. The FDA agrees that, in general, the demographic characteristics were similar between the two treatment arms. There were slightly more males (53%) than females (47%) enrolled in this study. The median age in both treatment arms was 15 (overall range: 3-21). The FDA notes that the majority of patients in both treatment arms were 12 to <18 years of age. There were only 9 patients <6 years of age enrolled in AHOD1331. Of these, there were 5 patients <6 years of age who received BV-AVEPC and 4 who received ABVE-PC. An Information Request was sent to the Applicant to request additional data with brentuximab in younger patients to support the proposed indication for pediatric patients 2 years and older. The Applicant provided additional data in the ISS dataset, which included 4 additional pediatric studies in addition to AHOD1331. In the ISS dataset, there were a total of 19 patients aged 2 to <6 years of age who received brentuximab vedotin in combination with chemotherapy (5

received BV-AVEPC in AHOD1331 and 14 received brentuximab vedotin in combination with other treatment regimens). The FDA notes that overall, cHL is a rare malignancy in children <6 years old with an incidence rate of <2.9 per million (National Cancer Institute 2022). In general, children <6 years of age with cHL are treated similarly to older children and adolescents with risk-adapted protocols and combined intensive chemotherapy. The FDA concluded that the age distribution of pediatric patients enrolled in AHOD1331 is representative of the incidence and prevalence of cHL in pediatric patients.

The FDA notes that the majority of patients enrolled in AHOD1331 were white (74%) and not Hispanic or Latino (75%). Approximately 11% of patients enrolled were Black or African American, and 20% were Hispanic or Latino. The FDA sent an Information Request to the Applicant to request justification that the results from AHOD1331 are applicable to the U.S. patient population. The Applicant provided additional information including data from a population-based study across three Phase 2 trials conducted by the Children's Oncology Group (COG) between 2012-2022.[1] In this study, the estimated percentage of pediatric patients with newly diagnosed cHL who were Black or African American was 13%.[1] Similarly, a study published in 2020 that utilized the U.S. National Cancer Database found that 12% of patients 21 years of age and younger diagnosed with Stage I-IV HL from 2004-2015 were Black or African American, and 15% were Hispanic.[2] AHOD1331 was conducted at 153 clinical sites in the U.S., and per the Applicant, the target accrual for Black or African American patients was 82/600 (13.7%), as described in the AHOD1331 protocol. Based on this justification, the FDA agrees that the study population in AHOD1331 is representative of the U.S. patient population for pediatric patients with cHL.

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

Data:
Baseline disease characteristics are presented in Table 14.

Table 14: Applicant – Summary of Baseline Disease Characteristics (ITT Analysis Set) – AHOD1331

	BV-AVEPC (N=300) n (%)	ABVE-PC (N=300) n (%)	Total (N=600) n (%)
Histologic Diagnosis			
Hodgkin lymphoma, NOS	52 (17)	46 (15)	98 (16)
Hodgkin lymphoma, lymphocyte-rich	4 (1)	3 (1)	7 (1)
Hodgkin lymphoma, mixed cellularity, NOS	19 (6)	18 (6)	37 (6)
Hodgkin lymphoma, nodular sclerosis, NOS	225 (75)	231 (77)	456 (76)
Missing	0	2 (1)	2 (<1)
Disease Stage[a]			
Stage IIB with bulk	62 (21)	60 (20)	122 (20)
Stage IIIB	59 (20)	57 (19)	116 (19)
Stage IVA	86 (29)	88 (29)	174 (29)

	BV-AVEPC (N=300) n (%)	ABVE-PC (N=300) n (%)	Total (N=600) n (%)
Stage IVB	93 (31)	95 (32)	188 (31)
B Symptoms			
Yes	213 (71)	211 (70)	424 (71)
Fever	148 (49)	144 (48)	292 (49)
Night Sweats	125 (42)	112 (37)	237 (40)
Weight Loss >10%	98 (33)	108 (36)	206 (34)
No	83 (28)	85 (28)	168 (28)
Missing	4 (1)	4 (1)	8 (1)
Bone Marrow Involvement			
Yes	47 (16)	44 (15)	91 (15)
No	253 (84)	254 (85)	507 (85)
Missing	0	2 (1)	2 (<1)
Sites of Disease			
Extranodal	159 (53)	164 (55)	323 (54)
Nodal Only	138 (46)	132 (44)	270 (45)
Unknown	3 (1)	2 (1)	5 (1)
Missing	0	2 (1)	2 (<1)
Large Mediastinal Adenopathy			
Yes	164 (55)	164 (55)	328 (55)
No	135 (45)	130 (43)	265 (44)
Missing	1 (<1)	6 (2)	7 (1)
FDG-PET			
Positive	295 (98)	295 (98)	590 (98)
Negative	3 (1)	2 (1)	5 (1)
Indeterminate	1 (<1)	0	1 (<1)
Missing	1 (<1)	3 (1)	4 (1)

a. Stratification factor at randomization.
Source: m5.3.5.1, AHOD1331 CSR, Table 14.2.2

The Applicant's Position:

Overall, baseline disease characteristics were similar between the 2 arms.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment that overall, the baseline disease characteristics were similar between the two treatment arms. Overall, disease stage was well-distributed in both treatment arms. Approximately 20% of patients in both arms had Stage IIB with bulk disease, 19% had stage IIIB, 29% had stage IVA, and 31% had stage IVB. The majority of patients in both arms had nodular sclerosis HL (BV-AVEPC: 75%; ABVE-PC: 77%), and approximately 71% of patients in both arms had B symptoms at diagnosis. The majority of patients in both arms did not have bone marrow involvement (BV-AVEPC: 84%; ABVE-PC: 85%). The site of disease (extranodal vs. nodal only) and the percentage of patients who had large mediastinal lymphadenopathy (55% in both arms) was well balanced in the two treatment arms.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Treatment Compliance:

Study drugs were administered by IV by site staff. Overall treatment exposure was similar across the 2 arms, and the majority of subjects (97%) in both arms had completed 5 cycles. In the BV-AVEPC arm, 288 subjects (97%) completed 5 cycles, 3 subjects (1%) completed only 1 cycle, 2 subjects completed only 2 cycles, and 3 additional subjects completed only 3 cycles in the BV-AVEPC arm. Similarly, in the ABVE-PC control arm, with a median of 5.0 cycles, 97% subjects (n=287) completed the 5 cycles of treatment. Overall, 85 subjects (29%) in the BV-AVEPC arm and 77 subjects (26%) in the ABVE-PC arm had at least 1 dose modification. A total of 24 subjects (8%) in the BV-AVEPC arm had at least 1 dose modification of brentuximab vedotin: 16 subjects (5%) had a planned dose modification during any cycle and 10 subjects (3%) had an unplanned dose modification during any cycle. Brentuximab vedotin dose modifications occurred at a similar frequency (2% to 3%) across all 5 cycles of treatment.

Concomitant Medications:

The AHOD1331 study allowed for the use of concomitant growth factor support to mitigate myelosuppressive toxicity. In addition, use of anti-emetics and dexrazoxane was allowed per protocol.

Rescue Medications:

Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care were allowed to be used as necessary.

The FDA's Assessment:

The FDA agrees with the Applicant's description of treatment compliance, concomitant medications, and rescue medications. The majority of patients in both treatment arms (97%) completed the planned five cycles of chemotherapy.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

The EFS analysis was conducted using the data snapshot date of 31-Dec-2021 (Table 15). A Kaplan-Meier plot of EFS is presented in Figure 12.

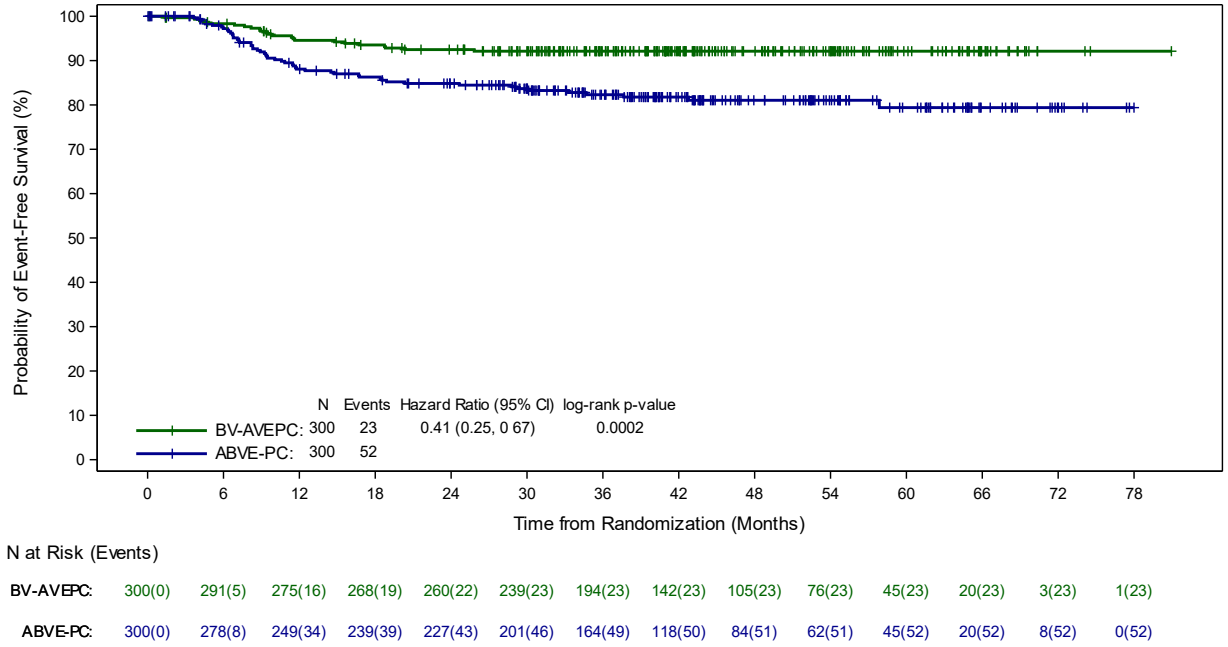
Table 15: Applicant – Event Free Survival (ITT Analysis Set) – AHOD1331

	BV-AVEPC (N=300)	ABVE-PC (N=300)
Subjects with an EFS event[a], n (%)	23 (8)	52 (17)
Relapse	19 (6)	41 (14)
Disease progression	3 (1)	9 (3)
Second malignancy	1 (<1)	1 (<1)
Death	0	1 (<1)
Estimated EFS rate[b] (95% CI)[c] at:		
1 year	94.6% (91.3%, 96.6%)	88.1% (83.7%, 91.3%)
2 years	92.5% (88.8%, 95.0%)	84.8% (80.1%, 88.5%)

	BV-AVEPC (N=300)	ABVE-PC (N=300)
3 years	92.1% (88.4%, 94.7%)	82.3% (77.2%, 86.3%)
Median EFS[b] (months)	-	-
95% C.I.[c]	(-, -)	(-, -)
25th, 75th percentile	-, -	-, -
Observed min, max	0.1+, 81.0+	0.0+, 78.0+
Stratified log-rank P-value[d]	0.0002	
HR (stratified Cox regression)[e]	0.41	
(95% CI)	(0.25, 0.67)	

'+' means the observed time is from censored subject. '-' means not estimable.
[a.] Relapse and progression were assessed by investigator.
[b.] As estimated using Kaplan-Meier methods.
[c.] Calculated using the complementary log-log transformation method.
[d.] Two-sided p-value from log-rank test stratified by clinical characteristic (disease stage).
[e.] Hazard ratio is BV-AVEPC over ABVE-PC.
Source: m5.3.5.1, AHOD1331 CSR, Table 14.3.2.1

Figure 12: Applicant – Kaplan-Meier Plot of EFS (ITT Analysis Set) – AHOD1331



Hazard ratio is BV-AVEPC over ABVE-PC from stratified Cox regression. Two-sided p-value is from log-rank test stratified by clinical characteristic (disease stage).
Source: m5.3.5.1, AHOD1331 CSR, Figure 14.3.3.1

In the BV-AVEPC arm, 277 subjects (92%) were censored, the majority (80%) were still on study and censored due to no documented progression or second malignancy (Table 16).

Table 16: Applicant – Summary of Censoring Reasons for EFS (ITT Analysis Set) – AHOD1331

	BV-AVEPC (N=300)	ABVE-PC (N=300)
Censored subjects	277 (92)	248 (83)
Reasons for censoring		
No documented progression or second malignancy, still on study	239 (80)	205 (68)
Off Study without event	38 (13)	43 (14)
Withdrawal of consent	4 (1)	6 (2)
Lost to follow-up	31 (10)	28 (9)
Patient enrollment onto another COG study	0	2 (1)
Other	3 (1)	7 (2)

Source: m5.3.5.1, AHOD1331 CSR, Table 14.3.2.4

A sensitivity analysis for EFS was also performed for subjects who were randomized and deemed eligible by the study chair (All Randomized Eligible Subjects, n=587). Results were similar in this analysis compared to the ITT analysis set (m5.3.5.1, AHOD1331 CSR, Table 14.3.2.6).

The Applicant's Position:
Treatment on the active BV-AVEPC arm resulted in a clinically meaningful and statistically significant 59% reduction in the risk of disease progression or relapse, second malignancy, or death compared to the ABVE-PC control arm (HR 0.41 [95% CI: 0.25, 0.67]; 2-sided p=0.0002). The clinical benefit of incorporating brentuximab vedotin into the AVEPC regimen is further demonstrated with the maintained high EFS rate in the active arm compared to ABVE-PC. At 2 years, the estimated EFS rate was 92.5% (95% CI: 88.8, 95.0) in the BV-AVEPC arm vs. 84.8% (95% CI: 80.1, 88.5) in the ABVE-PC arm. The 3-year EFS rate in the BV-AVEPC arm was estimated as 92.1% (95% CI: 88.4, 94.7) compared to 82.3% (95% CI: 77.2, 86.3) in the control arm.

The number of censored subjects was slightly higher in the BV-AVEPC arm due to no documented event of death, disease progression, or second malignancy. However, the incidence of other reasons for censoring was similar between the 2 arms.

The FDA's Assessment: The FDA independently conducted the primary analyses based on the ITT analysis set and was able to reproduce the results included in this section. As of the data cutoff of 12/31/2021, the median EFS was not reached in BV-AVEPC or ABVE-PC arms. The hazard ratio for EFS based on stratified Cox regression model was 0.41 (95% CI: 0.25, 0.67; p=0.0002) of the BV-AVEPC arm compared with the ABVE-PC arm in the ITT analysis set. Based on the Schoenfeld residuals proportionality assumption test, there was no violation to the PH assumption of the stratified Cox regression model. The FDA notes that the alpha allocation for the primary EFS analysis was pre-specified as 0.05 based on a 1-sided test. In the analysis, the 2-sided p=0.0002 was observed for the primary endpoint EFS between BV-AVEPC and ABVE-PC arms. The study met its pre-specified primary endpoint. The EFS rates at 1 year for patients in BV-AVEPC and ABVE-PC arms were 94.6% (91.3%, 96.6%) versus 88.1% (83.7%, 91.3%). The EFS

rates at 2-years were 92.5% (88.8%, 95.0%) versus 84.8% (80.1%, 88.5%), and the EFS rates at 3-years were 92.1% (88.4%, 94.7%) versus 82.3% (77.2%, 86.3%), in the ITT analysis set.

Sensitivity analyses for the primary endpoint EFS were based on all randomized eligible patients. The FDA independently conducted the sensitivity analyses. A total of 8% (23/298) of patients treated with BV-AVEPC experienced an EFS event while 18% (51/289) of patients treated with ABVE-PC experienced an EFS event. The median EFS was not reached in the BV-AVEPC or ABVE-PC arms. The hazard ratio for EFS based on stratified Cox regression model was 0.41 (95% C.I.: 0.25,0.67) of the BV-AVEPC arm compared with the ABVE-PC arm. The EFS rates at one year for patients in BV-AVEPC and ABVE-PC arms were 94.6% (91.3%, 96.6%) and 88.3% (83.9%, 91.5%), respectively. At 2-years, the EFS rates were 92.5% (88.8%, 95.0%) and 85.0% (80.3%, 88.7%), respectively, and at 3-years, the EFS rates were 92.1% (88.4%, 94.7%) versus 82.5% (77.4%, 86.5%). In summary, the sensitivity analysis results were consistent with those based on the ITT analysis set.

Data Quality and Integrity

The Applicant's Position:
Clinical Trials Monitoring Branch (CTMB) within CTEP DCTD/NCI has direct oversight responsibilities for the quality assurance and auditing programs used in the study. The study was monitored for subject accrual, eligibility and evaluability, study data, medical review, AE reporting, and subject safety. Audit records are retained by the DCTD/NCI (AHOD1331 CSR Appendix 16.1.8). Database management was performed by COG. An electronic data capture system was employed for this study. eCRF completion guidelines were provided to study site personnel. Queries resulting from edit checks and/or data verification procedures were posted electronically in the eCRF. Documentation of interlaboratory standardization methods and Quality Assurance procedures are provided in AHOD CSR Appendix 16.1.10.

Seagen Inc. personnel developed statistical programs and performed analyses pertaining to the SAP developed for the WR. Data listings, summary tables, and figures were examined for data accuracy and format. All analyses and data transformations were programmed using SAS version 9.4 or more recent (SAS Institute, Cary, NC).

The FDA's Assessment:
The FDA agrees with the Applicant's description. There were no identified data integrity concerns with Study AHOD1331.

Efficacy Results – Secondary and other relevant endpoints

Data:
Results of ERR and RTR are presented in Table 17 and

Table 18, respectively.

Table 17: Applicant – Early Response Rate (ITT Analysis Set) – AHOD1331

	BV-AVEPC (N=300)	ABVE-PC (N=300)
Subjects with early response[a], n (%)	238 (79.3)	237 (79.0)
95% CI[b] for early response rate	(74.3, 83.8)	(73.9, 83.5)

[a.] Subjects achieving early response are those with no SRL and no PD at all sites after cycle 2 determined by PET per Deauville criteria through central review.
[b.] Two-sided exact confidence interval, computed using the Clopper-Pearson method.
Source: m5.3.5.1, AHOD1331 CSR, Table 14.3.1.1

Table 18: Applicant – Response-Directed Radiotherapy Rate (ITT Analysis Set) – AHOD1331

	BV-AVEPC (N=300)	ABVE-PC (N=300)
Subjects needing response-directed RT[a], n (%)	40 (13.3)	43 (14.3)
95% CI[b] for response-directed RT rate	(9.7, 17.7)	(10.6, 18.8)

[a.] Subjects needing response-directed RT are those with SRL (at sites other than LMA) or PD after cycle 2 determined by PET per Deauville criteria through central review.
[b.] Two-sided exact CI, computed using the Clopper-Pearson method.
Source: m5.3.5.1, AHOD1331 CSR, Table 14.3.1.2

The Applicant's Position:
Secondary efficacy outcomes of ERR and RTR were similar between BV-AVEPC arm and control arm in the study.

The FDA's Assessment:
The FDA independently conducted the secondary efficacy analyses and the observed results were consistent with the Applicant's results shown in Table 17 and 18.

Dose/Dose Response

The Applicant's Position:
No relevant data for this submission.

The FDA's Assessment:
Refer to the Clinical Pharmacology review in Section 6 for information on the dose and dose response.

Durability of Response

The Applicant's Position:
No relevant data for this submission.

The FDA's Assessment:
The FDA agrees with the Applicant's statement that there is no relevant durability of response data for this submission.

Persistence of Effect

The Applicant's Position:
In the AHOD1331 study, after a median follow-up of 42.23 months the estimated EFS rates at 1,2 and 3 years are presented in Table 15.

Table 19: Applicant – Estimated EFS Rate (ITT Analysis Set) – AHOD1331

	BV-AVEPC (N=300)	ABVE-PC (N=300)
Estimated EFS rate[a] (95% CI)[b] at:		
1 year	94.6% (91.3%, 96.6%)	88.1% (83.7%, 91.3%)
2 years	92.5% (88.8%, 95.0%)	84.8% (80.1%, 88.5%)
3 years	92.1% (88.4%, 94.7%)	82.3% (77.2%, 86.3%)

[a.] As estimated using Kaplan-Meier methods.
[b.] Calculated using the complementary log-log transformation method.
Source: m5.3.5.1, AHOD1331 CSR, Table 14.3.2.1

The FDA's Assessment:
The FDA confirmed the Applicant's calculated EFS rates. The EFS rates in the BV-AVEPC arm were numerically higher than the EFS rates in the ABVE-PC arm at 1 year, 2 years, and 3 years.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The Applicant's Position:
No relevant data for this submission.

The FDA's Assessment:
The FDA agrees that there were no relevant secondary or exploratory COA (PRO) endpoints included in this submission.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:
As exploratory analyses, subgroup analyses for age (<12, 12-<18, and ≥18 years) were conducted for EFS. Subjects aged 12 to <18 years demonstrated a benefit consistent with the overall study population while results in the <12 years and ≥18 years subgroups were inconclusive due to the low number of EFS events as well as each age subgroup being a small subset of the randomized populations (m5.3.5.1, AHOD1331 CSR, Section 11.1.1.2).

The FDA's Assessment:
The FDA independently conducted the subgroup analyses for age (<12, 12-<18 and ≥18 years) as pre-specified in the SAP.

For the subgroup of age <12 years-old, 4% (2/52) patients randomized to BV-AVEPC arm experienced an EFS event; 13% (5/38) patients randomized to ABVE-PC arm experienced an EFS event. The hazard ratio for EFS based on an unstratified Cox regression model was 0.29 (95% C.I.: 0.06,1.50) for the BV-AVEPC arm compared with the ABVE-PC arm. The Kaplan-Meier Plot

of EFS for this subgroup analysis is shown in Figure 15. The analysis for this subgroup was underpowered due to a small sample size, thus the results were inconclusive.

For the subgroup of age 12 to <18 years-old, 8% (17/222) patients experienced an EFS event in BV-AVEPC arm, while 20% (45/226) patients experienced an EFS event in ABVE-PC arm. The hazard ratio for EFS based on unstratified Cox regression model for this subgroup was 0.34 (95% C.I.: 0.20,0.60) for the BV-AVEPC arm compared with the ABVE-PC arm. The nominal p-value based on an unstratified log-rank test was <0.0001. The Kaplan-Meier Plot of EFS for this subgroup analysis was shown in Figure 14. The analysis for this subgroup demonstrated a reduction in BV-AVEPC arm in the risk of disease progression or relapse, second malignancy, or death, compared to the ABVE-PC control arm. However, this analysis is considered as exploratory analysis only.

For the subgroup of age ≥18 years-old, 15% (4/26) of patients experienced an EFS event in BV-AVEPC arm while 6% (2/36) of patients experienced an EFS event in ABVE-PC arm. The hazard ratio for EFS for this subgroup based on an unstratified Cox regression model was 2.74 (95% C.I.: 0.50, 15.00) of the BV-AVEPC arm compared with the ABVE-PC arm. The Kaplan-Meier Plot of EFS for this subgroup analysis is shown in Figure 15. An Information Request was sent to the Applicant regarding the discordant results in patients ≥18 years old. The FDA requested any additional data available to support the use of BV in patients ≥18 years old. The Applicant provided justification, including the following:

- The number of patients included in this subgroup was small and represents only about 10% of the total sample size of the ITT population. The total number of EFS events in this subgroup represents less than 10% of the total number of EFS events in the ITT population. As a result, the HR in this subgroup has a wide 95% CI (0.50, 15.00), indicating that the estimated HR in this subgroup has lower precision than the ITT population.
- Due to the high variability of the HR in this subgroup, the Applicant implemented a Bayesian hierarchical model based on age subgroups (<12, 12 to <18, ≥18 years), allowing for borrowing information across these subgroups. This model showed improved consistency with the overall ITT results. The shrinkage estimates of the hazard ratios and the corresponding 95% credible intervals for the three age groups is shown in Table 20 below.

Table 20: Shrinkage Estimates of HR and Corresponding 95% Credible Intervals by Age Group

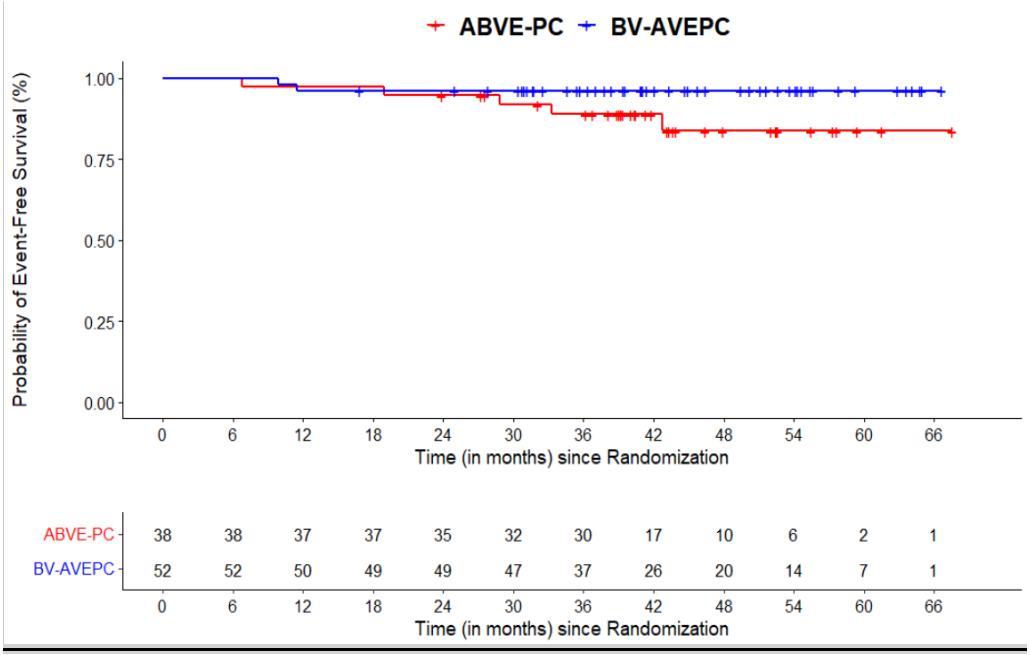
	Cox Regression		Bayesian[a]	
Age group (years)	HR	95% confidence interval	HR	95% credible interval
<12 (n=90)	0.29	(0.06, 1.50)	0.45	(0.11, 1.34)
12-<18 (n=448)	0.34	(0.20, 0.60)	0.37	(0.21, 0.62)
≥18 (n=62)	2.74	(0.50, 15.00)	1.34	(0.39, 7.52)

a. The Bayesian shrinkage estimates (posterior median) and 95% credible intervals are based on the prior with location of 0.5 and weight of 0.75.
Source: AHOD1331 CSR, Table 14.3.2.2; Bayesian Hierarchical Model Specification in APPENDIX I.

- Finally, an interaction test was performed to assess consistency in the EFS treatment effect across age groups. This demonstrated that there is no significant evidence that the treatment effect varies substantially among different age groups (P=0.062 from Wald test for quantitative interaction for treatment and age in Cox regression model; P=0.249 from Gail Simon test for qualities interaction of treatment and age).

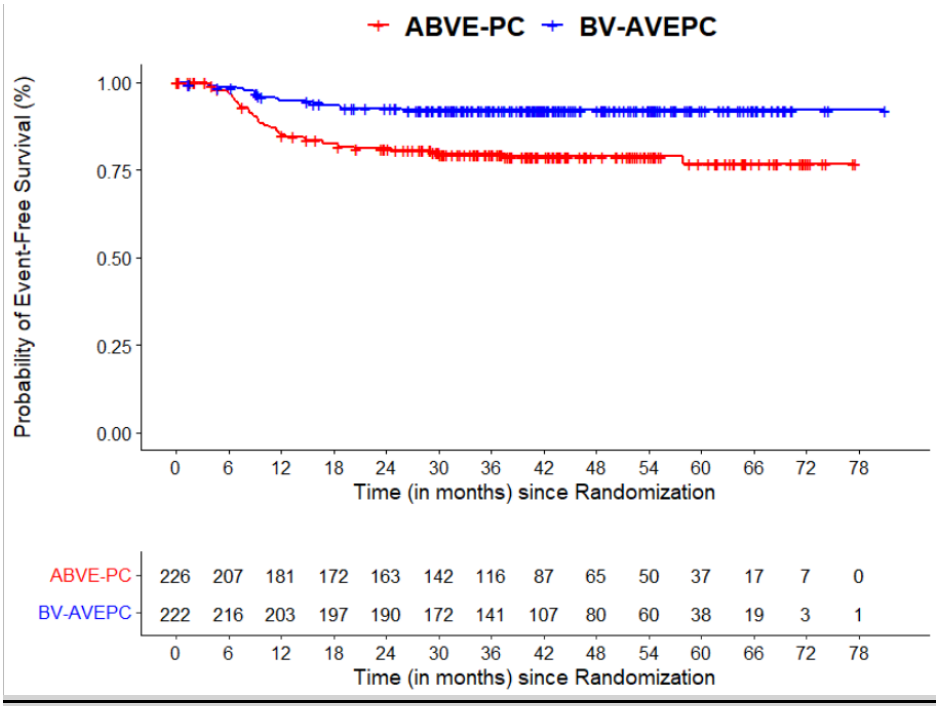
The FDA concluded that the analysis for this subgroup of patients ≥18 years was underpowered due to a small sample size, thus the result was inconclusive.

Figure 13: Kaplan-Meier Plot of EFS by Age (<12 Years) (ITT Analysis Set)



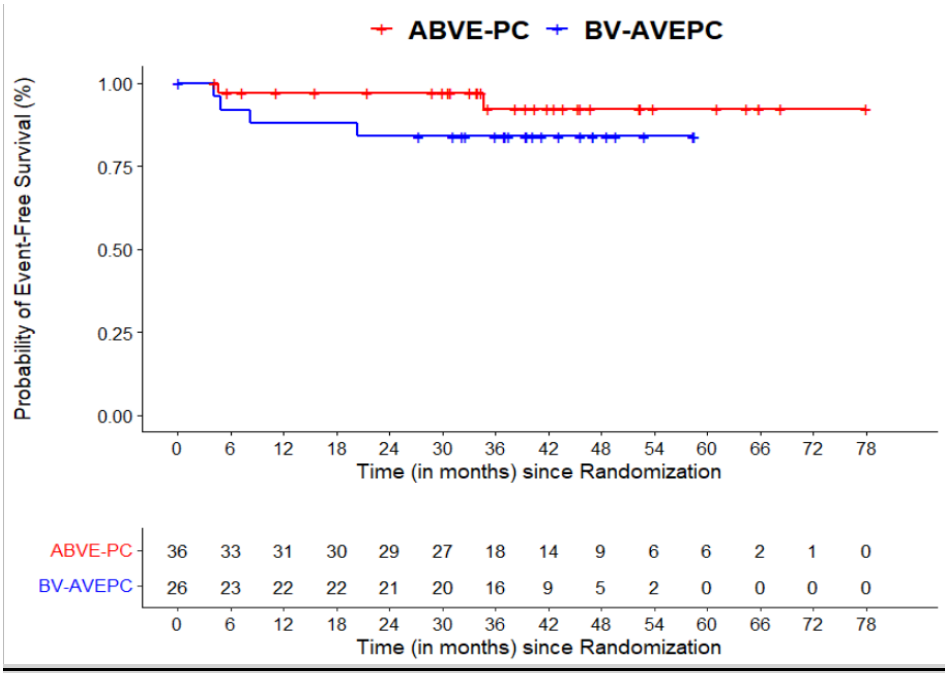
Source: FDA Analysis.

Figure 14: Kaplan-Meier Plot of EFS by Age (12 to <18 Years) (ITT Analysis Set)



Source: FDA Analysis.

Figure 15: Kaplan-Meier Plot of EFS by Age (≥18 Years) (ITT Analysis Set)



Source: FDA analysis.

The FDA conducted additional analyses of the primary endpoint EFS and the secondary endpoints (ERR and RTR) based on the following age groups: 2-<6, 6-<12, 12-<18 and ≥18 years. These results are provided in Table 21 below.

Table 21: Descriptive analysis of the primary endpoint EFS and secondary endpoints (ER and RTR) based on the age groups: 2-<6, 6-<12, 12-<18 and ≥18 years

Age group	ABVE-PC		BV-AVEPC	
	EFS Event/Total	**EFS Rate, %**	**EFS Event/Total**	**EFS Rate, %**
2-<6	1/4	25	0/5	0
6-<12	4/34	12	2/47	4
12-<18	45/226	20	17/222	8
>=18	2/36	6	4/26	15
	ER Event/Total	**ER rate, %**	**ER Event/Total**	**ER rate, %**
2-<6	4/4	100	4/5	80
6-<12	31/34	91	38/47	81
12-<18	176/226	78	177/222	80
>=18	26/36	72	19/26	73
	RT Event/Total	**RT rate, %**	**RT Event/Total**	**RT rate, %**
2-<6	0/4	0	1/5	20
6-<12	2/34	6	5/47	11
12-<18	34/226	15	28/222	13
>=18	7/36	19	6/26	23

Source: FDA analysis.

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:
See Section 8.1.5 for the FDA's Integrated Assessment of Efficacy.

8.1.4. Assessment of Efficacy Across Trials

Primary Endpoints

Data:
Studies AHOD1331 and HLHR13 evaluated the use of brentuximab vedotin in combination with chemotherapy in subjects with previously untreated high-risk cHL. A direct comparative analysis across AHOD1331 and HLHR13 studies was not conducted due to different chemotherapy regimens and brentuximab dosing. However, AHOD1331 and HLHR13 were selected for side by-side comparison due to their similar indication under study (previously untreated pediatric

subjects with high-risk cHL) and the primary endpoint of EFS which was defined similarly in both studies.

HLHR13 was a single-arm, open-label, phase 2 study in pediatric subjects with high-risk HL aimed to evaluate the efficacy and safety of brentuximab vedotin substituting vincristine in the OEPA regimen with or without radiation therapy. In this study, brentuximab vedotin was intravenously infused at 1.2 mg/kg on Days 1, 8, and 15 of 28-day cycle for 2 cycles as part of AEPA (brentuximab vedotin, etoposide, prednisone, and doxorubicin), followed by 4 cycles of 1.2 mg/kg intravenous dose on Days 1 and 8 of the 21-day cycle as part of CAPDac (cyclophosphamide, brentuximab vedotin, prednisone, and dacarbazine).

Table 22: Applicant – Summary of AHOD1331 and HLHR13 EFS Results

	AHOD1331		HLHR13
	BV-AVEPC (N=300)	**ABVE-PC (N=300)**	**AEPA/CAPDac (N=77)**
Subjects with an EFS event, n (%)	23 (8)	52 (17)	2 (3)
Relapse	19 (6)	41 (14)	0
Disease progression	3 (1)	9 (3)	1 (1)
Second malignancy	1 (<1)	1 (<1)	0
Death	0	1 (<1)	1 (1)
Estimated EFS rate [a] (95% CI) [b] at:			
1 year	94.6% (91.3%, 96.6%)	88.1% (83.7%, 91.3%)	97.4% (90.0%, 99.3%)
2 years	92.5% (88.8%, 95.0%)	84.8% (80.1%, 88.5%)	97.4% (90.0%, 99.3%)
3 years	92.1% (88.4%, 94.7%)	82.3% (77.2%, 86.3%)	97.4% (90.0%, 99.3%)
4 years	92.1% (88.4%, 94.7%)	81.0% (75.7%, 85.3%)	97.4% (90.0%, 99.3%)
5 years	92.1% (88.4%, 94.7%)	79.4% (73.0%, 84.4%)	97.4% (90.0%, 99.3%)
6 years	92.1% (88.4%, 94.7%)	79.4% (73.0%, 84.4%)	97.4% (90.0%, 99.3%)
Duration of follow-up [c] (months)			
n	300	300	77
Mean (STD)	43.67 (15.14)	42.20 (17.14)	40.13 (17.35)
Median	42.23	40.90	37.59
Min, Max	0.1, 81.0	0.0, 78.0	3.5, 73.0

[a] As estimated using Kaplan-Meier methods.
[b] Calculated using the complementary log-log transformation method (Collett, 1994).
[c] Time between randomization date (recorded as enrollment date) and last known alive date (for subjects who are alive) or death date.
Sources: m5.3.5.1, AHOD1331 CSR, Table 14.3.2.1; m5.3.5.2, HLHR13 CSR, Table 14.3.2.1.Comparison of Results of Subpopulations

The Applicant's Position:

These data demonstrate that brentuximab vedotin is active in previously untreated high-risk cHL. At the time of data snapshot or cutoff, follow-up times for EFS varied across studies. In general, EFS in subjects treated with brentuximab vedotin was consistent across studies. In Study AHOD1331, treatment on the BV-AVEPC arm resulted in a statistically significant and

clinically meaningful reduction in the risk of disease progression or relapse, second malignancy, or death compared to the ABVE-PC arm (HR 0.41 [95% CI: 0.25, 0.67]; 2-sided p=0.0002).

With a median follow-up of 42.23 months in Study AHOD1331, the estimated EFS rate was 92.1% (95% CI: 88.4, 94.7) at 3 years in the BV-AVEPC arm, compared to 82.3% (95% CI: 77.2, 86.3) in the ABVE-PC control arm. With a median follow-up of 37.6 months in Study HLHR13, the EFS rate was 97.4% (95% CI: 90.0, 99.3) at 2 and 3 years and remained constant over the remainder of follow-up.

The FDA's Assessment:
The FDA does not agree with the Applicant's statement that, "In general, EFS in patients treated with brentuximab vedotin was consistent across studies". The FDA notes that, although the indications were similar, studies AHOD1331 and HLHR13 had different chemotherapy regimens and different brentuximab dosing. In addition, approximately 8% (23/300) of patients in BV-AVEPC arm in AHOD 1331 study experienced an EFS event compared to 3% (2/77) of patients in HLHR13. In addition, study HLHR13 is a single-arm trial and time to event endpoints such as EFS are not interpretable in single-arm trials. Therefore, these results do not support the statement that EFS was consistent across studies.

Secondary and Other Endpoints

The Applicant's Position:
See Section 8.1.2 for results of secondary endpoints in Study AHOD1331.

The FDA's Assessment:
The secondary endpoints ERR and RTR were not available in other studies. Also, given the differences in study design between study AHOD1331 and HLHR13, no formal comparison tests should be conducted across the trials for these secondary endpoints.

Subpopulations

The Applicant's Position:
No relevant data for this submission.

The FDA's Assessment:
The FDA agrees with Application's statement regarding subpopulations.

Additional Efficacy Considerations

The FDA's Assessment:
The FDA sent an Information Request to the Applicant to request a summary of response data (overall response rate) for patients in both treatment arms in Study AHOD1331. The FDA also requested an efficacy dataset for response rate. The Applicant stated that they are unable to provide traditional response data, as the AHOD1331 study protocol incorporated metabolic responses using FDG-PET as a part of response assessments for patients on the study. Overall responses based on lesion measurements and Response Evaluation Criteria in Solid Tumors (RECIST) guidelines were not defined in the protocol and hence not reported in the study. Per

study protocol, patients underwent FDG-PET imaging at baseline and after completion of 2 and 5 cycles of study treatment. The COG definitions of response included complete metabolic response (CMR), incomplete metabolic response (IMR), and progressive disease (PD). The Applicant's analysis of End of Chemotherapy Response is provided in Table 23 below.

Table 23: AHOD1331 - End of Chemotherapy Response (ITT Analysis Set)

	BV-AVEPC (N=300) n (%)	ABVE-PC (N=300) n (%)
Response at end of therapy [a]		
Complete metabolic response	263 (88)	254 (85)
Incomplete metabolic response	27 (9)	35 (12)
Progressive disease	0	0
Missing	10 (3)	11 (4)

a. PET2 and PET5 response assessment per central review. Complete metabolic response is defined as subjects who achieved PET2 negative or complete metabolic response at PET5 among SRL subjects. Incomplete metabolic response is defined as SRL subjects who had incomplete metabolic response at PET5. Progressive disease defined as subjects who had a progressive disease lesion at PET2 or at PET5 among SRL subjects.
Data Snapshot: 31DEC2021
Source: Table 14.3.1.3 in APPENDIX I.

8.1.5. Integrated Assessment of Effectiveness

Data:

As previously agreed with the FDA at the pre-sBLA meeting (Reference ID: 4874306), due to the differences in indications, treatment lines, and chemotherapy combinations, efficacy data were presented separately for each individual study.

In Study AHOD1331, treatment on the BV-AVEPC arm resulted in a statistically significant and clinically meaningful reduction in the risk of disease progression or relapse, second malignancy, or death compared to the ABVE-PC arm (HR 0.41 [95% CI: 0.25, 0.67]; 2-sided p=0.0002). With a median follow-up of 42.23 months in Study AHOD1331, the EFS rates observed at 2- and 3-years were 92.5% and 92.1%, respectively, in the BV-AVEPC arm compared to 84.8% and 82.3%, respectively, in the ABVE-PC control arm. With a median follow-up of 37.6 months in Study HLHR13, the EFS rates 97.4% and 97.4%, respectively, for the AEPA/CAPDac regimen in the HLHR13 study and remained constant over the remainder of follow-up.

The Applicant's Position:

Studies AHOD1331 and HLHR13 evaluated the use of brentuximab vedotin in combination with chemotherapy in pediatric subjects with previously untreated high risk cHL. Both studies had

EFS as the primary efficacy endpoint, defined as time to disease relapse or progression, second malignancy, or death. Compared to currently existing treatment regimens for pediatric subjects with previously untreated high risk cHL, both regimens showed an improvement in EFS with a risk-adapted approach. Specifically, in the randomized AHOD1331 study, incorporation of brentuximab vedotin into the standard ABVE-PC regimen and elimination of bleomycin resulted in improved efficacy in this high-risk population. The EFS rates from both the studies demonstrate the efficacy of using a regimen incorporating brentuximab vedotin for subjects with previously untreated cHL.

The FDA's Assessment:

The FDA does not agree with the Applicant's statement, "Compared to currently existing treatment regimens for pediatric patients with previously untreated high risk cHL, both regimens showed an improvement in EFS with a risk-adapted approach". HLHR13 was a single-arm, open-label, phase 2 study in pediatric patients with high-risk cHL aimed to evaluate the efficacy and safety of brentuximab vedotin as a substitute for vincristine in the OEPA regimen with or without radiation therapy. There was no comparison analysis conducted in the HLHR13 study. In addition, study HLHR13 is a single-arm trial and time to event endpoints such as EFS are not interpretable in single-arm trials. Therefore, there is no available data to support the statement that, "the regimen in HLHR13 study showed an improvement in EFS with a risk-adapted approach", when compared to currently existing treatment regimens.

The efficacy of brentuximab vedotin was established in AHOD1331, a phase 3, global, randomized study in children and young adults with previously untreated high risk cHL. Patients aged 2 to <22 years with previously untreated, pathologically confirmed high risk (defined as Ann Arbor Stage IIB with bulk, Stage IIIB, Stage IVA, or Stage IVB) cHL were enrolled. Patients were stratified by disease stage and were randomized 1:1 to receive either brentuximab vedotin plus the chemotherapy backbone of doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide (AVEPC) or the control arm of doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide (ABVE-PC). Patients in the brentuximab vedotin (BV) arm received BV at 1.8 mg/kg IV over 30 minutes on Day 1 of each 21-day cycle in addition to AVEPC chemotherapy. After two cycles, early response was assessed by positron emission tomography (PET) for all patients in both arms. All patients subsequently received three additional cycles, for a total of five treatment cycles in each arm.

Efficacy:

- The primary endpoint in AHOD1331 was event free survival (EFS), defined as the time from randomization to any of the following events: disease progression or relapse, second malignancy, or death, whichever comes first.
- Median EFS was not reached in either arm. In the BV-AVEPC arm, the estimated EFS rate was 92.5% (95% CI: 88.8, 95.0) at 2 years and 92.1% (95% CI: 88.4, 94.7) at 3 years, compared to 84.8% (95% CI: 80.1, 88.5) at 2 years and 82.3% (95% CI: 77.2, 86.3) at 3 years in the ABVE-PC control arm. The hazard ratio (HR) was 0.41 (95% CI: 0.25, 0.67),

corresponding to a 59% reduction in the risk of an EFS event in the BV-AVEPC arm versus the ABVE-PC arm.

- Secondary efficacy endpoints were Early Response Rate (ERR) and Response-directed Radiation Therapy (RTR) rate.
- The Early Response Rate (ERR) was similar in the two treatment arms (BV-AVEPC: 79.3%; [95% CI: 74.3, 83.8]; ABVE-PC: 79%; [95% CI: 73.9, 83.5]).
- The Response-Directed Radiotherapy Rate (RTR) was similar in the two treatment arms (BV-AVEPC: 40%; [95% CI: 9.7, 17.7]; ABVE-PC: 43%; [95% CI: 10.6, 18.8]).

The efficacy results from Study AHOD1331 demonstrate substantial evidence of effectiveness for brentuximab vedotin in combination with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide for pediatric patients with newly diagnosed, high risk cHL.

8.2. Review of Safety

The Applicant's Position:

Five studies contribute data for the integrated safety analyses of brentuximab vedotin in the pediatric population. The primary clinical data to support this application are based on the phase 3 randomized clinical trial AHOD1331, with supportive safety data from pediatric studies HLHR13, AHOD1221, C25002, and ANHL12P1.

The FDA's Assessment:

The FDA agrees that the primary source of clinical data to support this application and the evaluation of safety for the proposed indication is Study AHOD1331. The FDA's review of safety focused on data from AHOD1331. Data from studies HLHR13, AHOD1221, C25002, and ANHL12P1 are supportive for the proposed indication. Data from the supportive studies was used to inform Section 8.4 of the USPI. Refer to Section 7 for additional information regarding the supportive studies and Section 11 for additional information regarding labeling.

8.2.1. Safety Review Approach

Data:

To provide a comprehensive assessment and fully characterize the safety of brentuximab vedotin in pediatric subjects, 4 ISS populations are generated from subjects in AHOD1331, HLHR13, AHOD1221, C25002, and ANHL12P1 studies. These 4 ISS populations are defined as per the following:

- Pivotal AHOD1331 – This population includes all subjects who received at least 1 dose of study treatment in study AHOD1331. The experimental arm evaluated brentuximab vedotin in combination with AVEPC, and the ABVE-PC control arm evaluated ABVE-PC. Safety data from AHOD1331 will be presented by actual treatment regimen, not assigned treatments.

- Pediatric Combo Other – This pooled population includes all subjects who received at least 1 dose of brentuximab vedotin in combination with chemotherapy, regardless of dose level or schedule, chemotherapy agents, or disease indications in studies HLHR13, AHOD1221, and ANHL12P1.
- Pediatric Mono – This population includes all subjects who received at least 1 dose of brentuximab vedotin as monotherapy, regardless of dose level or schedule, in study C25002.
- Pediatric Total – This pooled population includes all subjects who received at least 1 dose of brentuximab vedotin monotherapy, or brentuximab vedotin in combination with chemotherapy, regardless of dose level or schedule, or disease indication in all 5 pediatric studies (AHOD1331, HLHR13, AHOD1221, C25002, and ANHL12P1). Pooling of data from all 5 pediatric studies provides a comprehensive evaluation of the overall safety profile of brentuximab vedotin in pediatric subjects.

The safety population summarized in this submission comprises 5 clinical trials of brentuximab vedotin monotherapy or brentuximab vedotin in combination with chemotherapy including 521 unique subjects who received brentuximab vedotin. All subjects treated with study drug received a starting dose of 1.2 to 1.8 mg/kg brentuximab vedotin.

Table 24: Applicant - Safety Population in Brentuximab Vedotin Studies

Safety Analysis Group	AHOD1331		Pediatric Combo Other (AHOD1221, ANHL12P1, HLHR13)	Pediatric Mono (C25002)	Pediatric Total (AHOD1331 BV Arm, AHOD1221, ANHL12P1, HLHR13, C25002)
	BV Arm (BV-AVEPC)	Control Arm (ABVE-PC)			
Patient Population	Previously untreated cHL and aged 2 to <22 years	Previously untreated cHL and aged 2 to <22 years	r/r cHL and aged >12 months to ≤30 years (AHOD1221) Previously untreated ALCL and aged <22 years (ANHL12P1) Previously untreated CD30+ cHL and aged ≤18 years (HLHR13)	r/r sALCL and aged 2 to <18 years, and r/r cHL and aged 5 to <18 years	Previously untreated cHL; r/r cHL; previously untreated ALCL; previously untreated CD30+ cHL; r/r sALCL and r/r cHL
Total number of subjects included	296	297	189	36	521

Source: m2.7.4 Table 2

The Applicant's Position:
The primary evidence of safety is derived from the pivotal trial AHOD1331, which represents a subject population relevant to the proposed indication (previously untreated high risk cHL).

The FDA's Assessment:
The FDA agrees that the primary source of safety data was the pivotal trial, AHOD1331, which represents the patient population relevant to the proposed indication. The FDA's safety analyses were conducted on the complete datasets provided by the Applicant for AHOD1331. The data cut-off date was December 31, 2021. The additional safety analyses based on the four additional ISS populations listed by the Applicant were considered supportive.

8.2.2. Review of the Safety Database

Overall Exposure

Data:
Brentuximab vedotin dose was calculated according to individual study protocols. Brentuximab vedotin administration and exposure for the integrated safety analysis set is summarized in Table 25. A summary of disposition is provided in ISS Table 14.1.1.

Table 25: Applicant – Summary of Treatment Administration (Safety Analysis Set)

	AHOD1331		Pediatric Combo Other (N=189)	Pediatric Mono (N=36)	Pediatric Total (N=521)
	BV-AVEPC (N=296)	ABVE-PC (N=297)			
Duration of study treatment[a] (weeks), n	296	297	189	36	521
Mean (STD)	15.1 (1.8)	15.0 (1.7)	19.1 (5.3)	22.7 (16.0)	17.1 (5.9)
Median	15.0	15.0	20.1	21.0	15.6
Min, Max	3, 24	1, 19	6, 50	3, 63	3, 63
Number of cycles administered[b], n	296	297	189	36	521
Mean (STD)	4.9 (0.5)	4.9 (0.5)	5.4 (1.7)	7.4 (5.2)	5.3 (1.8)
Median	5.0	5.0	6.0	7.0	5.0
Min, Max	1, 5	1, 5	2, 16	1, 20	1, 20
Cumulative BV dose administered[c] (mg/kg), n	296	NA	189	36	521
Mean (STD)	8.6 (1.2)	NA	12.0 (4.6)	12.7 (9.2)	10.1 (4.2)
Median	9.0	NA	10.8	9.7	9.0
Min, Max	0, 11	NA	0, 29	2, 35	0, 35

Pediatric Combo Other includes subjects who received any amount of BV in HLHR13, AHOD1221, and ANHL12P1; Pediatric Mono includes subjects who received any amount of BV in C25002; Pediatric Total includes subjects who received any amount of BV in any of the 5 studies.

[a] Planned duration of study chemotherapy was 15 weeks (5 cycles) for AHOD1331, 18 weeks (6 cycles) for ANHL12P1 and 20 weeks (6 cycles) for HLHR13. AHOD1221 and C25002 allowed up to 16 cycles of treatments. Treatment duration is calculated as defined for each study.

[b] Cycle with any amount (>0) of any component of study treatment received (for AHOD1221, ANHL12P1, HLHR13, C25002 and AHOD1331 BV-AVEPC arm) or with a non-missing reporting period start date (AHOD1331 ABVE-PC

arm). In AHOD1331 ABVE-PC control arm, while reporting period start date was collected, actual dosing amount was not collected.

[c] All BV treated subjects received non-zero dose of BV during study; minimum of 0 cumulative doses are due to rounding.

Source: ISS Table 14.4.1

The Applicant's Position:

In the AHOD1331 pivotal trial, the median duration of treatment was 15.0 weeks (range 3 to 24 weeks) with a median of 5 cycles in the BV-AVEPC arm, and 15.0 weeks (range 1 to 19 weeks) with a median of 5 cycles in the ABVE-PC arm. Subjects in AHOD1331 had a predefined maximum dosing of 5 cycles. The median duration of treatment in the Pediatric Combo Other and Pediatric Mono groups were 20.1 and 21.0 weeks, respectively. Majority of subjects in AHOD1331 completed planned therapy in both arms of the study: 92% in the BV-AVEPC arm, and 89% in the ABVE-PC arm.

The FDA's Assessment:

The FDA agrees with the Applicant's summary of exposure data. The majority of patients in both treatment arms (97%) received the 5 planned cycles of treatment, and 92% of patients in the BV-AVEPC arm and 89% in the ABVE-PC arm completed the planned therapy, which included completion of both chemotherapy and radiotherapy, where required.

Relevant characteristics of the safety population:

Data:

Demographic characteristics are summarized for the safety analysis set in Table 26.

Table 26: Applicant – Summary of Demographic Characteristics (Safety Analysis Set)

	AHOD1331		Pediatric Combo Other (N=189)	Pediatric Mono (N=36)	Pediatric Total (N=521)
	BV-AVEPC (N=296)	ABVE-PC (N=297)			
Age (yrs.)					
N	296	297	189	36	521
Mean (STD)	14.3 (3.1)	14.8 (3.0)	13.8 (4.6)	13.1 (3.2)	14.0 (3.7)
Median	15.0	15.0	15.0	14.0	15.0
Min, Max	3, 21	4, 21	2, 28	7, 18	2, 28
Age Category, n (%)					
<6 years	5 (2)	4 (1)	14 (7)	0	19 (4)
6 - <12 years	47 (16)	34 (11)	33 (17)	12 (33)	92 (18)
12 - <18 years	220 (74)	222 (75)	103 (54)	22 (61)	345 (66)
≥18 years	24 (8)	37 (12)	39 (21)	2 (6)	65 (12)
Race, n (%)					
American Indian or Alaska Native	1 (<1)	0	1 (1)	0	2 (<1)
Asian	7 (2)	9 (3)	9 (5)	2 (6)	18 (3)
Black or African American	34 (11)	33 (11)	32 (17)	0	66 (13)
Native Hawaiian or Other Pacific Islander	2 (1)	3 (1)	0	0	2 (<1)

	AHOD1331		Pediatric Combo Other (N=189)	Pediatric Mono (N=36)	Pediatric Total (N=521)
	BV-AVEPC (N=296)	ABVE-PC (N=297)			
White	221 (75)	218 (73)	129 (68)	31 (86)	381 (73)
Others[a]	5 (2)	0	7 (4)	2 (6)	14 (3)
Not Reported	8 (3)	20 (7)	2 (1)	1 (3)	11 (2)
Unknown	18 (6)	14 (5)	9 (5)	0	27 (5)
Ethnicity, n (%)					
Hispanic or Latino	62 (21)	57 (19)	28 (15)	4 (11)	94 (18)
Not Hispanic or Latino	217 (73)	225 (76)	155 (82)	29 (81)	401 (77)
Not reported / Unknown	17 (6)	15 (5)	6 (3)	3 (8)	26 (5)
Sex, n (%)					
Male	159 (54)	158 (53)	101 (53)	25 (69)	285 (55)
Female	137 (46)	139 (47)	88 (47)	11 (31)	236 (45)

[a] Other races included multiple races (n=5 in AHOD1331, n=1 in ANHL12P1, n=4 in HLHR13) and other (n=2 in HLHR13 and n=2 in C25002).
Source: ISS Table 14.2.1

Baseline characteristics are summarized in Table 27.

Table 27: Applicant – Summary of Baseline Disease Characteristics (Safety Analysis Set-cHL only)

	AHOD1331		Pediatric Combo Other (N=122) n (%)	Pediatric Mono (N=19) n (%)	Pediatric Total (N=437) n (%)
	BV-AVEPC (N=296) n (%)	ABVE-PC (N=297) n (%)			
Histologic diagnosis					
Classical Hodgkin disease, NOS	49 (17)	47 (16)	16 (13)	6 (32)	71 (16)
Classical nodular sclerosing	224 (76)	229 (77)	64 (52)	11 (58)	299 (68)
Classical mixed cellularity	19 (6)	18 (6)	5 (4)	2 (11)	26 (6)
Classical lymphocyte rich	4 (1)	2 (1)	4 (3)	0	8 (2)
Others[a]	0	0	4 (3)	0	4 (1)
Unknown[b]	0	1 (<1)	29 (24)	0	29 (7)
Disease stage at study entry					
IA, IIA	0	0	14 (11)	0	14 (3)
IIB[c]	60 (20)	61 (21)	17 (14)	0	77 (18)
IIIA	0	0	5 (4)	0	5 (1)
IIIB	59 (20)	57 (19)	24 (20)	0	83 (19)
IVA	86 (29)	86 (29)	21 (17)	0	107 (24)
IVB	91 (31)	93 (31)	41 (34)	0	132 (30)
Unknown[d]	0	0	0	19 (100)	19 (4)

[a] Others include 'Hodgkin's disease, NOS' in HLHR13 (n=1), (b) (6) Hodgkin lymphoma, nodular sclerosis, cellular phase' and (b) (6) Hodgkin Lymphoma' in AHOD1221 (n=1 and 2, respectively).
[b] Histological diagnosis subtype not collected in AHOD1221 part B subjects; 1 subject in AHOD1331 missing histologic diagnosis
[c] All AHOD1331 subjects in this category had Stage IIB disease with bulk.

[d] C25002 study did not collect stage at study entry. All subjects enrolled in the C25002 study had advanced stage cHL in the relapsed/refractory setting.
Source: ISS Table 14.2.2

The Applicant's Position:
Demographic characteristics were generally similar among the 296 and 297 subjects in the BV-AVEPC and ABVE-PC arms of the AHOD1331 trial, and the Pediatric Combo Other and Pediatric Total analysis groups. For the pivotal AHOD1331 study, the majority of the baseline factors were balanced between BV-AVEPC and ABVE-PC arms.

The FDA's Assessment:
The FDA agrees that in general, the demographic characteristics were similar among the patients in the two treatment arms in Study AHOD1331. See Section 8.1.2 for additional discussion of the demographic data for patients in Study AHOD1331.

Adequacy of the safety database:

Data:
The safety population comprises 5 clinical trials of brentuximab vedotin monotherapy or brentuximab vedotin in combination with chemotherapy including 521 unique subjects who received a starting dose of 1.2 to 1.8 mg/kg brentuximab vedotin. In the AHOD1331 pivotal trial, the median duration of treatment was 15.0 weeks (range 3 to 24 weeks) with a median of 5 cycles in the BV-AVEPC arm, and 15.0 weeks (range 1 to 19 weeks) with a median of 5 cycles in the ABVE-PC arm. The median duration of treatment in the Pediatric Combo Other and Pediatric Mono groups were 20.1 and 21.0 weeks, respectively.

The Applicant's Position:
The primary evidence of safety is derived from the pivotal trial AHOD1331, a randomized and controlled study in the population relevant to the proposed indication, which comprised 296 subjects treated with brentuximab vedotin with a median duration of treatment 15 weeks. Overall, patient demographic, other baseline, and disease characteristics were generally concordant with the target population in the US.

The FDA's Assessment:
The FDA agrees that safety analyses were primarily based on findings from the pivotal trial, AHOD1331. The FDA also agrees with the Applicant's statement that, overall patient demographic, other baseline, and disease characteristics were generally concordant with the US patient population of pediatric cHL. The size of the safety database from AHOD1331 was adequate to provide a reasonable estimate of the adverse reactions that may occur with treatment with brentuximab vedotin in pediatric patients with cHL, and adequate to inform regulatory decisions. However, the FDA identified several significant limitations with the safety data that was collected and submitted for AHOD1331. See Section 8.2.3. below for additional discussion of the limitations in safety data.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:
Each study sponsor had direct oversight responsibilities for quality assurance. For pivotal study AHOD1331, database management was performed by COG.

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 FDA disagrees with the Applicant's statement that "no issues with data integrity and/or analysis were identified that precluded inclusion of data in the analysis or conclusions regarding the safety assessment". While there were no issues with data integrity itself, the FDA identified several significant limitations with the safety data collected and submitted, which are detailed below. Several Information Requests were sent to the Applicant throughout to obtain additional safety information, as available.

The limitations identified include the following:

- The protocol had different reporting requirements for the two treatment arms. For the BV-AVEPC arm, expedited reports were required for all serious adverse events (SAEs) except Specific Protocol Exceptions to Expedited Reporting (SPEER) events, secondary AML, MDS, pregnancy and fetal and neonatal death. However, in the ABVE-PC arm, expedited reports were only required for Grade 4 unexpected adverse events and Grade 5 adverse events. Despite the fact that AHOD1331 was a large, randomized trial, because the reporting requirements were different between the two treatment arms, the FDA is unable to make safety comparisons between the two treatment arms.
- Per the protocol reporting guidance, most Grade 1 and 2 adverse events were generally not reported. Therefore, the overall incidences of adverse events that occurred in patients treated on AHOD1331 are not able to be determined.
- Serious adverse events were not included in the datasets. Therefore, the FDA was not able to conduct independent data analyses of the SAEs that occurred in patients treated on AHOD1331. However, COG refers to treatment-emergent SAEs interchangeably with AEs submitted as expedited reports to the NCI CTEP-AERS system in the AHOD1331 protocol and study case report forms (CRF). All SAEs were reported as expedited reports, as required in the protocol. However, as per above, because the reporting requirements were different between the two treatment arms, the FDA is unable to make comparisons regarding the occurrence of SAEs in the two treatment arms.

- Treatment discontinuations were recorded. However, specific adverse events leading to discontinuations or modifications were not collected in AHOD1331. Therefore, information on specific adverse events leading to treatment discontinuation or modifications is not available.
- Clinical laboratory tests/abnormalities were not captured in the clinical trial database and were not included in the CSR.

Categorization of Adverse Event

The Applicant's Position:
TEAEs are coded to standard PTs and SOCs using the MedDRA (Version 24.1) for all trials at the ISS level. TEAEs that were associated with disease progression were excluded from the safety analysis.

AE reporting, as outlined in the respective protocols to ensure safety of enrolled subjects, aimed to identify potential new safety signals when brentuximab vedotin is combined with chemotherapy as well as SAE and events requiring expedited reporting per CTEP AERS at DCTD/NCI. There were minor differences across studies in the definition of TEAEs as described below and captured in each study specific CSR and the ISS SAP.

TEAE grades were based on the grades as reported in each of the studies. Safety was evaluated according to the following versions of the NCI CTCAE unless otherwise specified:

- AHOD1331: modified Balis scale for peripheral neuropathy (PN) only; for other AEs, CTCAE version 4.0/version 5.0
- HLHR13, AHOD1221, ANHL12P1: version 4.0
- C25002: version 4.03

An SAE is defined as having non-missing SAE designation per investigator as recorded in the study case report forms (CRFs). SAEs were designated and recorded in study CRFs for studies HLHR13 and C25002. For studies AHOD1331, AHOD1221 part B, and ANHL12P1, SAE designation per the investigator was not available in the study CRFs. As specified in protocols AHOD1331, AHOD1221, and ANHL12P1, all TE SAEs and other protocol-specified AEs were required to be submitted as expedited reports to the CTEP-AERS unless the event met protocol specified exceptions. AEs submitted via expedited report per CRF are summarized together with SAEs.

Peripheral neuropathy: PN is considered an AESI due to the toxic effect of vedotin on microtubules. AEs of PN are considered AEs of special interest within the scope of the Written Request. PN is defined in AHOD1331 as investigator-assessed peripheral sensory neuropathy or peripheral motor neuropathy according to the modified Balis scale for pediatric subjects. The Balis instrument has been commonly used to grade neurotoxicity occurring in children and is based on a "1–4" scale. For all the other studies, PN is identified by the peripheral neuropathy

standardized MedDRA queries (SMQ) broad search which includes peripheral sensory neuropathy and peripheral motor neuropathy.

The number of total deaths, deaths that occurred within safety reporting period, and deaths that occurred beyond the safety reporting period are summarized by primary cause of death. The safety reporting period is the time interval when TEAEs were reported for each of the studies as defined above. Death information is also listed by subject in individual study CSRs.

The FDA's Assessment:

In general, the FDA agrees with the Applicant's description of the categorization of adverse events. For AHOD1331, adverse events, except for peripheral sensory/motor neuropathy, were graded using CTCAE version 4.0 or 5.0, as recorded on CRF, and coded by MedDRA Version 24.1. Peripheral sensory/motor neuropathy were graded using the modified Balis scale (Section 19.5). Treatment-emergent adverse events (TEAEs) were defined as events that occurred between the first reporting period start date and the last chemotherapy reporting period end date. Per the protocol, most AEs of Grade 1 or 2 in severity were not required to be collected. However, Grade ≥2 peripheral neuropathy by Balis scale was required to be reported in both treatment arms.

AHOD1331 Expedited Reporting Requirements – Serious Adverse Events:

Any AE that is serious qualifies for expedited reporting. An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. A Serious Adverse Event (SAE) is any adverse drug event (experience) occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- An adverse event resulting in inpatient hospitalization or prolongation of existing hospitalization (for ≥24 hours). This does not include hospitalizations that are part of routine medical practice.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

In AHOD1331, SAEs that were clinically meaningful, regardless of grade, were required to be reported unless one of the following criteria were met:

- In the BV-AVEPC arm: Events that met the Specific Protocol Exceptions to Expedited Reporting (SPEER) definition for brentuximab vedotin were exempted for reporting as SAEs.

- In the ABVE-PC arm: Only Grade 4 unexpected AEs and Grade 5 events were required to be reported as SAEs.

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a list of reported and/or potential AEs associated with an agent. The Specific Protocol Exceptions to Expedited Reporting appears in a separate column. Per the AHOD1331 protocol, AEs listed in the SPEER were to be reported only if they exceeded the grade noted in parentheses next to the AE in the SPEER. The CAEPR with SPEER for Brentuximab vedotin is provided in Table 28 below.

Table 28: Comprehensive Adverse Events and Potential Risks List (CAEPR) for Brentuximab Vedotin

Version 2.2, August 9, 2013[1]

Adverse Events with Possible Relationship to SGN-35 (Brentuximab Vedotin) (CTCAE 4.0 Term) [n= 249]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
GASTROINTESTINAL DISORDERS			
	Constipation		
Diarrhea			*Diarrhea (Gr 2)*
Nausea			*Nausea (Gr 2)*
		Pancreatitis	
	Vomiting		*Vomiting (Gr 2)*
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills Edema limbs		
Fatigue			*Fatigue (Gr 2)*
Fever			*Fever (Gr 2)*
	Infusion related reaction		
IMMUNE SYSTEM DISORDERS			
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Upper respiratory infection		*Upper respiratory infection (Gr 2)*
INVESTIGATIONS			
Neutrophil count decreased			*Neutrophil count decreased (Gr 2)*
	Platelet count decreased		
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
		Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		*Arthralgia (Gr 2)*
	Back pain		
	Myalgia		*Myalgia (Gr 2)*
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Headache		*Headache (Gr 2)*
		Nervous system disorders - Other (progressive multifocal leukoencephalopathy)	
	Peripheral motor neuropathy		
Peripheral sensory neuropathy			*Peripheral sensory neuropathy (Gr 2)*
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Dyspnea		
		Pneumonitis[2]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		*Alopecia Gr 2)*
	Pruritus Rash maculo-papular		*Pruritus (Gr 2)*
		Stevens-Johnson syndrome	

Source: AHOD1331 Protocol

Routine Clinical Tests

Data:
Routine clinical evaluations were performed during study treatment for study AHOD1331, AHOD1221, and ANHL12P1; however, routine laboratory results were not collected per CRF design. Study C25002 collected clinical laboratory data in the CRF and evaluations are summarized in the CSR (m5.3.5.2).

The Applicant's Position:
Routine clinical laboratory data that were collected as AEs were analyzed within the context of overall AEs.

The FDA's Assessment:
The FDA agrees with the Applicant's statement regarding routine clinical laboratory data. In AHOD1331, clinical laboratory tests were performed for study treatment, but were not captured in the clinical trial database, and were not included in the CSR. Laboratory abnormalities may have been reported as AEs for routinely monitored laboratory parameters. However, the AE reporting of laboratory abnormalities underestimates the true incidence. An Information Request was sent to the Applicant to request an integrated analysis using AE data and any available laboratory data to inform the incidence of specific Grade and Grade ≥3 toxicities (neutropenia, thrombocytopenia, anemia, hyperglycemia, and AST/ALT elevation) in order to better inform labeling. The intent was to identify any patients that may have had a laboratory abnormality that was not reported as an adverse event. The Applicant responded that since laboratory data from AHOD1331 were not collected in the clinical trial database, and reside only in the individual patient medical records, they are unable to provide an integrated analysis for AHOD1331.

The Applicant did provide an integrated analysis for the following pediatric trials included in this application:

- Brentuximab vedotin monotherapy (ISS Pediatric Mono): Integrated AE and laboratory data from Study C25002
- Brentuximab vedotin in combination with other chemotherapy regimens (ISS Pediatric Combo Other): Integrated AE data from Studies HLHR13, AHOD1221 and ANHL12P1, and laboratory data from Study HLHR13.

In the two studies from which laboratory data were integrated (C25002 and HLHR13), the integrated data include all available laboratory values within each study's safety reporting period for the requested toxicities of cytopenias, hyperglycemia and transaminase elevation. See results below under "laboratory findings". The data from these trials showed consistency with the Grade ≥3 laboratory abnormalities reported in the AHOD1331 study, providing supportive evidence for the use of Grade ≥3 laboratory adverse events reported in AHOD1331.

8.2.4. Safety Results

Deaths

Data:

A summary of deaths within /outside of safety reporting periods is provided in Table 29. The majority of the deaths across all safety analysis groups occurred after the safety reporting period and were disease related.

Table 29: Applicant – Summary of Deaths Within/Outside of Safety Reporting Periods (Safety Analysis Set)

	AHOD1331		Pediatric Combo Other (N=189) n (%)	Pediatric Mono (N=36) n (%)	Pediatric Total (N=521) n (%)
	BV-AVEPC (N=296) n (%)	ABVE-PC (N=297) n (%)			
Overall	2 (1)	4 (1)	12 (6)	8 (22)	22 (4)
Primary Cause of Death					
Disease related deaths	1 (<1)	2 (1)	7 (4)	8 (22)	16 (3)
Other	1 (<1)	2 (1)	5 (3)	0	6 (1)
Deaths within the safety reporting period[a]	0	0	1 (1)	1 (3)	2 (<1)
Primary Cause of Death					
Disease related deaths	0	0	0	1 (3)	1 (<1)
Other	0	0	1 (1)	0	1 (<1)
Deaths after the safety reporting period[a]	2 (1)	4 (1)	11 (6)	7 (19)	20 (4)
Primary Cause of Death					
Disease related deaths	1 (<1)	2 (1)	7 (4)	7 (19)	15 (3)
Other	1 (<1)	2 (1)	4 (2)	0	5 (1)

[a] Safety reporting period as defined in ISS SAP Section 3.1.3.
Source: ISS Table 14.7.1

The Applicant's Position:

In the AHOD1331 study, 6 deaths were reported in total, 2 (1%) on the BV-AVEPC arm and 4 (1%) on the ABVE-PC control arm, and all were outside of the safety reporting period during long-term follow-up. Three of these deaths were disease related, the other 3 deaths were due to other causes. Of the 3 subjects who died as a result of other cause, 1 subject each in the ABVE-PC arm died from fungal infection and a car crash, and 1 subject in the BV-AVEPC arm died as a result of respiratory failure due to pulmonary hemorrhage 6 months after entering follow-up. Deaths within and after the safety reporting period were more frequently reported in the Pediatric Combo Other and Pediatric Mono groups. The majority of these deaths were disease related.

The FDA's Assessment:

The FDA agrees with the Applicant's description and assessment of the deaths that occurred in

patients enrolled in AHOD1331. A total of six patients died (BV-AVEPC: N=2; ABVE-PC: N=4). There were no deaths during the safety reporting period, defined as the first reporting period start date to the last chemotherapy end date. A summary of the FDA's analysis of the deaths for Study AHOD1331 is presented in Table 30 below.

Table 30: AHOD1331 - Summary of Deaths

	BV-AVEPC N=296 n(%)	ABVE-PC N=297 n(%)	Total N=593 n(%)
Total Deaths	2 (1)	4 (1)	6 (1)
Deaths during safety reporting period*	0	0	0
Deaths after safety reporting period	2 (1)	4 (1)	6 (1)
Cause of Death			
Disease-related	1 (<1)	2 (1)	3 (1)
Respiratory failure/pulmonary hemorrhage	1 (<1)	0	1 (<1)
Fungal infection	0	1 (<1)	1 (<1)
Car accident	0	1 (<1)	1 (<1)

* Safety Reporting Period = First reporting period start date to the last chemotherapy reporting period end date
Source: FDA Analysis

Serious Adverse Events

Data:

Per study protocol, for subjects who received BV in AHOD1331, AHOD1221, and ANHL12P1, expedited reports to the NCI via CTEP-AERS were required for all SAEs, secondary acute myeloid leukemia and myelodysplastic syndrome, pregnancy, fetal death, and neonatal death. However certain SAEs were not required to be submitted as expedited reports if the event met the Specific Protocol Exceptions to Expedited Reporting definition included in the protocol. For AHOD1331, expedited reporting on the ABVE-PC control arm was only required for Grade 4 unexpected AEs and Grade 5 AEs, therefore it is expected there will be an imbalance in the number of expedited reports between the BV-AVEPC arm and ABVE-PC arm due to the different reporting requirements. AHOD1221 part A, HLHR13 and C25002 had standard SAE designations collected in the study.

SAEs or TEAEs submitted as an expedited report are summarized in Table 31.

Table 31: Applicant – Treatment-Emergent SAEs or TEAEs Submitted for Expedited Reporting in ≥2% of Subjects by PT in AHOD1331 BV-AVEPC Arm (Safety Analysis Set)

Preferred Term	AHOD1331		Pediatric Combo Other (N=189) n (%)	Pediatric Mono (N=36) n (%)	Pediatric Total (N=521) n (%)
	BV-AVEPC (N=296) n (%)	ABVE-PC (N=297) n (%)			
Subjects with any event	64 (22)	11 (4)	43 (23)	8 (22)	115 (22)
Hypotension	10 (3)	4 (1)	4 (2)	0	14 (3)
Febrile neutropenia	9 (3)	4 (1)	5 (3)	1 (3)	15 (3)

Preferred Term	AHOD1331		Pediatric Combo Other (N=189) n (%)	Pediatric Mono (N=36) n (%)	Pediatric Total (N=521) n (%)
	BV-AVEPC (N=296) n (%)	ABVE-PC (N=297) n (%)			
Colitis	7 (2)	0	0	0	7 (1)
Embolism	7 (2)	0	4 (2)	0	11 (2)
Sepsis	7 (2)	5 (2)	2 (1)	0	9 (2)
Abdominal pain	6 (2)	0	0	0	6 (1)
Peripheral sensory neuropathy	6 (2)	0	0	0	6 (1)
Stomatitis	6 (2)	0	12 (6)	0	18 (3)
White blood cell count decreased	6 (2)	0	1 (1)	0	7 (1)
Dehydration	5 (2)	0	1 (1)	0	6 (1)

Source: ISS Table 14.5.8

The Applicant's Position:

In the AHOD1331 BV-AVEPC arm, 64 subjects (22%) experienced at least 1 SAE or TEAE submitted as an expedited report compared to 11 subjects (4%) in the ABVE-PC arm. An imbalance in the number of expedited reports between the BV-AVEPC arm and ABVE-PC arm was expected due to the different reporting requirements. Overall, when analyzed by PT the incidence of treatment-emergent SAEs or TEAEs submitted as expedited reports was low and similar across all brentuximab vedotin groups.

The FDA's Assessment:

The FDA agrees with the Applicant's description of adverse events that were submitted as expedited reports. Because AHOD1331 is a COG study, the COG methodologies for data collection and reporting were used. In AHOD1331, SAEs that were clinically meaningful, regardless of grade, were required to be reported unless one of the following criteria were met:

- In the BV-AVEPC arm: Events that met the Specific Protocol Exceptions to Expedited Reporting (SPEER) definition for brentuximab vedotin were exempted for reporting as SAEs.
- In the ABVE-PC arm: Only Grade 4 unexpected AEs and Grade 5 events were required to be reported as SAEs.

The FDA agrees that the imbalance in the number of expedited reports between the two treatment arms may have been due to the different reporting requirements for the two arms. However, because of these different reporting requirements, direct comparisons of the incidence of SAEs/Expedited reports between the two arms are not able to be made. In the brentuximab arm, the most common AEs submitted as expedited reports included hypotension (N=10; 3%), febrile neutropenia (N=9; 3%), sepsis (N=7; 2%), colitis (N=7; 2%), and embolism (N=7; 2%).

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:

For AHOD1331, AHOD1221, and ANHL12P1, study drug discontinuations were not linked to specific AEs in the study CRF. Therefore, information on AEs leading to study drug

discontinuation is unavailable for these studies. For study HLHR13, AEs leading to discontinuation of treatment are presented in m5.3.5.2, HLHR13 CSR Section 12.2.1.3. TEAEs leading to study drug discontinuation are available from m5.3.5.2, C25002 CSR, Section 12.3.3.1

The FDA's Assessment:
The FDA agrees that information leading to study drug discontinuation is not available for AHOD1331. An Information Request was sent to the Applicant to request all available data on adverse events that lead to treatment discontinuations and dose modifications for patients in both treatment arms. The Applicant provided all available information. The FDA notes that overall, 97% of patients in both treatment arms received all 5 cycles of planned chemotherapy per protocol. Approximately 3% of patients discontinued treatment early. Reasons for discontinuation of any component of treatment, if applicable, were collected at the end of therapy, and included "physician decision", "progressive disease", "patient or guardian refusal of further treatment", "eligibility issues", and "missing". "Adverse event" was not listed as a reason for discontinuation of treatment in the CRF. Therefore, treatment discontinuations could not be linked to specific adverse events. However, treatment discontinuations were low overall, and the majority of patients received the planned regimen, indicating acceptable safety and tolerability of the regimen.

Dose Interruption/Reduction Due to Adverse Effects

The Applicant's Position:
For AHOD1331, AHOD1221, and ANHL12P1, dose modifications were not linked to specific AEs in the study CRF. Therefore, information on AEs leading to dose modification is unavailable for these studies. TEAEs leading to dose modification for study C25002 are presented within the individual study CSR (m5.3.5.2). For study HLHR13, dose modifications due to specific adverse events are not presented as they were not consistently captured in the study database. Summaries of dose modifications, including those due to toxicity, are presented in m5.3.5.2, HLHR13 CSR, Section 10.6.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment of dose modifications due to adverse events. Similar to treatment discontinuations, dose modifications due to adverse events were not collected for AHOD1331. The FDA requested additional information regarding dose modifications from the Applicant. Overall data for dose modifications were collected by cycle and included in the planned and unplanned modification designations on the CRF. Overall, dose modifications (both planned and unplanned) were comparable between the treatment arms. The majority of patients in both treatment arms did not require a brentuximab dose modification. A summary of the dose modifications for Study AHOD1331 is provided in Table 32 below.

Table 32: AHOD1331 - Dose Modifications

	ABVE-PC (N=297) n (%)	BV-AVEPC (N=296) n (%)
Subjects with any dose modification [a]	77 (26)	85 (29)
Planned	46 (15)	51 (17)
Unplanned	39 (13)	45 (15)
Subjects with BV modification [a]	NA	24 (8)
Planned	NA	16 (5)
Unplanned	NA	10 (3)
Subjects with any Vincristine modification [a]	12 (4)	40 (14)
Planned	9 (3)	33 (11)
Unplanned	4 (1)	10 (3)

a. Dose modifications included planned and unplanned modifications collected on CRF. Planned = treatment was changed according to protocol guidelines; unplanned = treatment change was not part of protocol guidelines. Subject is counted once under each reason of dose modification.
Source: AHOD1331 CSR, Table 14.4.2

Significant Adverse Events

Data:
Grade 3 or higher TEAEs occurring in ≥4% of subjects in the BV-AVEPC arm of AHOD1331, regardless of causality, are presented in Table 33.

Table 33: Applicant - Treatment-emergent Grade 3 and Higher AEs Reported in ≥4% of Subjects by PT in the AHOD1331 BV-AVEPC Arm (Safety Analysis Set)

	AHOD1331		Pediatric Combo Other (N=189) n (%)	Pediatric Mono (N=36) n (%)	Pediatric Total (N=521) n (%)
Preferred Term	BV-AVEPC (N=296) n (%)	ABVE-PC (N=297) n (%)			
Subjects with any event	220 (74)	203 (68)	173 (92)	16 (44)	409 (79)
Neutrophil count decreased	149 (50)	119 (40)	123 (65)	1 (3)	273 (52)
White blood cell count decreased	128 (43)	105 (35)	87 (46)	0	215 (41)
Anaemia	108 (36)	90 (30)	44 (23)	1 (3)	153 (29)
Platelet count decreased	96 (32)	81 (27)	41 (22)	0	137 (26)
Febrile neutropenia	92 (31)	96 (32)	41 (22)	1 (3)	134 (26)
Lymphocyte count decreased	71 (24)	77 (26)	81 (43)	0	152 (29)
Stomatitis	31 (10)	21 (7)	22 (12)	0	53 (10)

Preferred Term	AHOD1331		Pediatric Combo Other (N=189) n (%)	Pediatric Mono (N=36) n (%)	Pediatric Total (N=521) n (%)
	BV-AVEPC (N=296) n (%)	ABVE-PC (N=297) n (%)			
Hypokalaemia	18 (6)	20 (7)	15 (8)	1 (3)	34 (7)
Peripheral sensory neuropathy	17 (6)	13 (4)	1 (1)	1 (3)	19 (4)
Alanine aminotransferase increased	12 (4)	9 (3)	34 (18)	0	46 (9)
Hypotension	11 (4)	17 (6)	4 (2)	0	15 (3)
Nausea	11 (4)	6 (2)	5 (3)	0	16 (3)
Vomiting	11 (4)	4 (1)	6 (3)	0	17 (3)

Source: ISS Table 14.5.9

The Applicant's Position:

In the pivotal AHOD1331 study, the frequency and types of AEs were generally similar in both treatment arms. The most frequently reported Grade 3 or higher TEAEs were hematologic lab abnormalities and stomatitis in both the BV-AVEPC and ABVE-PC arms. Compared with the ABVE-PC arm, neutrophil count decrease was reported at a higher rate on BV-AVEPC arm, however, the frequency of grade 3 or higher febrile neutropenia was similar across the 2 arms. Similar types of frequently reported Grade 3 or higher TEAEs were observed in the Pediatric Combo Other group with some variations in overall frequencies for certain events which may reflect the various chemotherapy combinations used (i.e., gemcitabine, AEPA/CAPDac) and disease populations studied (i.e., r/r cHL, and sALCL).

The FDA's Assessment:

The FDA's analysis of Grade ≥3 adverse events for Study AHOD1331 was consistent with the Applicant's. There were no Grade 5 adverse events in either treatment arm. The FDA agrees with the Applicant's statement that the frequency and types of AEs were generally similar in both treatment arms. However, the FDA notes that the following Grade 3-4 adverse events occurred with ≥5% greater frequency in the BV-AVEPC arm compared to the ABVE-PC arm: Grade 4 neutropenia (BV-AVEPC: 43%; ABVE-PC: 36%), Grade 4 thrombocytopenia (BV-AVEPC: 22%; ABVE-PC: 16%), and Grade 3 anemia (BV-AVEPC: 35%; ABVE-PC: 28%). The FDA's summary of Grade 3 and 4 adverse events is provided in Table 34 below.

Table 34: AHOD1331 - Adverse Reactions Reported in ≥2% of Patients Treated with BV-AVEPC

	BV-AVEPC N=296 n(%)		ABVE-PC N=297 n(%)	
System Organ Class Preferred Term	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Blood and lymphatic system disorders				
Anemia	103 (35)	5 (1.7)	84 (28)	6 (2.0)
Febrile neutropenia	82 (28)	10 (3.4)	91 (31)	5 (1.7)
Lymphopenia	38 (13)	33 (11)	23 (7.7)	54 (18)
Thrombocytopenia[a]	32 (10)	65 (22)	32 (11)	49 (16)
Neutropenia	23 (7.8)	126 (43)	13 (4.4)	106 (36)
Gastrointestinal disorders				
Stomatitis	31 (10)	0 (0)	21 (7.1)	0 (0)
Nausea	11 (3.7)	0 (0)	6 (2.0)	0 (0)
Vomiting	11 (3.7)	0 (0)	4 (1.3)	0 (0)
Diarrhea	7 (2.4)	0 (0)	1 (0.3)	0 (0)
Colitis	6 (2.0)	1 (0.3)	3 (1.0)	0 (0)
Infections and infestations				
Infections[b]	27 (9.1)	8 (2.7)	21 (7.1)	10 (3.4)
Nervous system disorders				
Peripheral sensory neuropathy	16 (5.4)	0 (0)	11 (3.7)	0 (0)
Metabolism and nutrition disorders				
Hypokalemia	16 (5.4)	2 (0.7)	17 (5.7)	3 (1.0)
Hyponatremia	10 (3.4)	0 (0)	9 (3.0)	0 (0)
Decreased appetite	8 (2.7)	0 (0)	5 (1.7)	0 (0)
Dehydration	8 (2.7)	0 (0)	3 (1.0)	0 (0)
Hepatobiliary disorders				
Alanine aminotransferase increased	11 (3.7)	1 (0.3)	8 (2.7)	1 (0.3)
General disorders and administration site conditions				
Infusion-related reactions[c]	10 (3.0)	1 (0.3)	16 (5.4)	3 (1.0)

[a] Includes preferred terms: thrombocytopenia and platelet count decreased

[b] Includes preferred terms: 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 preferred terms: anaphylactic reaction, hypersensitivity, drug hypersensitivity, infusion related reaction, and bronchospasm

Source: FDA Analysis

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Per study protocol, only certain pre-specified categories of AEs were required to be reported on the AHOD1331, AHOD1221, and ANHL12P1 studies. Most notably, Grade 1 and Grade 2 AEs were not required to be systematically reported per protocol, unless leading to a treatment dose modification, included in an expedited safety report, or belonging to pre-specified categories for that protocol (PN for AHOD1331; respiratory, PN, and skin AEs for AHOD1221). Additionally, some asymptomatic laboratory abnormalities for routinely monitored labs were also captured as AEs in AHOD1331, AHOD1221, and ANHL12P1. HLHR13 and C25002 studies had standard safety collection for all TEAEs and SAEs. An overview of TEAEs reported per study protocol, across safety analysis groups is presented in Table 35.

Table 35: Applicant – Summary of TEAEs (Safety Analysis Set)

	AHOD1331		Pediatric Combo Other (N=189) n (%)	Pediatric Mono (N=36) n (%)	Pediatric Total (N=521) n (%)
	BV-AVEPC (N=296) n (%)	ABVE-PC (N=297) n (%)			
Subjects with any TEAE	225 (76)	216 (73)	174 (92)	36 (100)	435 (83)
With any ≥ Grade 3 TEAE	220 (74)	203 (68)	173 (92)	16 (44)	409 (79)
Subjects with any TE SAE or TEAE submitted expedited report[a]	64 (22)	11 (4)	43 (23)	8 (22)	115 (22)
Max severity of TEAE					
Grade 1	0	0	0	9 (25)	9 (2)
Grade 2	5 (2)	13 (4)	1 (1)	11 (31)	17 (3)
Grade 3	66 (22)	72 (24)	48 (25)	13 (36)	127 (24)
Grade 4	154 (52)	131 (44)	124 (66)	2 (6)	280 (54)
Grade 5	0	0	1 (1)	1 (3)	2 (<1)

a AHOD1331 study protocol had different expedited reporting requirements for BV-AVEPC arm and ABVE-PC arm.
Source: ISS Table 14.5.1

The most commonly reported TEAEs (occurring in ≥4% of subjects in the BV-AVEPC arm of AHOD1331, regardless of causality) are presented in Table 36.

Table 36: Applicant – TEAEs with Incidence Rate ≥4% by PT in the AHOD1331 BV-AVEPC Arm (Integrated Safety Analysis Set)

	AHOD1331		Pediatric Combo Other (N=189) n (%)	Pediatric Mono (N=36) n (%)	Pediatric Total (N=521) n (%)
Preferred Term	BV-AVEPC (N=296) n (%)	ABVE-PC (N=297) n (%)			
Subjects with any event	225 (76)	216 (73)	174 (92)	36 (100)	435 (83)
Neutrophil count decreased	149 (50)	119 (40)	133 (70)	2 (6)	284 (55)
White blood cell count decreased	128 (43)	105 (35)	111 (59)	1 (3)	240 (46)
Anaemia	110 (37)	91 (31)	106 (56)	2 (6)	218 (42)

Preferred Term	AHOD1331		Pediatric Combo Other (N=189) n (%)	Pediatric Mono (N=36) n (%)	Pediatric Total (N=521) n (%)
	BV-AVEPC (N=296) n (%)	ABVE-PC (N=297) n (%)			
Platelet count decreased	96 (32)	81 (27)	93 (49)	0	189 (36)
Febrile neutropenia	92 (31)	96 (32)	41 (22)	1 (3)	134 (26)
Lymphocyte count decreased	71 (24)	77 (26)	106 (56)	3 (8)	180 (35)
Peripheral sensory neuropathy	48 (16)	42 (14)	17 (9)	4 (11)	69 (13)
Stomatitis	34 (11)	22 (7)	43 (23)	0	77 (15)
Hypokalaemia	18 (6)	20 (7)	34 (18)	3 (8)	55 (11)
Peripheral motor neuropathy	17 (6)	28 (9)	3 (2)	1 (3)	21 (4)
Alanine aminotransferase increased	13 (4)	10 (3)	94 (50)	1 (3)	108 (21)
Nausea	13 (4)	6 (2)	63 (33)	13 (36)	89 (17)
Vomiting	12 (4)	4 (1)	50 (26)	6 (17)	68 (13)
Hypotension	11 (4)	17 (6)	11 (6)	0	22 (4)

Source: ISS Table 14.5.3

The Applicant's Position:

In the pivotal study AHOD1331, the overall rate of any TEAEs were similar between the BV-AVEPC and ABVE-PC arms, with 225 subjects (76%) and 216 subjects (73%), respectively. The most commonly reported TEAEs in the AHOD1331 study were mostly hematologic lab related and generally consistent with the other analysis groups. Compared to the AHOD1331 BV-AVEPC arm, other frequently reported (≥20%) TEAEs in the Pediatric Combo Other or Pediatric Mono analysis groups included stomatitis, nausea, vomiting, weight increased, alanine aminotransferase increased, aspartate aminotransferase increased, pyrexia, hyperglycemia, and hypoalbuminemia. Some of these differences may reflect different AE reporting requirements per study protocols as well as different chemotherapy combinations and disease populations studied.

The AE profile seen on the BV-AVEPC arm in the AHOD1331 study and the supportive safety analysis groups were generally consistent with the established safety profile reported in the brentuximab vedotin prescribing information for adult cHL subjects. For adults with previously untreated Stage III or IV cHL, brentuximab vedotin in combination with AVD is known to have a tolerable and manageable safety profile. The most common adverse reactions (≥20%) in combination with AVD in this setting in adults included peripheral neuropathy, neutropenia, nausea, constipation, vomiting, fatigue, diarrhea, pyrexia, alopecia, decreased weight, abdominal pain, anemia, and stomatitis (ADCETRIS Prescribing Information, February 2022).

The FDA's Assessment:
The FDA agrees with the Applicant's statement that, based on the data available and provided, the overall rates of TEAEs in AHOD1331 were similar in the two treatment arms. However, the FDA notes that, per the AHOD1331 protocol, Grade 1 and 2 AEs were generally not reported. Therefore, the true incidence of TEAEs, including AEs of all severities, is not able to be determined. The most common AEs in both treatment arms were neutropenia, leukopenia, anemia, thrombocytopenia, and febrile neutropenia. The FDA agrees with the Applicant's statement that the AE profile seen on the BV-AVEPC arm in the AHOD1331 study was generally consistent with the established safety profile reported in the brentuximab vedotin prescribing information for adult patients with cHL.

Laboratory Findings

Data:
Some abnormal clinical laboratory values were reported as AEs in AHOD1331, AHOD1221, and ANHL12P1 for routinely monitored labs, even if the abnormality was asymptomatic. Study C25002 collected clinical laboratory data and evaluations are summarized in the CSR (m5.3.5.2).

The Applicant's Position:
Integrated analysis for clinical laboratory data was not performed due to limitations in data availability.

The FDA's Assessment:
The FDA agrees with the Applicant's statement that an integrated analysis for clinical laboratory data from Study AHOD1331 was not performed due to limitations in data (see above). In AHOD1331, clinical laboratory tests were performed for study treatment, but were not captured in the clinical trial database, and were not included in the CSR. Laboratory abnormalities may have been reported as AEs for routinely monitored laboratory parameters. However, the AE reporting of laboratory abnormalities underestimates the true incidence. The FDA sent an Information Request to the Applicant requesting additional information to better inform labeling. As per above, The Applicant provided an integrated analysis for the following pediatric trials included in this application:

- Brentuximab vedotin monotherapy (ISS Pediatric Mono): Integrated AE and laboratory data from Study C25002
- Brentuximab vedotin in combination with other chemotherapy regimens (ISS Pediatric Combo Other): Integrated AE data from Studies HLHR13, AHOD1221 and ANHL12P1, and laboratory data from Study HLHR13.

Table 37 below, presents a side-by-side comparison of AE data only versus combined AE and laboratory data (from Study HLHR13) for the ISS Pediatric Combo Other population. There were no meaningful differences in the frequencies of laboratory abnormalities of All Grade and Grade ≥3 cytopenias, hyperglycemia, and transaminase elevation after combining the laboratory data with the AE data.

Table 37: Comparison of Laboratory Abnormality Frequencies in Pediatric Combo Other (N=189)

	All Grade		Grade 3 or Higher	
Preferred Term	AE Only (N=189) n (%)	AE + Lab Data (N=189) n (%)	AE Only (N=189) n (%)	AE + Lab Data (N=189) n (%)
Neutropenia	133 (70)	134 (71)	123 (65)	126 (67)
Neutrophil count decreased	133 (70)	134 (71)	123 (65)	126 (67)
Neutropenia	0	0	0	0
Thrombocytopenia	93 (49)	94 (50)	41 (22)	42 (22)
Platelet count decreased	93 (49)	94 (50)	41 (22)	42 (22)
Thrombocytopenia	0	0	0	0
Anaemia	106 (56)	110 (58)	44 (23)	45 (24)
Anaemia	106 (56)	110 (58)	44 (23)	45 (24)
RBC count decreased	0	0	0	0
Hyperglycaemia	52 (28)	54 (29)	13 (7)	13 (7)
Aspartate aminotransferase increased	54 (29)	63 (33)	20 (11)	21 (11)
Alanine aminotransferase increased	94 (50)	100 (53)	34 (18)	34 (18)

Source: Applicant's Response to Clinical IR; September 30, 2022.

Table 38 below presents a comparison of AE data only compared to combined AE and laboratory data for the ISS Pediatric Mono population (Study C25002). After combining laboratory data with AE data, the frequencies of All Grade neutropenia, thrombocytopenia, anemia, hyperglycemia, AST increased, and ALT increased all increased. These results suggest that the AE data underestimated the true occurrence of laboratory abnormities in this study.

However, overall, studies C25002 and HLHR13 demonstrated good concordance of TEAEs and laboratory values for Grade ≥3 laboratory abnormalities. Therefore, the FDA assessed that Grade ≥3 laboratory TEAEs may be representative of the occurrence of Grade ≥3 laboratory abnormalities.

The data provided from Study AHOD1331 were adequate to inform the incidence of Grade ≥3 relevant laboratory toxicities, including cytopenias, hyperglycemia, and AST/ALT elevation, and were sufficient to inform labeling.

Table 38: Comparison of Laboratory Abnormality Frequencies in Pediatric Monotherapy (N=36)

	All Grade		Grade 3 or Higher	
Preferred Term	AE Only (N=36) n (%)	AE + Lab Data (N=36) n (%)	AE Data (N=36) n (%)	AE + Lab Data (N=36) n (%)
Neutropenia	7 (19)	24 (67)	5 (14)	5 (14)
Neutrophil count decreased	2 (6)	24 (67)	1 (3)	2 (6)
Neutropenia	5 (14)	5 (14)	4 (11)	4 (11)
Thrombocytopenia	1 (3)	18 (50)	1 (3)	1 (3)
Platelet count decreased	0	18 (50)	0	0
Thrombocytopenia	1 (3)	1 (3)	1 (3)	1 (3)
Anaemia	2 (6)	22 (61)	1 (3)	1 (3)
Anaemia	2 (6)	22 (61)	1 (3)	1 (3)
RBC count decreased	0	0	0	0
Hyperglycaemia	0	14 (39)	0	0
Aspartate aminotransferase increased	1 (3)	12 (33)	0	0
Alanine aminotransferase increased	1 (3)	16 (44)	0	0

Source: Applicant's Response to Clinical IR; September 30, 2022.

Vital Signs

Data:
For study C25002 vital signs and weight data were measured from screening through the last treatment cycle for safety population (m5.3.5.2, C25002 CSR, Section 12.5.1).

The Applicant's Position:
Vital signs were not analyzed as part of this submission.

The FDA's Assessment:
The FDA agrees with the Applicant's statement that vital signs were not analyzed as part of this submission. Per the AHOD1331 CSR, vital signs may have been performed per protocol, but were not captured in the clinical trial database, and as such were not presented in the CSR.

Electrocardiograms (ECGs)

Data:
No ECG data are available from the studies included in this submission.

The Applicant's Position:
N/A

The FDA's Assessment:
The FDA agrees that no ECG data are available from the studies included in this submission.

QT

Data:
No QT data are available from the studies included in this submission.

The Applicant's Position:
N/A

The FDA's Assessment:
The FDA agrees that no QT data are available from the studies included in this submission.

Immunogenicity

Data:
There are no relevant data in this submission.

The Applicant's Position:
N/A

The FDA's Assessment:
The FDA disagrees with the Applicant's statement that there are no relevant immunogenicity data in this submission. Twenty-six pediatric patients with cHL were tested for antibodies to brentuximab using a sensitive electrochemiluminescence immunoassay. None of the patients tested positive for anti-brentuximab vedotin antibodies. FDA's assessment of immunogenicity performed by the Clinical Pharmacology review team is discussed in Section 6.

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1 Peripheral Neuropathy

Data:
PN is presented in Table 39 and Table 40. For AHOD1331, PN is defined as investigator-assessed peripheral sensory neuropathy or peripheral motor neuropathy per the modified Balis scale, and data collection focused on Grade 2 or higher events. For all the other studies, PN is defined by the peripheral neuropathy MedDRA SMQ broad search.

Table 39: Applicant – Summary of Treatment Emergent PN AEs (Safety Analysis Set)

	AHOD1331		Pediatric Combo Other (N=189) n (%)	Pediatric Mono (N=36) n (%)	Pediatric Total (N=521) n (%)
	BV-AVEPC (N=296) n (%)	ABVE-PC (N=297) n (%)			
Subjects with treatment-emergent peripheral neuropathy	59 (20)	55 (19)	30 (16)	12 (33)	101 (19)
Worst severity Grade 1	3 (1)	1 (<1)	18 (10)	9 (25)	30 (6)
Worst severity Grade 2	35 (12)	37 (12)	11 (6)	2 (6)	48 (9)
Worst severity Grade 3	21 (7)	17 (6)	1 (1)	1 (3)	23 (4)
Worst severity Grade 4	0	0	0	0	0
Worst severity Grade 5	0	0	0	0	0
Subjects with any treatment-emergent serious peripheral neuropathy or PN submitted to expedited report[a]	9 (3)	1 (<1)	1 (1)	0	10 (2)

[a] AHOD1331 study protocol had different expedited reporting requirements for BV-AVEPC arm and ABVE-PC arm.
Source: ISS Table 14.5.11.1

Table 40: Applicant – Treatment-emergent PN by PT (Safety Analysis Set)

	AHOD1331		Pediatric Combo Other (N=189) n (%)	Pediatric Mono (N=36) n (%)	Pediatric Total (N=521) n (%)
Preferred Term	BV-AVEPC (N=296) n (%)	ABVE-PC (N=297) n (%)			
Subjects with any event	59 (20)	55 (19)	30 (16)	12 (33)	101 (19)
Peripheral sensory neuropathy	48 (16)	42 (14)	17 (9)	4 (11)	69 (13)
Peripheral motor neuropathy	17 (6)	28 (9)	3 (2)	1 (3)	21 (4)
Dysaesthesia	0	0	1 (1)	0	1 (<1)
Muscular weakness	0	0	3 (2)	0	3 (1)
Neuralgia	0	0	2 (1)	0	2 (<1)
Neuropathy peripheral	0	0	0	1 (3)	1 (<1)
Paraesthesia	0	0	13 (7)	7 (19)	20 (4)

Source: ISS Table 14.5.11.2

The Applicant's Position:

In the AHOD1331 study, the frequency, severity, and type of treatment-emergent PN were similar between BV-AVEPC and ABVE-PC arms. In the BV-AVEPC arm 59 subjects (20%) reported any treatment-emergent PN, and in the ABVE-PC arm 55 subjects (19%) reported any treatment-emergent PN. The majority of the subjects with PN had maximum Grade 2 on both treatment arms, with 12% of subjects each. Similarly, peripheral sensory neuropathy was more frequent on both arms, with 48 subjects (16%) and 42 subjects (14%) on BV-AVEPC arm and ABVE-PC arm, respectively. Fewer subjects reported peripheral motor neuropathy, at 17 subjects (6%), and 28 subjects (9%) on the BV-AVEPC arm and ABVE-PC arm, respectively. Treatment-emergent PN across all analysis groups were similar to AHOD1331 with majority of the events being Grades 1 and 2 and sensory in nature.

The FDA's Assessment:

The FDA agrees that peripheral neuropathy has been identified as an adverse event of special interest with brentuximab vedotin. The FDA's analysis of peripheral neuropathy focused on Study AHOD1331 and was generally consistent with the Applicant's analysis. For AHOD1331, peripheral neuropathy is defined as investigator-assessed peripheral sensory neuropathy or peripheral motor neuropathy, as measured by the modified Balis scale (Section 19.5). The FDA agrees with the Applicant's statement that in the AHOD1331 study, the frequency, severity, and type of treatment-emergent peripheral neuropathy were similar between BV-AVEPC (N=59, 20%) and ABVE-PC (N=55, 19%) arms. In both arms, the majority of cases of peripheral neuropathy were sensory neuropathy. A summary of the FDA's analysis of peripheral neuropathy from Study AHOD1331 is provided in Table 41.

Table 41: AHOD1331 - Summary of Peripheral Neuropathy

	BV-AVEPC N=296 n(%)	ABVE-PC N=297 n(%)
Any Event of Peripheral Neuropathy	59 (20)	55 (19)
Grade 3	21 (7.1)	17 (5.7)
Grade 4	0 (0)	0 (0)
Peripheral Sensory Neuropathy	48 (16)	42 (14)
Peripheral Motor Neuropathy	17 (5.7)	28 (9.4)

Source: FDA Analysis

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

No new information is provided in the current submission.

8.2.7. Safety Analyses by Demographic Subgroups

No new information is provided in the current submission.

8.2.8. Specific Safety Studies/Clinical Trials

No new information is provided in the current submission.

8.2.9. Additional Safety Explorations

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose

Overdoses were reported in individual studies according to each study's protocol requirements. No AEs related to overdose of brentuximab vedotin were reported.

Drug Abuse

Brentuximab vedotin is not likely a drug of abuse potential. The potential for brentuximab

vedotin abuse and dependence is unknown.

Withdrawal and Rebound
Not applicable.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment. There is no known drug abuse potential with brentuximab vedotin.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience
Data:
The PBRER addendum included in the sBLA presents an analysis of safety data for the period from 19-Aug-2021 to 20-Mar-2022, cumulative ADRs since the first worldwide approval of brentuximab vedotin on 19 August 2011, and safety data on cumulative SAEs from clinical trials since the IBD. No new safety concerns have been identified based on this PBRER.

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 FDA agrees with the Applicant's assessment that the cumulative review of the safety data from the post-marketing period has not identified any new safety concerns. The post-marketing safety profile is consistent with the known safety profile of brentuximab vedotin.

Expectations on Safety in the Postmarket Setting
Safety information collected from the post-market setting is expected to be consistent with data collected in the clinical trials included in this submission.

The FDA's Assessment:
The FDA agrees with the Applicant's statement that safety information collected from the post-marketing setting is expected to be consistent with data collected in the clinical trials included in this submission.

8.2.11. Integrated Assessment of Safety

Data:
The integrated safety profile of brentuximab vedotin in this submission is based upon a total of 521 pediatric subjects with cHL and sALCL. The majority of subjects who had cHL were treated at the recommended dose of 1.8 mg/kg. The pivotal trial AHOD1331 included 296 subjects in the BV-AVEPC arm and 297 subjects in the ABVE-PC arm with cHL. Overall exposure to brentuximab vedotin monotherapy or brentuximab vedotin in combination was similar and is adequate to support the characterization of the safety profile.

In AHOD1331, the safety of brentuximab vedotin in combination with AVEPC was tolerable and had a comparable safety profile as the ABVE-PC control arm, and most subjects completed their

planned therapy. The frequency of overall TEAEs and Grade 3 and higher TEAEs was similar in both arms. The most common (≥10% of subjects) Grade 3 and higher TEAEs in the BV-AVEPC arm were laboratory related and included neutrophil count decreased, white blood cell count decreased, anemia, platelet count decreased, febrile neutropenia, and lymphocyte count decreased. The frequency and severity of PN was similar between the BV-AVEPC and ABVE-PC arms in AHOD1331, indicating that vincristine and brentuximab vedotin can be administered together with proper management without additional toxicity. The majority of the PN events across safety analysis groups were Grade 1 or 2, and sensory in nature. No deaths occurred during the safety reporting period on the AHOD1331 study.

Data from the pediatric combination and monotherapy safety analysis groups indicate that brentuximab vedotin can be administered safely in these subject populations with an adverse event profile that is similar to the established safety profile in the brentuximab vedotin label for adult cHL subjects and the individual treatment components. No new safety signals were identified in pediatric subjects in these studies.

The Applicant's Position:

Based on the safety results observed in pivotal trial AHOD1331 and the supporting studies, brentuximab vedotin administered at 1.8 mg/kg Q3W in combination with chemotherapy has a manageable and tolerable safety profile in pediatric subjects, with an adverse event profile similar to the established safety profile of its treatment components. These studies demonstrated the safety and tolerability of brentuximab vedotin when administered as a single agent or in combination with other agents in the pediatric cHL or ALCL population.

The FDA's Assessment:

The FDA agrees that the integrated safety profile of brentuximab vedotin in this submission is based on a total of 521 pediatric patients with cHL and sALCL. Because Studies C25002, AHOD1221, ANHL12P1, and HLHR13 had different patient populations, prior treatment lines, and chemotherapy combinations, the FDA did not independently conduct pooled safety analyses based on the ISS patient population included in this application. Studies C25002, AHOD1221, ANHL12P1, and HLHR13 were considered separately and were supportive. The FDA review of the totality of safety data did not identify any new safety signals with BV in the pediatric population or any clinically relevant differences in safety between pediatric and adult patients treated with BV. All of the studies included in this application were used to support and inform labeling of Section 8.4 of the USPI.

The Applicant proposed an indication in pediatric patients 2 years and older. The FDA notes that despite the AHOD1331 eligibility criteria including patients aged ≥2 to <22, the youngest patient enrolled in this study was 3 years old. Because cHL tends to be a disease of older children, and is rare in very young children, the FDA concluded that the patient population enrolled in AHOD1331 was representative of the normal distribution of cHL in pediatric patients, and was acceptable. The clinical course of newly diagnosed high risk cHL in 2 year olds is expected to be similar to that of 3 year olds, and in practice, these patients are expected to

be treated with the same chemotherapy regimens as older children. Therefore, based on the data provided, the safety and efficacy of BV+AVEPC in 2 year olds with previously untreated high risk cHL should be similar to the safety and efficacy established in pediatric patients in Study AHOD1331. Further, the Applicant provided additional safety information from other studies in children less than 6 that demonstrated a similar safety profile to older children. Thus, the FDA determined that the proposed indication for use in patients 2 years and older was acceptable.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

There were no major statistical issues identified in this submission; however, the caveats described below need to be considered when interpreting the results.

The primary efficacy analysis (EFS) was based on the ITT analysis set. The ITT analysis set defined in the SAP included all randomized patients. The FDA notes that all randomized patients included patients older than 18 years old.

There was no alpha allocation proposed for the interim analysis; however, there was no interim analysis conducted.

In the SAP, the final efficacy (EFS) analysis was proposed to be conducted after a total of approximately 77 EFS events or 3-year follow-up from last enrollment, whichever occur first. The data snapshot for final analysis was planned to be 12/31/2021. As of data cut-off date 12/31/2021, only 75 EFS events were observed.

The primary efficacy analysis has pre-specified an allocation of alpha of 1-sided 0.05 rather than the typical 0.025 for a 1-sided test. The primary analysis in this CSR reported a 2-sided p-value of p=0.0002.

8.4. Conclusions and Recommendations

The FDA's Assessment:

Study AHOD1331 met its primary efficacy objective. The hazard ratio for EFS based on stratified Cox regression model was 0.41 (95% C.I.: 0.25,0.67; p=0.0002) for the BV-AVEPC arm compared with the ABVE-PC arm in the ITT analysis set. The safety profile for brentuximab vedotin in pediatric patients with previously untreated high risk cHL was generally consistent with the established safety profile in adult patients, and no new safety findings were identified. Based on the benefit/risk of brentuximab vedotin in pediatric patients with newly diagnosed high-risk cHL, the clinical and statistical reviewers recommend approval of:

Brentuximab vedotin for the treatment of pediatric patients 2 years and older with previously untreated high risk classical Hodgkin lymphoma (cHL), in combination with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide.

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:
This efficacy supplement was not presented to the Oncologic Drugs Advisory Committee as this application did not identify any significant efficacy or safety concerns that required discussion at an advisory committee meeting.

10 Pediatrics

The Applicant's Position:
Brentuximab vedotin (SGN-35) for the treatment of Hodgkin lymphoma (HL) has an orphan designation (designation number 06-2356), hence is exempt from the Pediatric Research Equity Act (PREA) (Reference ID: 5019193).

The FDA's Assessment:
The FDA agrees with the Applicant's assessment regarding orphan designation and is exempt from PREA.

The five studies included in this application (C25002, AHOD1221, ANHL12P1, HLHR13, and AHOD1331) were submitted in accordance with an FDA Written Request.

11 Labeling Recommendations

Data: Table 42 below provides a high level summary of the changes made to the USPI for Adcetris (brentuximab vedotin) BLA 125388. See the USPI attached to the approval letter for final labeling.

Table 42: Summary of Significant Labeling Changes

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
Indication and Usage	• Added indication for treatment of pediatric patients 2 years and older with previously untreated high risk cHL, in combination with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide.	FDA agreed.
Dosage and Administration	• Added recommended dose, frequency, and duration for pediatric patients. • Added recommended prophylactic medications for pediatric patients	FDA agreed with the dosage and recommended prophylactic medications and dosage modifications for peripheral neuropathy or

	• Added dose modification for peripheral neuropathy or neutropenia in pediatric patients	neutropenia in pediatric patients. FDA added new subsections 2.3 Dosage in Renal Impairment and 2.4 Dosage in Hepatic Impairment to streamline presentation in the label.
6. Adverse Reactions	• Added pediatric safety data from study AHOD 1331 • Added immunogenicity data for pediatric patients	FDA modified this section to align with current labeling practice for the presentation of adverse reaction data. FDA moved the Immunogenicity subsection to a new subsection 12.6 to align with recent FDA guidance, *Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling*. Per recommendations in this Guidance, a new heading added to 6.1 for ADA-associated adverse reactions to describe a higher incidence of infusion-related reactions in patients who developed persistently positive ADA.
8.4 Use in Special Population, Pediatric Use	• Added summary for HLRH13, AHOD 1221, C25002, ANHL12P1	FDA modified this section to align with recommendations from FDA guidance for the presentation of pediatric use data. Separate subsections for each pediatric indication studied added. For brevity, a cross reference to the Indications and Usage section 1 added for all adult-only indications.

12.3 Clinical Pharmacology, Pharmacokinetics	• Added PK data for pediatric population	FDA modified this section to include the following pediatric age range statements to describe PK/exposure differences: age 3 to <6, age 6 to <12, age 12 to <17; FDA added median and range of body weight for each pediatric age range (age 3 to <6, age 6 to <12, age 12 to <17) to reflect the association between body weight and exposure. FDA removed (b) (4)
14.1 Clinical Studies, Classical Hodgkin Lymphoma	• Added efficacy data for AHOD 1331	FDA generally agreed but modified this section to remove (b) (4). FDA recommended expansion of the hazard ratio and 95% confidence interval described in the efficacy results table footnote to include Cox proportional hazard regression model stratified by clinical characteristics (disease stage) as recorded at randomization.

The Applicant's Position:

Based on the data from Study AHOD1331, the Applicant is proposing the aforementioned changes in the ADCETRIS label.

The FDA's Assessment:

FDA modified the sections of the USPI as described in the table above.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:
Not applicable.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:
No postmarketing requirements or commitments were issued with this application.

FDA PMC/PMR Checklist for Trial Diversity and U.S. Population Representativeness

The following were evaluated and considered as part of FDA's review:		Is a PMC/PMR needed? No
□	The patients enrolled in the clinical trial are representative of the racial, ethnic, and age diversity of the U.S. population for the proposed indication.	_X_ Yes ___ No
□	Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g. race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	___ Yes _X_ No
□	Other considerations (e.g.: PK/PD), if applicable:	___ Yes _X_ No

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:
References available upon request.

The FDA's References:
1. Kahn JM, Kelly KM, Pei Q, et al. Survival by race and ethnicity in pediatric and adolescent patients with hodgkin lymphoma: a Children's Oncology Group Study. J Clin Oncol. 2019;37(32):3009-17.
2. Khullar K, Rivera-Nunez Z, Jhawar SR, et al. Pediatric Hodgkin lymphoma: disparities in survival by race. Leuk Lymphoma. 2020;61(3):546-56.

19.2. Financial Disclosure

The Applicant's Position:
Financial disclosures information for pivotal study AHOD1331 is described in Section 8.1.2.

The FDA's Assessment:
The FDA notes the disclosable financial arrangement for one investigator as reported below, and agrees that this issue is not anticipated to impact the integrity of the trial.

Covered Clinical Study (Name and/or Number):* AHOD1331

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 603		
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): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 0		

Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☒ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
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.

19.3. Nonclinical Pharmacology/Toxicology

No new information is provided in the current submission.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Population PK Analysis

19.4.1.1. Executive Summary

The FDA's Assessment:

The proposed dosing regimen of 1.8 mg/kg IV brentuximab vedotin Q3W in combination with AVEPC is generally supported by the population pharmacokinetic (PPK) analyses of ADC and MMAE. The results of the PPK analyses do not support the need for therapeutic individualization according to covariates other than body weight.

Following the proposed dosage of 1.8 mg/kg IV Q3W in pediatric patients aged 2 years and older with previously untreated high risk cHL, patients with low body weight (i.e., patients aged 2 to <6 years) are expected to have lower ADC and MMAE exposure compared to patients with higher body weight (i.e., 12 to <18 years). Given that no clear difference in EFS was observed in patients aged 2 to < 6 years, 6 to <12 years, and 12 to <18 years in the BV-AVEPC arm and no apparent relationships between exposure and efficacy endpoints were identified, the lower exposure in younger pediatric patients does not appear to have a clinically relevant impact on efficacy.

19.4.1.2. Population PK Assessment Summary

The Applicant's Position:

The PK of brentuximab vedotin ADC and MMAE in pediatric subjects is consistent with that in adult subjects, where pediatric subjects with higher body weight were found to have higher CL and higher central volume of distribution for ADC and MMAE. Consistent with adults, pediatric MMAE concentrations declined over time with repeated dosing of brentuximab vedotin; the median decline of MMAE AUC_{21D} at Cycle 4 from Cycle 1 was ~ 57%. Body weight was identified as the only significant factor for the PK of brentuximab vedotin. After adjusting for body weight, factors including age, sex, race, disease indication, baseline albumin, and immunogenicity had no impact on the PK of ADC and MMAE. Consistent with the observations in adults, the PK of ADC and MMAE in pediatric subjects when administered in combination with chemotherapy agents and prednisone were consistent with those administered as monotherapy. For pediatric subjects aged 2 to <12 years and 12 to <18 years, the typical ADC CL values were 0.65 L/d and 1.17 L/d, respectively, based on median body weights of 21 kg and 54 kg sampled from CDC growth chart, respectively. Overall, weight-based dosing provides similar exposures in pediatric subjects aged 12 to <18 years compared to adult subjects, and numerically lower exposures in subjects aged 2 to <12 years due to their lower body weights.

General Information	
Objectives of PPK Analysis	• To develop pediatric PPK models that describes the PK of ADC and its cytotoxic payload MMAE respectively following IV administration of brentuximab vedotin using previously validated adult PPK structural model. • To estimate PPK parameters of the model, individual PK parameters, and interindividual variability of model parameters in the subject population. • To identify and estimate the effect intrinsic and extrinsic covariate factors that influence PK and exposures of ADC and MMAE. • To summarize the systemic exposures of ADC and MMAE from the studied pediatric subjects and a virtual population using model-based simulations and compare simulated exposures with those from the adult reference population.
Study Included	Studies C25002 (N=36), AHOD1331 (N=26), and HLHR13 (N=16)
Dose(s) Included	C25002: 1.4 or 1.8 mg/kg on Day 1 Q3W up to 16 cycles HLHR13: Cycles 1 and 2: 1.2 mg/kg in AEPA on Days 1, 8, and 15 Q4W; Cycles 3 to 6: 1.2 mg/kg in CAPDac given on Days 1 and 8 Q3W AHOD1331: 1.8 mg/kg BV Q3W + AVEPC or ABVE-PC for 5 21-day cycles
Population Included	Pediatric subjects with r/r cHL or r/r sALCL, previously untreated high risk cHL
General	Age median: 12.0 (range: 3-19)

Population Characteristics (m5.3.3.5 PPK Report,Table 4 and Table 5)		Weight median: 50.6 kg (range: 15.4-104 kg) 45 (57.7%) male 64 (82.1%) white, 5 (6.4%) Black or African American, 2 (2.6%) Asian, 2 (2.6%) Other, 5 (6.4%) Missing
	Organ Impairment	Hepatic (NCI classification): 45 (57.7%) normal, 6 (7.7%) mild impairment, 27 (34.6%) missing Renal (eGFR using Shwartz equation): 51 (65.4%) normal, 27 (34.6%) missing
	Pediatrics (if any)	Age median: 12.0 (range: 3-19) 3 (3.8%) <6 yrs. 30 (38.5%) 6 to <12 yrs. 41 (52.6%) 12 to <18 yrs. 4 (5.1%) ≥18 yrs. Weight median (range): 50.6 kg (15.4-104 kg)
No. of Patients, PK Samples, and BLQ		Excluded BLQ samples before first does: 47 (4.6%) for ADC and 48 for MMAE (4.9%). Excluded BLQ samples: 20 (2.0%) for ADC and 46 for MMAE (4.7%)
Sampling Schedule	Rich Sampling	C25002 (Phase 1/2): Predose and EOI for all cycles Cycles 1 and 8 at 24, 48, 96, and 312 hr. after dose Cycle 2 at 24, 48, and 96 hr. after dose
	In ITT Population	AHOD1331 (pivotal Phase 3): Cycle 4: Predose; EOI, 24, 48, and 96 h post dose Cycle 5: Predose in PK subjects
Covariates Evaluated	Static	Age, sex, disease indication, baseline albumin, Immunogenicity
	Time-varying	N/A

Final Model	**Summary**	**Acceptability [FDA's comments]**
Software and Version	NONMEM® (version 7.4; ICON, Hanover, MD, US)	
Model Structure	Serum/plasma concentrations of ADC and MMAE were well described by a linear 3-compartment model for ADC and by a semi-mechanistic, linear, 2-compartment model for MMAE with first-order elimination following a sequential modeling approach.	The final ADC and MMAE model structures and final parameter estimates appear acceptable for characterizing ADC and MMAE PK in pediatric patients aged 2 years and older. Final ADC parameter estimates: Table 44. Final MMAE parameter estimates: Table 45.
Model Parameter Estimates	m5.3.3.5 PPK Report Table 8 for ADC and Table 10 for MMAE	
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	m5.3.3.5 PPK Report Table 8 for ADC and Table 10 for MMAE	
BLQ for Parameter Accuracy	BLQ samples are not included in the analysis	
GOF, VPC	GOF: m5.3.3.5 PPK Report Figure 7 for ADC and Figure 16 for MMAE	The final ADC and the final MMAE model adequately fit PK data in pediatric patients aged 2 years and older

	VPC: m5.3.3.5 PPK Report Figure 8 for ADC and Figure 17 for MMAE	ADC GOF: Figure 17. ADC VPC: Figure 18. MMAE GOF: Figure 20. MMAE VPC: Figure 21.
Significant Covariates and Clinical Relevance	Body weight was captured a priori by unfixed allometric scaling. Covariate effects were evaluated by a stepwise covariate search. During the initial univariate forward step, none of the covariates passed significance criteria ($p<0.01$) for model improvement. Therefore, no covariates were included in the final model.	Higher body weight was associated with higher CL. Following 1.8 mg/kg IV Q3W, higher body weight was associated with higher exposure of ADC and MMAE. After accounting for body weight, no other investigated covariates were associated with significant differences in ADC or MMAE PK. ADC covariate effects: Figure 22. Predicted ADC exposure: Figure 2 and Table 46. MMAE covariate effects: Figure 23. Predicted MMAE exposure: Figure 2 and Table 47. Predicted median PK profiles: Figure 28.
Analysis Based on Simulation (optional)	m5.3.3.5 PPK Report Figures 28 and 29	
Labeling Language	Description	Acceptability [FDA's comments]
12.3 PK	The PK of brentuximab vedotin were evaluated in 78 pediatric patients. The results of population modeling showed that the PK of brentuximab vedotin ADC and MMAE in pediatric subjects aged 2 to <12 years (N=33) and 12 to <18 years (N=41) were generally consistent with those of adults. Except for body weight, age, sex, race, baseline albumin, and immunogenicity had no clinically significant effect on the PK of ADC and MMAE in pediatric patients. The predicted AUC_{21d} values for ADC are 59.0 and 83.3	ADC and MMAE exposure are predicted to decrease with lower body weight following 1.8 mg/kg IV Q3W. FDA agrees that the dose-normalized steady state exposure of ADC and MMAE did not differ significantly in patients 12 to <17 years of age compared to adults. Patients aged 2 to <6 years and 6 to <12 years have lower predicted exposure compared to patients aged 12 to <18 and

	day·µg/mL for pediatric patients aged 2 to < 12 years and 12 to <18 years, based on a median body weight of 21 kg and 54 kg, respectively. Results from exploratory E-R analysis suggested no impact of lower exposures on efficacy in subjects aged 2 to <12 years.	adults following 1.8 mg/kg IV Q3W. After accounting for body weight, neither ADC nor MMAE PK is significantly impacted by age, sex, race, or baseline albumin.

All Tables and Figures listed below are from m5.3.3.5 PPK Report:
Table 4 and Table 5. Summary of Baseline Characteristics and Laboratory Values in the Dataset, Stratified by Study.
Table 8 and Table 10. Parameter Estimates and SE from Final Population PK Model.
Figure 7 and Figure 16. Goodness-of-fit Plots for the Final Population PK Model (OBS-PRED/IPRED, CWRES-TIME/PRED).
Figure 8 and Figure 17. VPC of Final Population PK Models, Stratified by Dose.
Figure 12 and Figure 21. Impact of Significant Covariates on Exposure.
Figure 28 and Figure 29. Simulation results (optional, tentative figure title).

The FDA's Assessment:
The Applicant's PPK models for ADC and for MMAE are generally acceptable for the purposes of characterizing pharmacokinetics (PK) and exposure for ADC and MMAE. Higher body weight was associated with higher ADC and MMAE exposure following the proposed dosage of 1.8 mg/kg IV Q3W. Pediatric patients aged 12 to <18 years are predicted to have similar ADC and MMAE exposure to adults following 1.8 mg/kg IV Q3W. Pediatric patients with lower body weight are predicted to have lower exposure compared to patients aged 12 to <18 years. After accounting for association between exposure and body weight, no other clinically meaningful differences in exposure were identified according to patient subgroups.

PPK Data

The PPK analysis utilized ADC and MMAE concentrations from 78 total pediatric and young adult patients. The PPK dataset of 78 total patients included 26 pediatric patients with previously untreated high risk cHL who received BV-AVEPC in Study AHOD1331, 36 pediatric and young adult patients with relapsed or refractory (r/r) cHL or r/r systemic anaplastic large cell lymphoma (sALCL) who received BV monotherapy in Study C25002, and 16 pediatric and young adult patients with previously untreated high risk cHL who received AEPA/CAPDac in Study HLHR13. Patient characteristics are summarized for each study in Table 43.

Table 43: Baseline Characteristics and Demographics of Patients with PK Data by Study

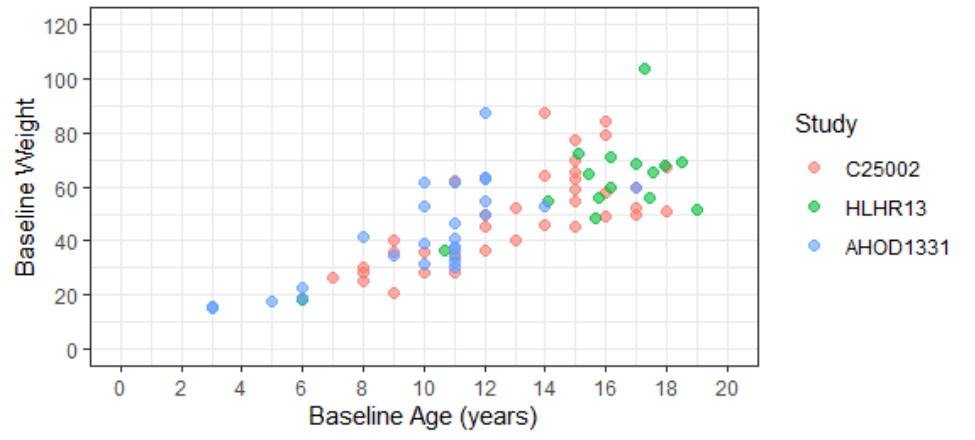
Covariate	Statistic	Study C25002 (n=36)	Study HLHR13 (n=16)	Study AHOD1331 (n=26)
Baseline Age (years)	Mean (SD)	13.1 (3.2)	15.6 (3.2)	10 (3.2)
	Median	14	16.17	11
	Min - Max	7 - 18	6 - 19	3 - 17
Age Category	2 to <6 years [n (%)]	0	0	3 (11.5%)
	6 to <12 years [n (%)]	12 (33.3%)	2 (12.5%)	16 (61.5%)
	12 to <18 years [n (%)]	22 (61.1%)	12 (75%)	7 (26.9%)
	18 to <22 years [n (%)]	2 (5.6%)	2 (12.5%)	0
Baseline Weight (kg)	Mean (SD)	50.1 (17.4)	60.2 (18.2)	42.4 (17.8)
	Median	49.9	62.05	40.1
	Min - Max	21.2 - 87	18.2 - 103.8	15.4 - 87.2
Sex	Female [n (%)]	11 (30.6%)	8 (50%)	14 (53.8%)
	Male [n (%)]	25 (69.4%)	8 (50%)	12 (46.2%)
Race	Asian [n (%)]	2 (5.6%)	0	0
	Black or African American [n (%)]	0	2 (12.5%)	3 (11.5%)
	Not reported or unknown [n (%)]	1 (2.8%)	0	4 (15.4%)
	Other [n (%)]	2 (5.6%)	0	0
	White [n (%)]	31 (86.1%)	14 (87.5%)	19 (73.1%)
Ethnicity	Hispanic or Latino [n (%)]	4 (12.1%)	2 (12.5%)	9 (39.1%)
	Not Hispanic or Latino [n (%)]	29 (87.9%)	14 (87.5%)	14 (60.9%)
Baseline Cockcroft-Gault Creatinine Clearance (mL/min)	N	35	16	0
	Mean (SD)	167.8 (46)	169.3 (61.3)	N/A
	Median	165.813	144.7285	N/A
	Min - Max	101.9 - 301.1	82.6 - 313.4	N/A
Baseline Hepatic Function*	Normal [n (%)]	30 (83.3%)	15 (93.8%)	0
	Mild hepatic impairment [n (%)]	5 (13.9%)	1 (6.2%)	0
	Missing [n (%)]	1 (2.8%)	0	26 (100%)
Baseline Albumin (g/L)	Mean (SD)	4.1 (0.6)	3.4 (0.5)	3.6 (0.6)
	Median	4.1	3.4	3.7
	Min - Max	2.7 - 5.1	2.4 - 4	2.2 - 4.5
Disease Type	Anaplastic large cell lymphoma [n (%)]	17 (47.2%)	0	0
	Frontline high risk or advanced cHL [n (%)]	0	16 (100%)	26 (100%)
	Hodgkin lymphoma [n (%)]	19 (52.8%)	0	0
Anti-Drug Antibody Status	Negative status [n (%)]	20 (55.6%)	16 (100%)	26 (100%)
	Persistently positive status [n (%)]	2 (5.6%)	0	0
	Transiently positive status [n (%)]	14 (38.9%)	0	0
Planned Brentuximab Vedotin Dose	1.2 mg/kg [n (%)]	0	16 (100%)	0
	1.4 mg/kg [n (%)]	3 (8.3%)	0	0
	1.8 mg/kg [n (%)]	33 (91.7%)	0	26 (100%)

*Hepatic impairment was derived according to the NCI classification: Normal, Mild (total bilirubin >1.0-1.5× ULN or AST >ULN), Moderate (total bilirubin >1.5-3× ULN), and Severe (total bilirubin >3×ULN).
cHL = classical Hodgkin lymphoma; N/A = not applicable; PK = pharmacokinetic; SD = standard deviation; ULN = upper limit of normal.
Source: FDA Reviewer analysis of Applicant's Population PK dataset

The PPK analyses did not evaluate the potential effects of AST, ALT, total bilirubin, estimated glomerular filtration rate, and creatinine clearance on ADC and MMAE PK because these covariates were not documented in Study AHOD1331. Visual inspection of standardized between-patient variability on ADC and MMAE clearance versus these covariates in patients from Studies C25002 and HLHR13 did not identify any clear trends.

Lower body weight was associated with lower age in pediatric patients aged 2 years and older with PK data, as shown in Figure 16. Data were limited in patients with low body weight, as the PPK analysis only included 4 patients weighing 15 to 20 kg and 1 patient weighing 20 to 30 kg. The patient with the lowest body weigh weighed 15.4 kg at baseline. For reference, the CDC growth charts indicate that the median weight is approximately 12 to 13 kg for a 24-month-old child and 14 kg for a 36-month-old child.

Figure 16: Baseline Weight versus Age in Patients with PK Data



Data shown for 78 pediatric and young adult patients with PK data. PK = pharmacokinetic.
Source: FDA Reviewer analysis of Applicant's Population PK dataset

ADC PPK Model

The final ADC PPK model is a 3-compartment model with first-order elimination. Body weight was the only intrinsic patient characteristic with a statistically significant impact on ADC PK, and higher body weight was associated with higher ADC clearance (CL) and higher central volume of distribution (V1).

The final parameter estimates of the ADC PPK model are described in Table 44. The Reviewer was able to run the final ADC PPK model without any significant discrepancies compared to Table 44.

Table 44: Final ADC Population PK Model Parameters

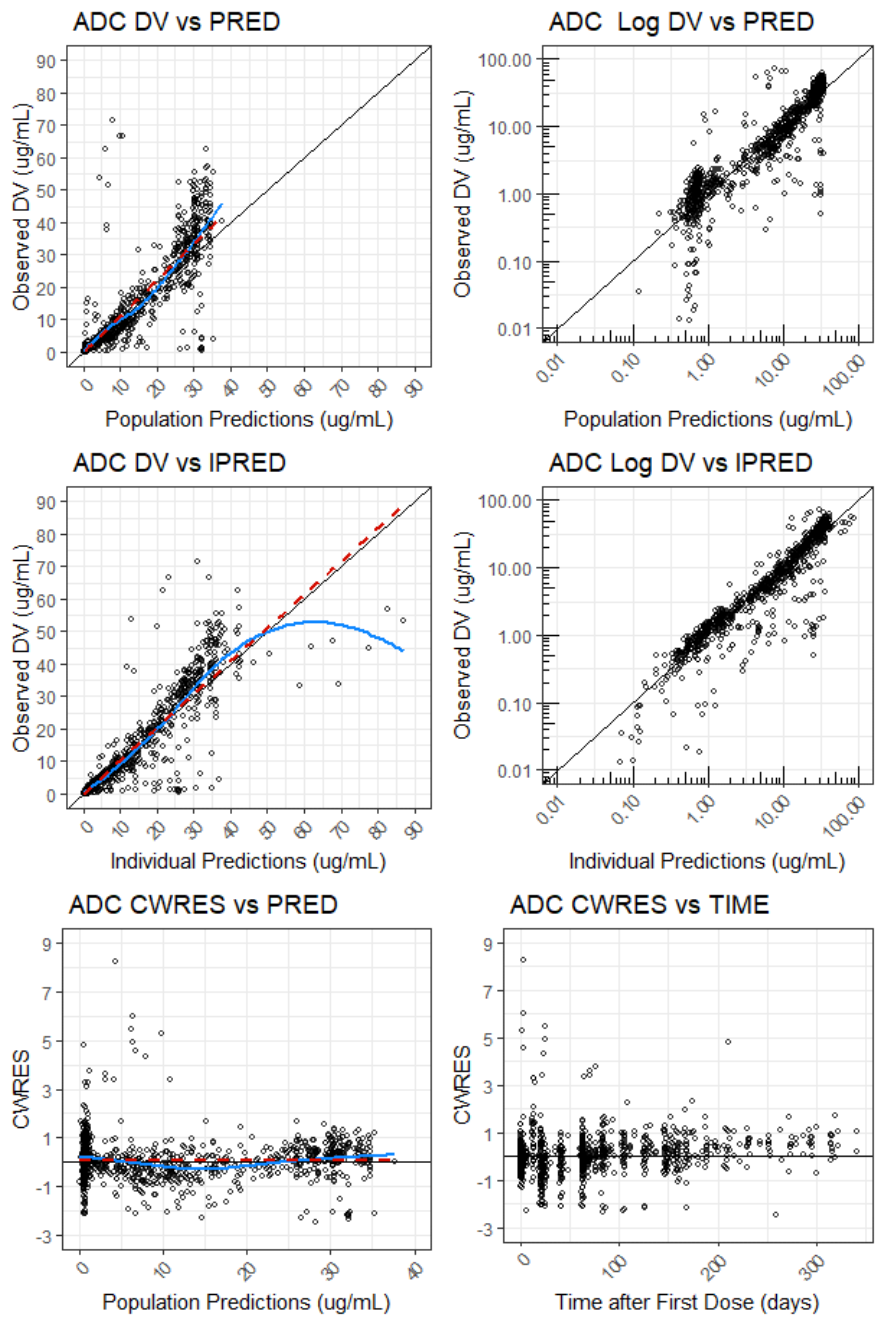
Parameter Model	Parameter Description	Population Estimate	SE	%RSE	Bootstrap Median [2.5th and 97.5th Percentiles]
θ_1 – CL	Clearance, L/day	1.44	0.145	10.0	1.45 [1.21, 1.73]
θ_2 – V1	Central volume of distribution, L	4.08	0.244	5.98	3.95 [3.56, 4.42]
θ_3 – Q2	Intercompartmental clearance for 1st peripheral compartment, L/day	1.63	0.271	16.7	1.60 [1.05, 2.67]
θ_4 – V2	First peripheral volume of distribution, L	1.13	0.361	31.9	1.13 [0.541, 3.41]
θ_5 – Q3	Intercompartmental clearance for 2nd peripheral compartment, L/day	0.46	0.101	21.9	0.569 [0.169, 0.786]
θ_6 – V3	Second peripheral volume of distribution, L	3.81	0.632	16.6	4.15 [3.03, 19.8]
θ_7	Weight exponent on clearance	0.63	0.110	17.5	0.637 [0.429, 0.86]
θ_8	Weight exponent on central volume of distribution	0.729	0.065	8.92	0.701 [0.581, 0.82]
θ_9	Proportional error	0.405	0.0448	11.1	0.381 [0.298, 0.459]
θ_{10}	Additive error, µg/mL	0.0573	0.0191	33.3	0.053 [0.0156, 0.102]
$\omega^2_{1,1}$	BSV on clearance (CL)	0.359	0.146	40.6	0.341 [0.115, 0.657]
$\omega^2_{2,2}$	BSV on central volume of distribution (V1)	0.0433	0.0184	42.6	0.0352 [0.00374, 0.0749]

Notes: Condition number for the model was 110.3. Shrinkages were 2.5% and 34.36% for BSV on the ADC clearance and central volume of distribution, respectively. All 1000 bootstrap runs minimized successfully.
ADC = antibody-drug conjugate; BSV = between subject variability; PK = pharmacokinetic; RSE = relative standard error; SE = standard error.
Source: Table 8 in Applicant's Population PK Report

As indicated by the standard goodness-of-fit plots displayed in Figure 17 and the VPC displayed in Figure 18, the PPK model adequately characterized the PK of ADC. The model fit did not appear to differ according to study (Study C25002, HLHR13, or AHOD1331), disease (HL, ALCL, or frontline cHL), or age category (2 to <6 years, 6 to <12 years, 12 to <18 years, or 18 to <22 years). PK data were only available from 3 patients aged 2 to <6 years (two 3-year-old patients and one 5-year-old patient), but age did not have an impact on ADC PK after accounting for body weight.

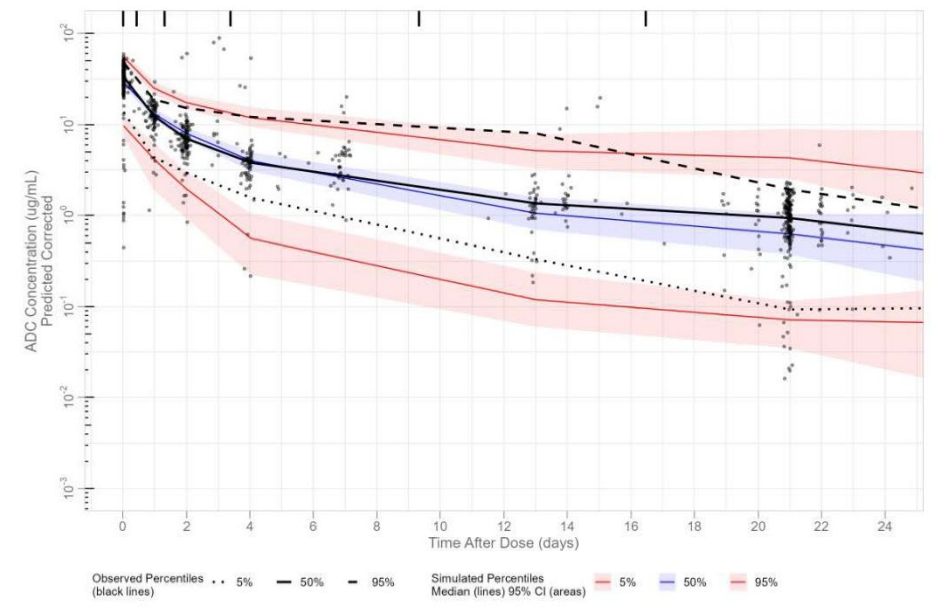
The ADC model is acceptable for characterizing PK of ADC in patients aged 2 to <18 years with previously untreated high risk cHL. The ADC model is also acceptable for predicting individual exposure in patients aged 2 to <18 years.

Figure 17: Standard Goodness-of-Fit Plots for the Final ADC Population PK Model



Loess in solid blue; Linear regression in dashed red. The lower limit of quantification was 0.0125 ug/mL.
ADC = antibody-drug conjugate; CWRES=conditional weighted residuals; DV=observed concentration; IPRED=individual prediction of concentration; PRED=population prediction of concentration.
Source: FDA Reviewer Analysis of Final Population PK Model

Figure 18: Visual Predictive Check of the Final ADC Population PK Model



Notes: VPC is prediction corrected. Time After Dose refers to time after most recent dose.
ADC = antibody-drug conjugate; CI = confidence interval; VPC = visual predictive check.
Source: Figure 8 in Applicant's Population PK Report

MMAE PPK Model

The final MMAE PPK model is a semi mechanistic 2-compartment model with first-order elimination. Body weight was the only intrinsic patient characteristic with a statistically significant impact on MMAE PK, and higher body weight was associated with higher MMAE clearance (CLM) and higher central volume of distribution (V4). Unconjugated MMAE appears in the central MMAE compartment according to the sigmoidal function in Equation (1). The decline in MMAE formation rate may be due to reduction of disease burden over time.

$$Input\ rate\ to\ MMAE_{central} = \frac{CL}{V1} \cdot ADC_{central}(t) \cdot DAR(t) \cdot e^{EMPIR(t)} \quad \text{Equation (1)}$$

$$DAR(t) = DAR_0 \cdot e^{-\beta \cdot (t - time_{last\ dose})} \quad \text{Equation (2)}$$

$$EMPIR(t) = TMAX \cdot \frac{t}{TC50 + t} \quad \text{Equation (3)}$$

where CL and V1 are individual ADC post hoc parameters estimated from the final ADC PPK model, $ADC_{central}(t)$ is the amount of ADC in the central ADC compartment (umol) at time *t*, *DAR(t)* is the apparent drug-antibody ratio at time *t* according to Equation (2), *EMPIR(t)* is the empirical decrease of MMAE exposure at time *t* according to Equation (3), *BETA* (β) is the slope

of the DAR decline function, TMAX is the maximum change of MMAE formation rate relative to baseline, and TC50 is the time of half maximal change of MMAE formation relative to baseline.

The final parameter estimates of the MMAE PPK model are described in Table 45. The Reviewer was able to run the final MMAE PPK model without any significant discrepancies compared to Table 45.

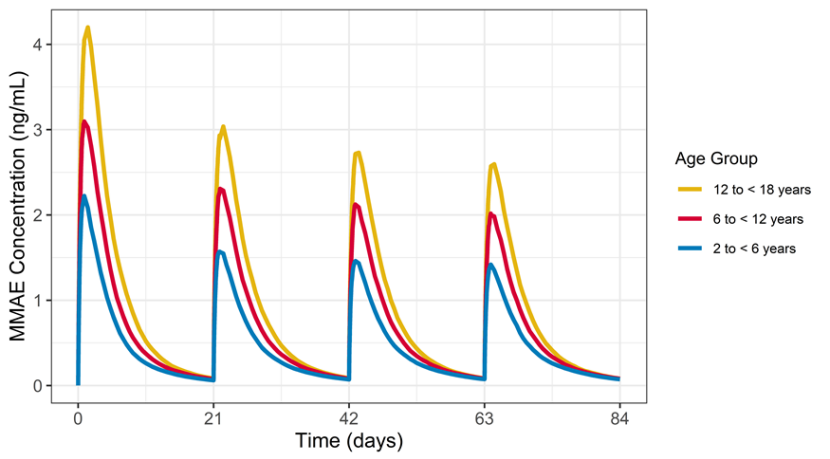
Table 45: Final MMAE Population PK Model Parameters

Parameter Model	Parameter Description	Population Estimate	SE	%RSE	Bootstrap Median [2.5th and 97.5th Percentiles]
θ_1 – CLM	MMAE apparent clearance, L/day	51.4	2.77	5.39	48.9 [36.2, 60.4]
θ_2 – V4	MMAE apparent central volume of distribution, L	69.6	5.07	7.28	66 [44.3, 85.8]
θ_3 – Q5	MMAE apparent inter-compartmental clearance, L/day	50.4	2.86	5.67	49 [30.7, 149]
θ_4 – V5	MMAE apparent peripheral volume of distribution, L	4.78	0.183	3.83	4.74 [2.48, 35.1]
θ_5 – β	Slope of DAR decline function, 1/day	0.0575	0.00165	2.87	0.0578 [0.0425, 0.082]
θ_6 – TMAX	Maximum change of MMAE formation rate relative to baseline	-0.81	0.159	19.6	-0.911 [-1.62, -0.567]
θ_7 – TC50	Time of half maximal change of MMAE formation rate relative to baseline, day	17.1	1.73	10.1	16.9 [5.43, 76.9]
θ_8	Weight exponent on apparent clearance	0.627	0.13	20.7	0.554 [0.148, 1.03]
θ_9	Weight exponent on apparent central volume of distribution	0.897	0.244	27.2	0.849 [0.282, 1.5]
θ_{10}	Proportional error	0.427	0.0119	2.79	0.421 [0.367, 0.477]
θ_{11}	Additive error, ng/mL	0.0261	0.000692	2.65	0.0249 [-0.00938, 0.039]
$\omega^2_{1,1}$	BSV on apparent clearance (CLM)	0.284	0.0615	21.6	0.259 [0.106, 0.47]
$\omega^2_{2,2}$	BSV on apparent volume of distribution (V4)	0.798	0.253	31.7	0.798 [0.463, 1.27]
$\omega^2_{3,3}$	BSV on TMAX	0.867	0.165	19.0	0.851 [0.376, 2.62]

Notes: Condition number for the model was 23.17. Shrinkages were 15.25% and 7.31% for BSV on the apparent MMAE clearance and apparent MMAE central compartment volume, respectively. Shrinkage for model parameter TMAX was 21.47%. 79.8% of bootstrap runs minimized successfully.
BSV = between subject variability; DAR = apparent drug-antibody ratio; MMAE = monomethyl auristatin E; PK = pharmacokinetic; RSE = relative standard error; SE = standard error.
Source: Table 10 in Applicant's Population PK Report

The fastest MMAE formation rate occurred at the time of the first BV dose. The declining MMAE formation rate is likely due to reduction of disease burden over time during treatment. The MMAE PPK analysis estimated that half of the maximal change in MMAE formation rate occurred 17.1 days after the first BV dose. As a result, plasma MMAE C_{max} and AUC were higher in Cycle 1 compared to later cycles, which is apparent in Figure 19.

Figure 19: Predicted Median of Individual MMAE Prediction Versus Time From the Virtual Pediatric Population by Age Group

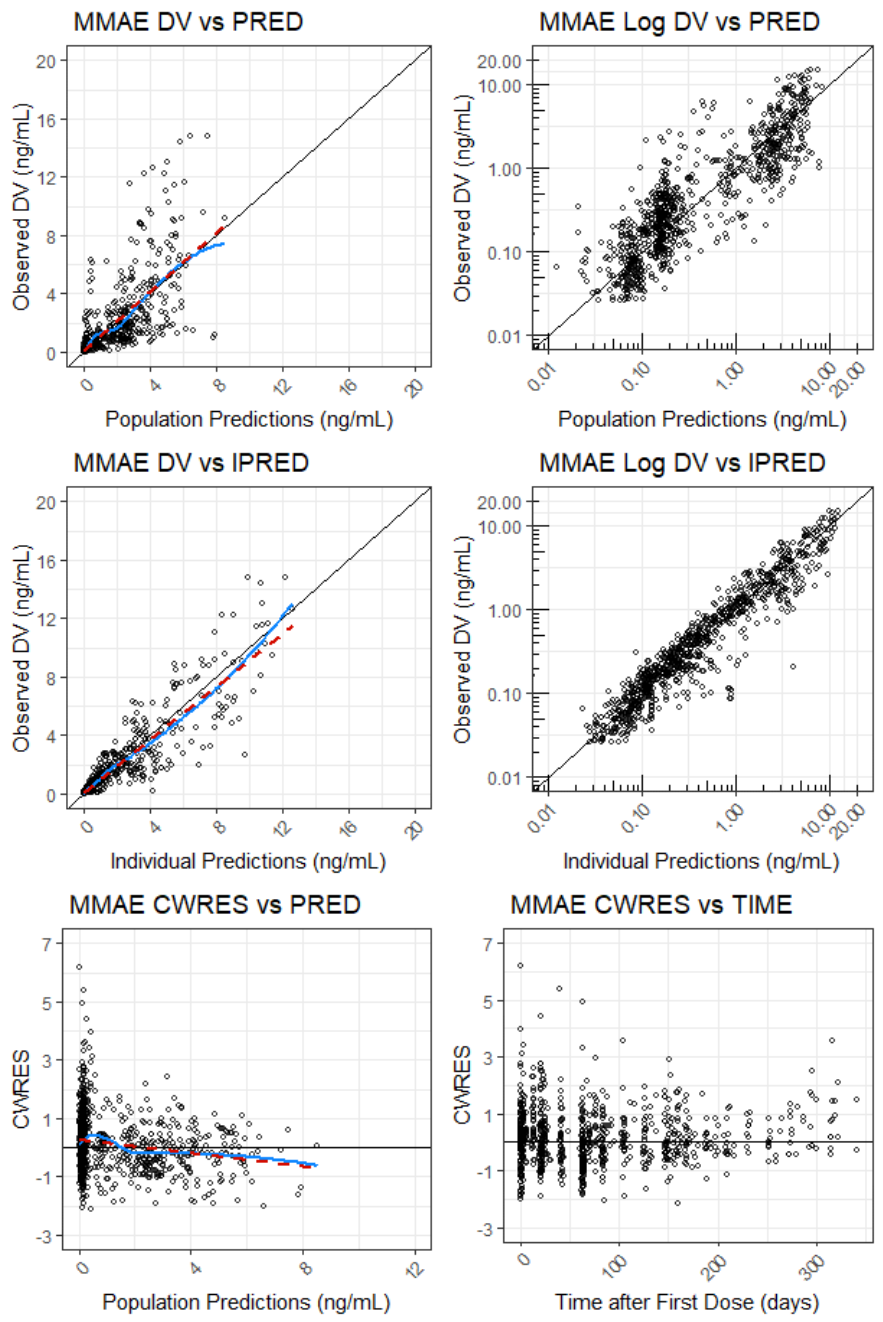


Virtual pediatric population contained 3000 virtual patients aged 2 to <18 years with body weight resampled from CDC weight chart by age and sex with similar proportions of male and female patients. All virtual patients received 1.8 mg/kg (up to 180 mg per dose) IV infused over 30 minutes every 3 weeks; 1 cycle = 21 days.
IV = intravenously; MMAE = monomethyl auristatin E.
Source: FDA Reviewer analysis of Applicant's Virtual Population Dataset and Final Population PK Model.

As indicated by the standard goodness-of-fit plots displayed in Figure 20 and the VPC displayed in Figure 21, the PPK model adequately characterized the PK of MMAE following administration of BV. The model fit did not appear to differ according to study, disease (HL, ALCL, or frontline cHL), or age category. PK data were only available from 3 patients aged 2 to <6 years, but age did not have an impact on MMAE PK after accounting for body weight.

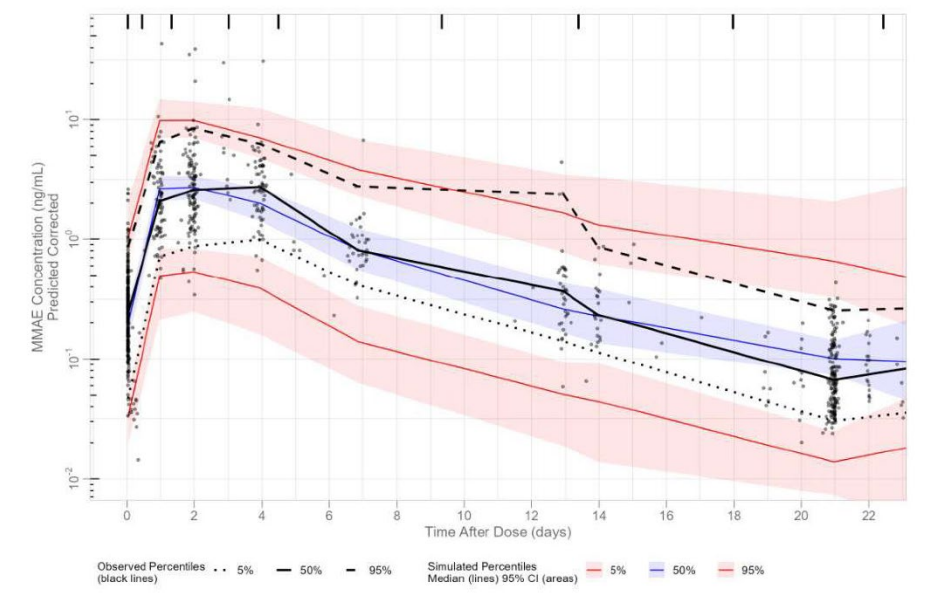
The MMAE model is acceptable for characterizing PK of MMAE following BV 1.8 mg/kg IV Q3W in patients aged 2 to <18 years with previously untreated high risk cHL. The model is also acceptable for predicting MMAE individual exposure following BV 1.8 mg/kg IV Q3W in patients aged 2 to <18 years.

Figure 20: Standard Goodness-of-Fit Plots for the Final MMAE PPK Model



Loess in solid blue; Linear regression in dashed red. The lower limit of quantification was 0.025 ng/mL.
CWRES=conditional weighted residuals; DV=observed concentration; hrs.=hours; IPRED=individual prediction of concentration; MMAE=monomethyl auristatin E; PRED=population prediction of concentration.
Source: FDA Reviewer Analysis of Final Population PK Model

Figure 21: Visual Predictive Check of the Final MMAE Population PK Model

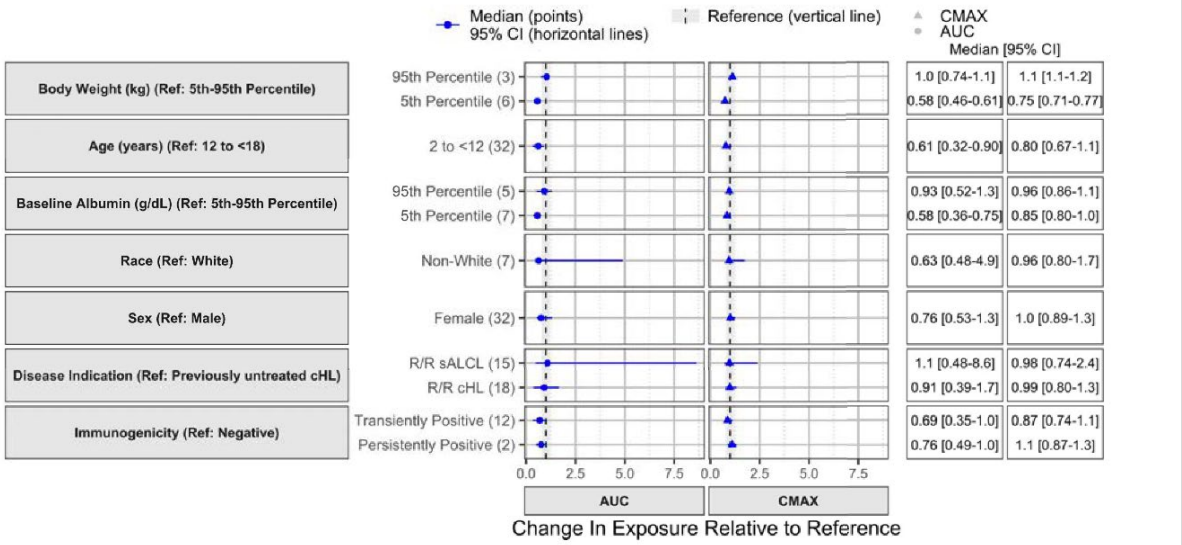


Notes: VPC is prediction corrected. Time After Dose refers to time after most recent dose.
CI = confidence interval; MMAE=monomethyl auristatin E; VPC = visual predictive check.
Source: Figure 17 in Applicant's Population PK Report

Predicted ADC and MMAE Exposure

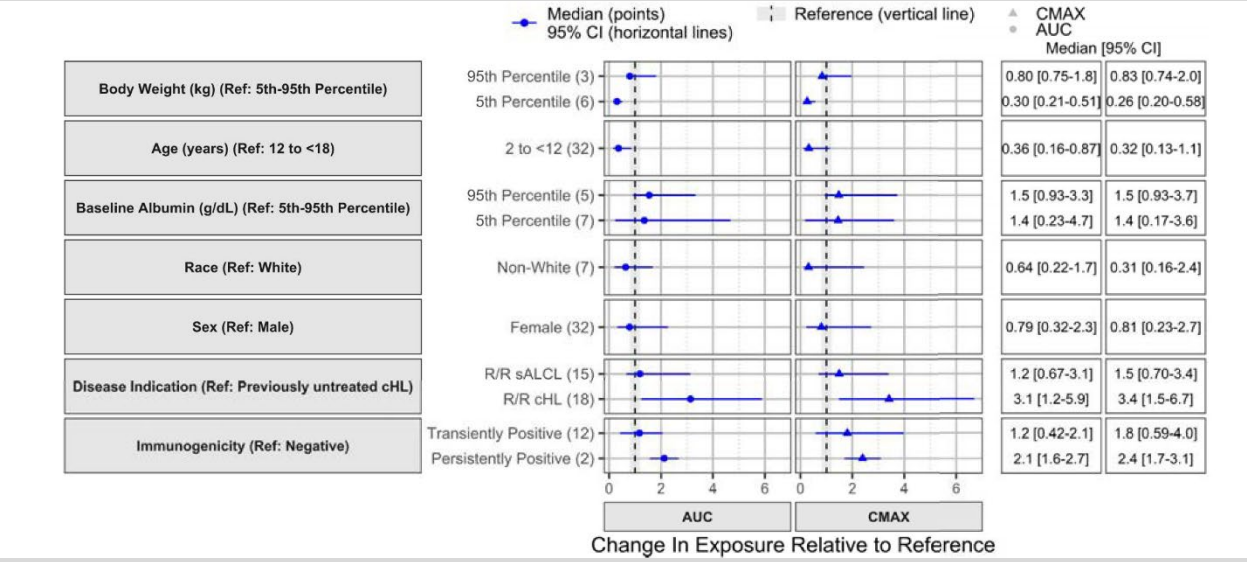
The effects of several relevant covariates on ADC and MMAE exposure are displayed in Figure 22 and Figure 23 respectively. Higher body weight was associated with higher clearance and higher central volume of distribution of both ADC and MMAE. Following administration of 1.8 mg/kg IV brentuximab vedotin Q3W, higher body weight was associated with increased exposure (C_{max}, C_{avg}, AUC) of ADC and MMAE. Figure 24 demonstrates that Cycle 1 exposure is associated with body weight and that younger patients tend to have lower exposure because younger patients have lower body weights.

Figure 22: Evaluation of the Effect of Intrinsic Factors on ADC Exposures at Steady State



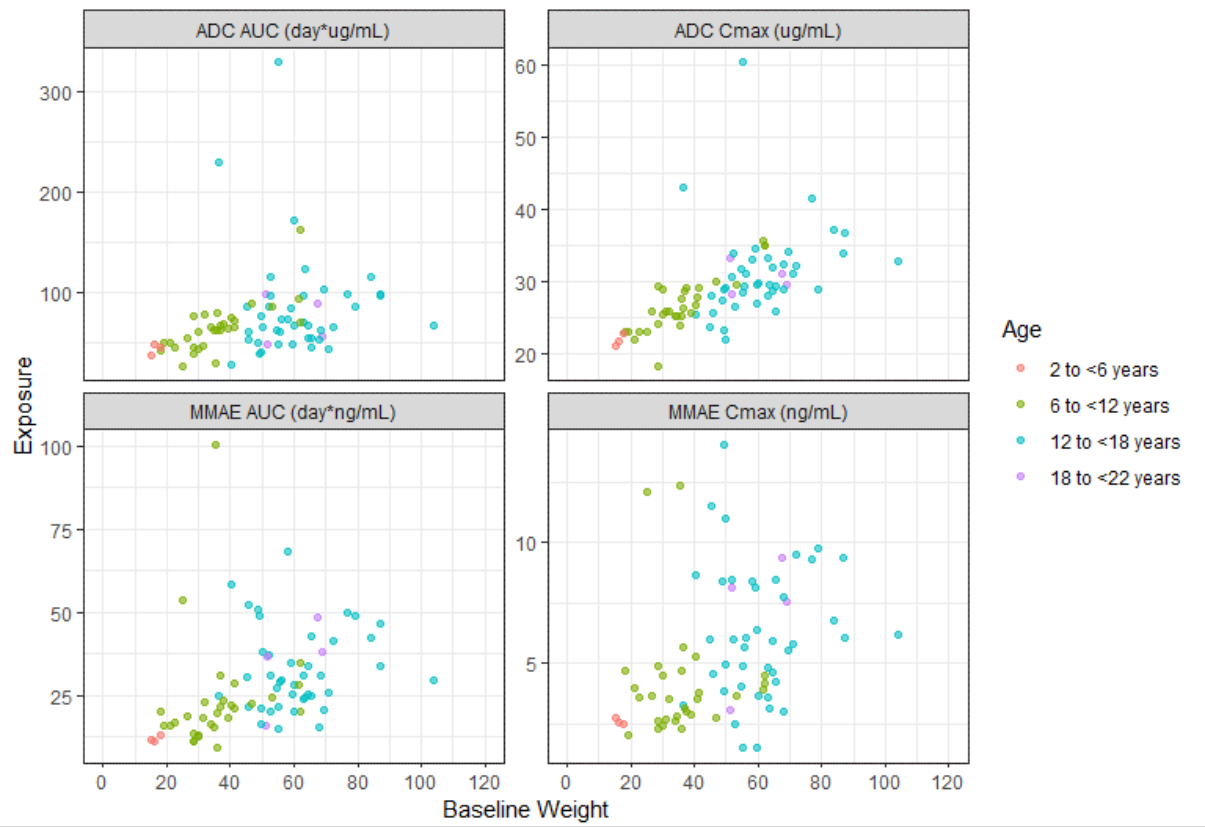
5^{th} percentile of body weight = patients weighing 18.9 kg or less; 95^{th} percentile of body weight = patients weighing 79.7 kg or greater. Median body weight = 50.6 kg.
5^{th} percentile of baseline albumin = patients with albumin 2.7 g/L or lower; 95^{th} percentile of baseline albumin = patients with albumin 4.9 g/L or greater. Median baseline albumin = 3.9 g/L.
Steady state Cmax and AUC = predicted AUC and Cmax during Cycle 4 of 1.8 mg/kg IV Q3W where 1 cycle is 21 days. The dotted vertical lines were calculated based on a reference patient of 50 kg, with a shaded region of 20% variability. Reference groups used for normalization for each category are indicated in each panel.
"Non-White" race category refers to patients who identify as Black or African American or Asian.
ADC=antibody-drug conjugate; AUC=area under the concentration-time curve; cHL = classical Hodgkin lymphoma; CI = confidence interval; Cmax=maximum concentration; IV = intravenously; Q3W = every 3 weeks; R/R = relapsed/refractory; sALCL=systemic anaplastic large cell lymphoma.
Source: Figure 12 in Applicant's Population PK Report

Figure 23: Evaluation of the Effect of Intrinsic Factors on MMAE Exposures at Steady State



5th percentile of body weight = patients weighing 18.9 kg or less; 95th percentile of body weight = patients weighing 79.7 kg or greater. Median body weight = 50.6 kg.
5th percentile of baseline albumin = patients with albumin 2.7 g/L or lower; 95th percentile of baseline albumin = patients with albumin 4.9 g/L or greater. Median baseline albumin = 3.9 g/L.
Steady state Cmax and AUC = predicted AUC and Cmax during Cycle 4 of 1.8 mg/kg IV Q3W where 1 cycle is 21 days. The dotted vertical lines were calculated based on a reference patient of 50 kg, with a shaded region of 20% variability. Reference groups used for normalization for each category are indicated in each panel.
"Non-White" race category refers to patients who identify as Black or African American or Asian.
AUC=area under the concentration-time curve; cHL = classical Hodgkin lymphoma; CI = confidence interval; Cmax=maximum concentration; IV = intravenously; MMAE=monomethyl auristatin E; Q3W = every 3 weeks; R/R = relapsed/refractory; sALCL=systemic anaplastic large cell lymphoma.
Source: Figure 21 in Applicant's Population PK Report

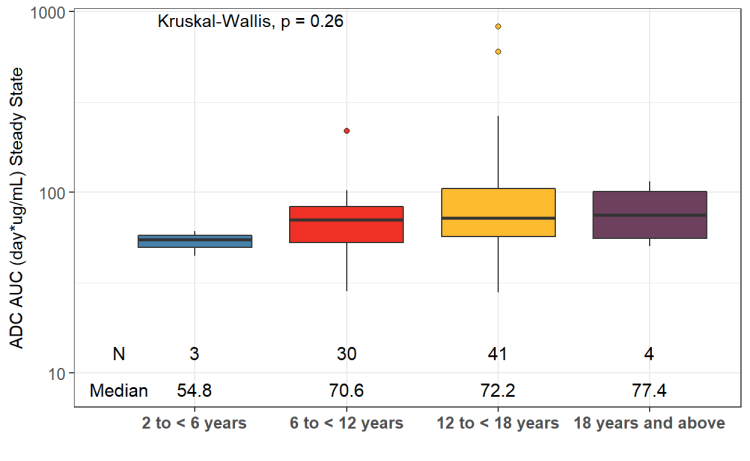
Figure 24: Individual Predicted Cycle 1 Exposure at 1.8 mg/kg IV Q3W versus Body Weight in Patients with PK Data



Exposure predicted following 1.8 mg/kg (up to 180 mg) IV Q3W in all patients.
ADC=antibody-drug conjugate; AUC=area under the concentration-time curve; Cmax=maximum concentration; IV = intravenous; MMAE = monomethyl auristatin E; Q3W = every 3 weeks.
Source: Reviewer Analysis of Applicant's Exposure-Response Dataset ("exposures-simultaneous-pkparms.csv")

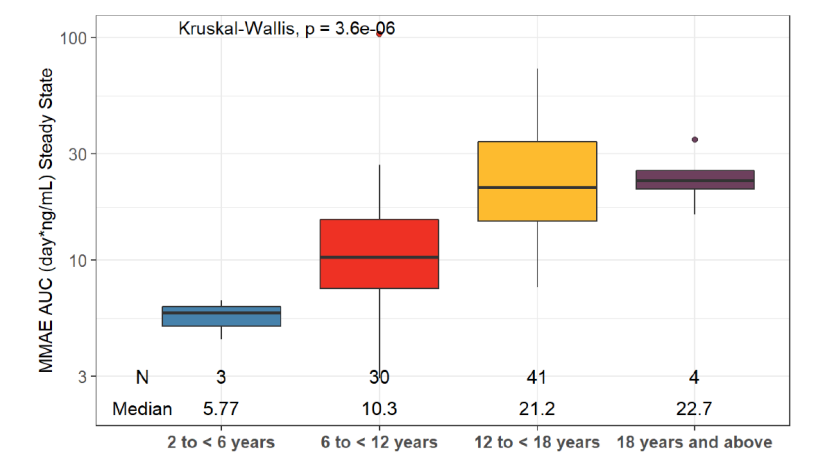
Individual predicted AUC_{ss} values in patients with PK data are summarized according to age group in Figure 25 and Figure 26 for ADC and MMAE, respectively. The median (range) weight was 16.1 kg (15.4 to 18.0 kg) in patients aged 6 to <12 years, 35.1 kg (18.2 to 62 kg) in patients aged 6 to <12 years, and 59.6 kg (36.5 to 103.8 kg) in patients aged 12 to <18 years. Individual predicted median ADC AUC_{ss} was 24% lower and median MMAE AUC_{ss} was 73% lower in patients aged 2 to <6 years (n=3) compared to patients aged 12 to <18 years (n=41). Individual predicted ADC and MMAE AUC_{ss} did not differ significantly in patients aged 12 to <18 years and patients aged 18 and older. However, due to the relatively small numbers of patients, accuracy of the median exposure is somewhat uncertain.

Figure 25: Individual Predicted Steady State ADC AUC at 1.8 mg/kg IV Q3W According to Age Category in Patients with PK Data, Semi-log Scale



Steady state AUC = AUC during Cycle 4 with planned dosing of 1.8 mg/kg (up to 180 mg) IV Q3W; 1 cycle = 21 days.
ADC=antibody-drug conjugate; AUC=area under the concentration-time curve; Cmax=maximum concentration;
IV = intravenous; Q3W = every 3 weeks.
Source: Figure 10 in Applicant's Population PK Report

Figure 26: Individual Predicted Steady State MMAE AUC at 1.8 mg/kg IV Q3W According to Age Category in Patients with PK Data, Semi-log Scale

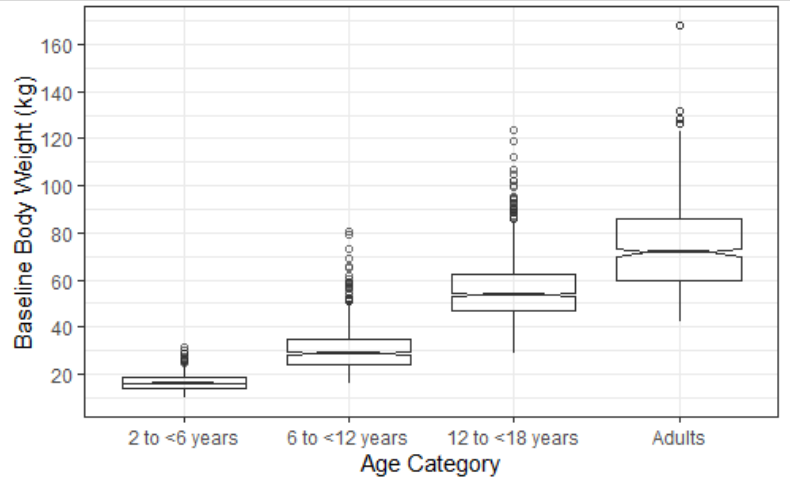


Steady state AUC = AUC during Cycle 4 with planned dosing of 1.8 mg/kg (up to 180 mg) IV Q3W; 1 cycle = 21 days.
AUC=area under the concentration-time curve; Cmax=maximum concentration; IV = intravenous;
MMAE = monomethyl auristatin E; Q3W = every 3 weeks.
Source: Figure 19 in Applicant's PopPK Report

To overcome some of the limitations from the limited number of patients with PK data per age category, ADC and MMAE clearance and exposure were also predicted in a virtual population. The virtual population contained 1000 patients aged 2 to <6 years, 1000 patients aged 6 to <12 years, 1000 patients aged 12 to <18 years, and 500 patients aged 18 years and older. patient demographics for virtual patients aged 2 to <18 years were resampled from the CDC

growth chart of weight according to sex and age, and proportions of male and female patients were similar. Patient demographics for virtual patients aged 18 years and older were resampled from two pivotal Phase 2 studies of BV in adults with HL and sALCL (Studies SG035-0003 and SG035-0004). A summary of body weight by age category in the virtual population is displayed in Figure 27.

Figure 27: Distribution of Body Weight by Age Group in the Virtual Population



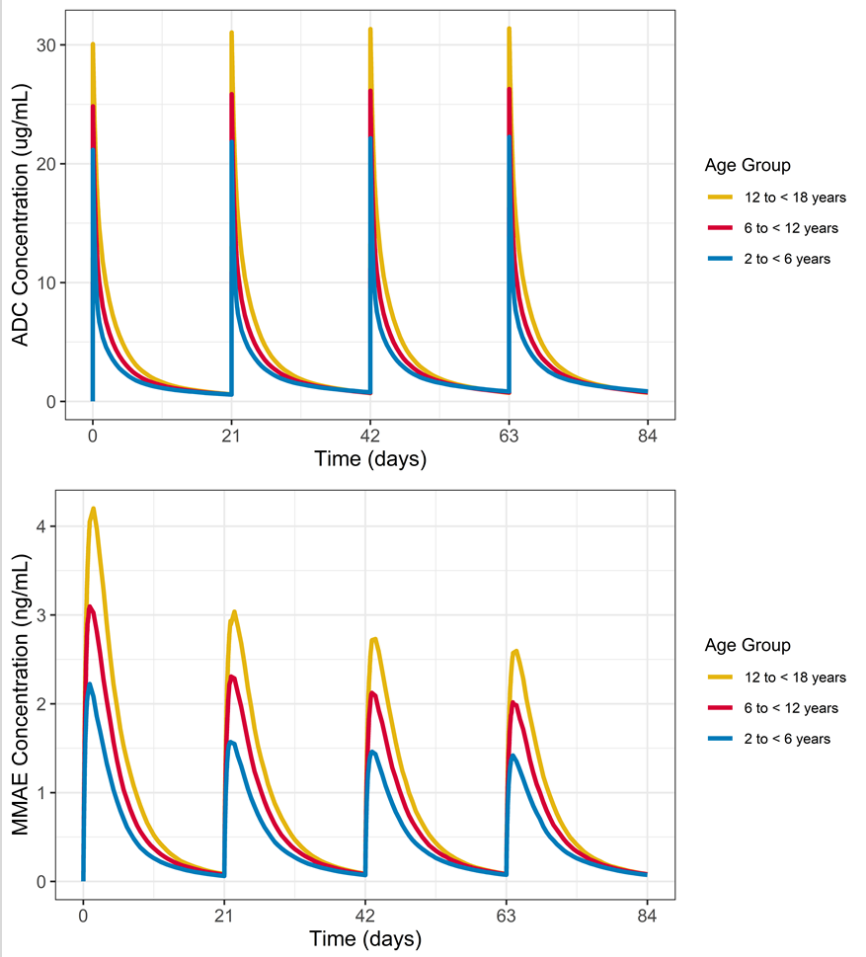
	2 to <6 years	6 to <12 years	12 to <18 years	Adults
n	1000	1000	1000	500
Median weight (kg)	16.1	28.8	53.8	71.6
5th to 95th percentile weight (kg)	11.9 to 22.4	19.8 to 45.7	37.5 to 78.7	48.6 to 119.2

Virtual pediatric population contained 3000 virtual patients aged 2 to <18 years with body weight resampled from CDC weight chart by age and sex with similar proportions of male and female patients. Virtual adult population contained 500 patients aged ≥18 years with body weight resampled from two pivotal Phase 2 studies of BV in adults with HL and sALCL (Studies SG035-0003 and SG035-0004).
Source: FDA Reviewer Analysis of Applicant's Virtual Population Dataset

Differences in predicted median AUC_{ss} may be due to small differences in demographic distributions, as the distribution of body weight appeared more normal within each age group in the virtual population. Predicted exposure in the virtual population is more likely to be accurate for a given age group compared to predicted exposure in patients with PK data because the virtual population contains greater numbers of patients and more normal distributions of body weight which majorly impacts predicted exposure.

Predicted median PK profiles for ADC and MMAE according to age group are displayed in Figure 28. Predicted clearance and exposure are summarized according to age category for patients with PK data (n=78) and the virtual population (n=3500) for ADC in Table 46 and for MMAE in Table 47. Exposure (AUC and C_{max}) of ADC appeared slightly higher at steady state (i.e., Cycle 4) compared to Cycle 1. Exposure of MMAE during Cycle 1 was higher than exposure of MMAE at steady state which is explained by the time-dependent decrease in unconjugated MMAE formation rate described in the MMAE PPK model (see Equations 1, 2, and 3 above).

Figure 28: Predicted Median of Individual ADC and MMAE Prediction Versus Time From the Virtual Pediatric Population by Age Group



Virtual pediatric population contained 3000 virtual patients aged 2 to <18 years with body weight resampled from CDC weight chart by age and sex with similar proportions of male and female patients. All virtual patients received 1.8 mg/kg (up to 180 mg) IV infused over 30 minutes every 3 weeks; 1 cycle = 21 days.
ADC=antibody-drug conjugate; IV = intravenously; MMAE = monomethyl auristatin E.
Source: FDA Reviewer Analysis of Applicant's Virtual Population Dataset and Final Population PK Models.

Table 46: Summary of Predicted ADC Exposures at Steady State following Brentuximab Vedotin 1.8 mg/kg IV Q3W

		Patients with PK Data (n=78)				Virtual Population (n=3500)			
Exposure Metric	**Statistic**	**2 to <6 years (N=3)**	**6 to <12 years (N=30)**	**12 to <18 years (N=41)**	**≥18 years (N=4)**	**2 to <6 years (N=1000)**	**6 to <12 years (N=1000)**	**12 to <18 years (N=1000)**	**≥18 years (N=500)**
ADC Cycle 1 AUC (day*ug/mL)	Mean (CV%)	43.9 (12.4%)	64.3 (38.8%)	84.1 (63.7%)	73.0 (34.0%)	44.1 (40.2%)	60.1 (43.6%)	82.1 (45.9%)	75.2 (38.3%)
	Median	45.7	63.2	67.8	72.3	42.9	57.0	76.3	71.5
	Min, Max	37.8, 48.2	27.2, 163	27.4, 329	48.2, 99.1	6.29, 121	8.97,167	11.1, 249	17.9, 182
	25th, 75th pct	41.7, 47.0	47.3, 73.5	54.8, 96.6	53.8, 91.4	30.7, 56.0	39.8, 75.4	55.2, 103	54.5, 92.1
ADC AUCss (day*ug/mL)	Mean (CV%)	53.5 (15.7%)	74.2 (45.7%)	113 (128%)	80.0 (38.8%)	59.8 (57.5%)	75.1 (57.9%)	97.7 (59.5%)	92.8 (48.5%)
	Median	54.8	70.6	72.2	77.4	52.5	65.7	84.0	84.8
	Min, Max	44.6, 61.2	28.4, 219	28.0, 826	50.3, 115	6.33, 251	9.01, 309	11.1, 414	18.6, 312
	25th, 75th pct	49.7, 58.0	53.0, 83.6	57.0, 105	55.9, 102	34.6, 78.3	43.3, 95.4	58.3, 122	60.6, 117
ADC Cycle 1 Cmax (ug/mL)	Mean (CV%)	21.8 (4.2%)	26.7 (14.6%)	31.2 (20.5%)	30.5 (7.1%)	21.8 (21.9%)	25.6 (22.0%)	30.7 (21.9%)	31.7 (17.2%)
	Median	21.6	25.8	29.6	30.3	21.4	25.2	29.9	31.2
	Min, Max	20.9, 22.7	18.3, 35.5	21.9, 60.4	28.2, 33.2	9.08, 43.4	12.4, 44.7	14.0, 56.9	18.5, 65.3
	25th, 75th pct	21.3, 22.2	24.3, 29.0	28.1, 32.9	29.1, 31.6	18.5, 24.3	21.5,29.2	25.9, 34.8	27.7, 34.6
ADC Cmax,ss (ug/mL)	Mean (CV%)	22.6 (4.4%)	27.6 (15.6%)	33.0 (32.5%)	31.2 (8.7%)	22.9 (21.1%)	26.8 (21.3%)	32.0 (21.7%)	33.0 (17.7%)
	Median	22.6	26.7	31.2	30.8	22.5	26.4	31.1	32.5
	Min, Max	21.5, 23.5	18.8, 39.3	22.1, 86.8	28.4, 34.6	10.0, 43.8	13.3, 47.1	14.5, 59.3	18.7, 70.9
	25th, 75th pct	22.1, 23.1	24.7, 29.8	28.6, 33.5	29.4, 32.6	19.6, 25.6	22.7, 30.5	26.8, 36.3	28.9, 36.2
ADC Clearance at Steady State (L/day)	Mean (CV%)	0.559 (14.2%)	0.940 (35.6%)	1.49 (43.9%)	1.51 (40.0%)	0.676 (69.1%)	0.968 (64.1%)	1.39 (64.5%)	1.74 (53.4%)
	Median	0.588	0.886	1.48	1.55	0.554	0.821	1.19	1.49
	Min, Max	0.469, 0.619	0.501, 2.11	0.0590, 2.85	0.799, 2.15	0.0830, 3.37	0.134, 4.40	0.231, 10.1	0.49, 6.76
	25th, 75th pct	0.529, 0.604	0.756, 1.02	1.10, 2.00	1.14, 1.93	0.365, 0.856	0.537, 1.21	0.787, 1.75	1.09,2.18

Virtual pediatric population contained 3000 virtual patients aged 2 to <18 years with body weight resampled from CDC weight chart by age and sex with similar proportions of male and female patients. Virtual adult population contained 500 patients aged ≥18 years with body weight resampled from two Phase 2 studies (SG035-0003 and SG035-0004). Steady state exposure = exposure during Cycle 4 of 1.8 mg/kg (up to 180 mg) IV infused over 30 minutes Q3W; 1 cycle = 21 days.

ADC=antibody-drug conjugate; AUC=area under the concentration-time curve; Cmax=maximum concentration; CV = coefficient of variation; IV = intravenous; pct = percentile; Q3W = every 3 weeks; SS = steady state.

Source: Table 13 in Applicant's Population PK Report.

Table 47: Summary of Predicted MMAE Exposures at Cycle 1 and Steady State Brentuximab Vedotin 1.8 mg/kg IV Q3W

		Patients with PK Data (n=78)				Virtual Population (n=3500)			
Exposure Metric	**Statistic**	**2 to <6 years (N=3)**	**6 to <12 years (N=30)**	**12 to <18 years (N=41)**	**≥18 years (N=4)**	**2 to <6 years (N=1000)**	**6 to <12 years (N=1000)**	**12 to <18 years (N=1000)**	**≥18 years (N=500)**
MMAE Cycle 1 AUC (day*ng/mL	Mean (CV%)	12.0 (7.6%)	23.5 (72.0%)	32.8 (38.0%)	34.7 (39.2%)	17.6 (65.4%)	24.4 (65.4%)	32.3 (59.6%)	33.7 (74.8%)
	Median	11.5	20.0	29.8	37.4	14.8	20.1	27.6	25.5
	Min, Max	11.3, 13.0	9.40, 100	15.0, 68.4	15.8, 48.3	2.49, 88.0	3.04, 129	3.29, 128	2.75, 150
	25^{th}, 75^{th} pct	11.4, 12.3	15.9, 23.5	24.6, 41.4	31.5, 40.6	9.47, 22.6	13.4, 30.9	18.9,40.7	17.3, 42.3
MMAE AUCss (day*ng/mL)	Mean (CV%)	5.58 (19.7%)	14.4 (123%)	27.0 (61.2%)	24.0 (32.5%)	16.5 (119%)	21.9 (119%)	27.8 (106%)	26.8 (95.2%)
	Median	5.77	10.3	21.2	22.7	10.4	13.8	18.7	18.6
	Min, Max	4.39, 6.57	2.94, 103	7.51, 72.6	16.0, 34.7	0.520, 219	0.584, 286	0.732, 302	0.713, 226
	25^{th}, 75^{th} pct	5.08, 6.17	7.44, 15.2	14.9, 34.1	21.0, 25.7	5.59, 19.9	7.42, 24.9	10.2, 35.8	10.0, 35.0
MMAE Cycle 1 Cmax (ng/mL)	Mean (CV%)	2.60 (5.9%)	4.13 (58.0%)	6.27 (44.6%)	7.03 (38.9%)	3.49 (71.8%)	4.81 (67.4%)	6.06 (73.5%)	6.62 (71.1%)
	Median	2.52	3.60	6.00	7.85	2.81	3.97	4.98	5.32
	Min, Max	2.50, 2.78	2.03, 12.4	1.51, 14.1	3.09, 9.35	0.333, 22.1	0.357, 22.9	0.462, 50.3	0.619, 31.6
	25^{th}, 75^{th} pct	2.51, 2.65	2.77, 4.51	4.23, 8.38	6.43, 8.45	1.70, 4.38	2.52, 6.21	3.09, 7.69	3.32, 8.83
MMAE Cmax,ss (ng/mL)	Mean (CV%)	0.958 (17.4%)	2.32 (101%)	4.94 (71.5%)	4.49 (30.1%)	2.75 (120%)	3.66 (109%)	4.71 (116%)	4.84 (101%)
	Median	0.895	1.63	3.92	4.48	1.71	2.33	2.97	3.38
	Min, Max	0.833, 1.15	0.445, 12.6	0.865, 14.5	2.87, 6.15	0.0990,28.3	0.110, 32.9	0.0820, 62.8	0.0950, 35.6
	25^{th}, 75^{th} pct	0.864, 1.02	1.10, 2.60	2.58, 6.15	3.90, 5.07	0.909, 3.23	1.22, 4.51	1.58, 5.71	1.61, 6.18
MMAE Clearance at Steady State (L/day)	Mean (CV%)	23.9 (1.7%)	36.4 (40.9%)	47.1 (46.8%)	45.7 (37.5%)	22.9 (61.0%)	33.2 (59.2%)	48.1 (57.3%)	54.9 (80.2%)
	Median	23.8	36.8	43.8	40.9	19.6	28.6	41.1	43.3
	Min, Max	23.6, 24.4	9.87, 83.8	3.93,111	31.3, 69.8	4.01, 135	3.31, 189	7.73, 205	6.29, 353
	25^{th}, 75^{th} pct	23.7, 24.1	26.7, 41.8	32.8, 54.6	34.7, 52.0	13.7, 27.7	19.8, 41.4	28.6, 59.4	26.4, 67.8

Virtual pediatric population contained 3000 virtual patients aged 2 to <18 years with body weight resampled from CDC weight chart by age and sex with similar proportions of male and female patients. Virtual adult population contained 500 patients aged ≥18 years with body weight resampled from two Phase 2 studies (SG035-0003 and SG035-0004). Steady state exposure = exposure during Cycle 4 of 1.8 mg/kg (up to 180 mg) IV infused over 30 minutes Q3W; 1 cycle = 21 days.

AUC=area under the concentration-time curve; Cmax=maximum concentration; CV = coefficient of variation; IV = intravenous; MMAE=monomethyl auristatin E; pct = percentile; Q3W = every 3 weeks; SS = steady state.

Source: Table 12 and Table 13 in Applicant's Population PK Report.

Individual predicted ADC and MMAE AUC_{ss} values in the virtual population are presented according to age group in Figure 2. Predicted ADC and MMAE exposure did not differ significantly in virtual patients aged 12 to <18 years and virtual patients aged 18 and older, which is expected given the significant overlap of weight ranges between these age groups. Table 48 summarizes differences in predicted ADC and MMAE exposure in younger age groups compared to patients aged 12 to <18 years.

Individual predicted median ADC Cycle 1 AUC was 44% lower and median ADC AUC_{ss} was 38% lower in virtual patients aged 2 to <6 years old (n=1000) compared to virtual patients aged 12 to <18 years (n=1000). Individual predicted median MMAE Cycle 1 AUC was 46% lower and median MMAE AUC_{ss} was 44% lower in virtual patients aged 2 to <6 years old compared to virtual patients aged 12 to <18 years. Differences in ADC AUC appeared greater than differences in ADC C_{max} according to age group, while differences in MMAE AUC and C_{max} appeared similar according to age group.

Table 48: Comparison of Predicted Exposure by Age Group at Cycle 1 and Steady State

		Cycle 1		Steady State	
Exposure Metric	**Age Group**	**Median [Min, Max]**	**% Change in Median Exposure Compared to 12 to <18 years**	**Median [Min, Max]**	**% Change in Median Exposure Compared to 12 to <18 years**
ADC AUC (day*ug/mL)	12 to <18 years	76.3 [11.1, 249]	-	84.0 [11.1, 414]	-
	6 to <12 years	57.0 [8.97, 167]	25.3% lower	65.7 [9.01, 309]	21.8% lower
	2 to <6 years	42.9 [6.29, 121]	43.8% lower	52.5 [6.33, 251]	37.5% lower
ADC Cmax (ug/mL)	12 to <18 years	29.9 [14.0, 56.9]	-	31.1 [14.5, 59.3]	-
	6 to <12 years	25.2 [12.4, 44.7]	15.7% lower	26.4 [13.3, 47.1]	15.1% lower
	2 to <6 years	21.4 [9.08, 43.4]	28.4% lower	22.5 [10.0, 43.8]	27.7% lower
MMAE AUC (day*ng/mL)	12 to <18 years	27.6 [3.29, 128]	-	18.7 [0.732, 02]	-
	6 to <12 years	20.1 [3.04, 129]	27.2% lower	13.8 [0.584, 86]	26.2% lower
	2 to <6 years	14.8 [2.49, 88.0]	46.4% lower	10.4 [0.520, 19]	44.4% lower
MMAE Cmax (ng/mL)	12 to <18 years	4.98 [0.462, 50.3]	-	2.97 [0.0820, 62.8]	-
	6 to <12 years	3.97 [0.357, 22.9]	20.3% lower	2.33 [0.110, 32.9]	21.5% lower
	2 to <6 years	2.81 [0.333, 22.1]	43.6% lower	1.71 [0.0990, 28.3]	42.4% lower

Virtual pediatric population contained 3000 virtual patients (1000 patients aged 2 to <6 years, 1000 patients aged 6 to <12 years, and 1000 patients aged 12 to <18 years) with body weight resampled from CDC weight chart by age and sex with similar proportions of male and female patients. Steady state exposure = exposure during Cycle 4.
1 cycle = 21 days. All virtual patients received 1.8 mg/kg (up to 180 mg) IV infused over 30 minutes every 3 weeks.
AUC=area under the concentration-time curve; Cmax=maximum concentration; CV = coefficient of variation;
IV = intravenously; MMAE=monomethyl auristatin E.
Source: FDA Reviewer Analysis of Applicant's Exposure-Response Dataset

Using the same virtual patient population, steady state ADC and MMAE exposure in patients aged 3 to <6 years and patients aged 6 to <12 years was compared to exposure in patients aged 12 to <17 years. These comparisons are summarized in Table 7.

Overall, the PPK analyses of ADC and MMAE support the proposed dosing regimen of 1.8 mg/kg IV brentuximab vedotin Q3W in pediatric patients aged 2 and older with previously untreated high risk cHL. Patients with low body weight (i.e., patients aged 2 to <6 years) are expected to have lower ADC and MMAE exposure following 1.8 mg/kg IV dosage compared to patients with higher body weight (i.e., patients aged 12 to <18 years). Due to the limited number of patients with low body weight with PK data, it is unclear if this exposure difference is associated with any different clinical outcomes. Current data do not support the need for therapeutic individualization according to covariates other than body weight.

19.4.2. Exposure-Response Analysis

19.4.2.1. E-R Efficacy Executive Summary

The FDA's Assessment:

The E-R efficacy analysis was limited by the relatively small number of patients with PK data (n=26). No associations were identified between ADC exposure and secondary efficacy endpoints of early response rate (ERR), rate of response-directed radiation therapy (RTR), or complete metabolic response rate (CMR).

Although higher body weight was associated with higher ADC exposure, no differences in event-free survival (EFS), ERR, or RTR were identified between weight quartiles in the ITT population of Study AHOD1331 (n=300 randomized to receive BV). The lack of association between weight and efficacy is congruent with the lack of association between exposure and efficacy.

Overall, the E-R efficacy analysis did not identify any concerns and supports the proposed 1.8 mg/kg (up to 180 mg) IV Q3W dosage in pediatric patients aged 2 years and older with previously untreated high risk cHL.

19.4.2.2. E-R Efficacy Assessment Summary

The Applicant's Position:

Due to the limited PK population (N=26) in AHOD1331, and since the PK population primarily consisted of ages <13 years by design, age-specific analysis in the treated population was generated to supplement the exploratory E-R analysis for efficacy. Based on results from age subgroup and exploratory E-R analyses, there was no indication of differential efficacy with exposure; subjects aged 2 to <12 years had numerically lower exposure but there was no apparent impact on EFS. Additionally, exposures (Cycle 1 average concentration [C_{ave}]) to ADC in the 26 PK subjects from AHOD 1331 were similar in subjects grouped by early response or requiring response-directed RT.

General Information			
Goal of ER analysis		To confirm that 1.8 mg/kg Q3W brentuximab vedotin provides positive benefit-risk to pediatric subjects with previously untreated high-risk cHL and that no subgroup, such as pediatric subjects aged <12 years, will require a dose adjustment.	
Study Included		AHOD1331	
Endpoint		Primary: EFS Secondary: early response rate and rate of response-directed radiation therapy	
No. of Patients (total, and with individual PK)		Total patients=296, Patients having PK=26	
Population Characteristics (Table 11)	General	Age median: 15 yrs. (range 3-21 yrs.) Weight median: 57.4 kg (range: 15.4-178.4 kg) 159 (53.7%) male *159 (53.7%) male* *221 (74.7%) White* *34 (11.5%) Black or African American* *7 (2.4%) Asian* *8 (2.7%) Others* *26 (8.7%) Unknown/Not reported*	
	Pediatrics (if any)	Age median: 15 (3-21 yrs., 1.7% < 6 yr, 15.8% 6 to < 12 yrs., 74.3% 12 to <18 yrs.)	
Dose(s) Included		1.8 mg/kg Q3W	
Exposure Metrics Explored (range)		Cave	
Covariates Evaluated		No applicable	
Final Model Parameters		**Summary**	**Acceptability [FDA's comments]**
Model Structure		N/A	
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		m2.7.2 Figures 18 and Figure 19	The E-R efficacy analysis was limited by the relatively small number of patients (n=26). Relationships between EFS and exposure could not be evaluated because no EFS events occurred in patients with PK data (n=26). No E-R associations were identified with ERR, RTR, or CMR. Higher weight is associated with higher exposure, but no differences in EFS, ERR, or RTR were identified across weight quartiles. The E-R efficacy analysis did not identify any concerns with the proposed BV dosage.
Overall Clinical Relevance for ER		No apparent relationship between exposure and efficacy	
Labeling Language		**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics		N/A	N/A

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.

m2.7.2 Figure 18 Kaplan-Meier Curves for EFS with 95% Confidence Intervals by Age Group (2 to <12 and 12 to ≤18)
m2.7.2 Figure 19 Cycle 1 Cave of ADC Grouped by (A) Early Response or (B) Rate of Response Directed Radiation Therapy

The FDA's Assessment:

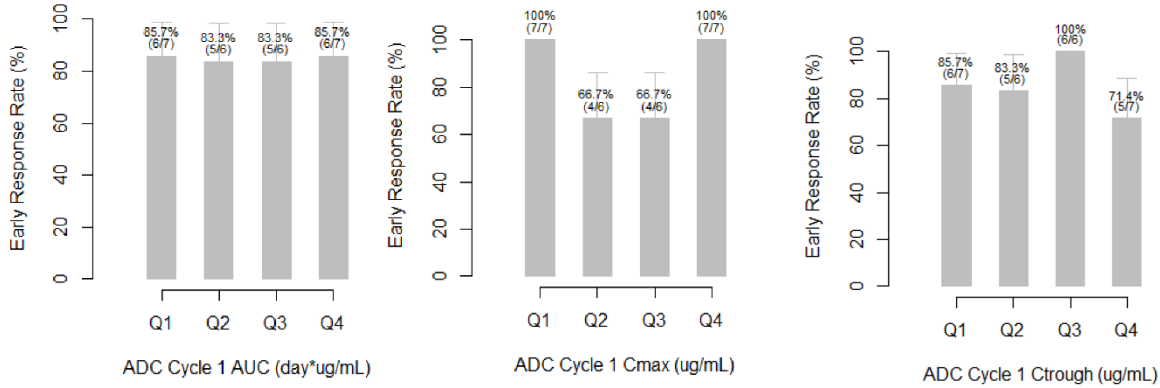
The E-R efficacy dataset contained data from 26 pediatric patients with PK data aged 3 years and older in Study AHOD1331 who were scheduled to receive 1.8 mg/kg IV Q3W of BV for treatment of previously untreated high risk cHL. Baseline patient demographics are summarized in Table 43. Based on the mechanism of action, only ADC exposure was evaluated for associations with efficacy endpoints.

No event of relapse/progression, second malignancy, or death occurred in patients with PK data (n=26) in Study AHOD1331 as of the data cutoff date of 31 December 2021, at a median duration of follow-up of 42.2 months. Therefore, the primary efficacy endpoint of event-free survival (EFS) could not be evaluated in the E-R efficacy dataset.

No clear trends in the secondary efficacy outcomes of early response rate (ERR), rate of response-directed radiation therapy (RTR), or complete metabolic response rate were identified across quartiles of Cycle 1 ADC exposure (AUC, C_{max}, and C_{trough}). However, the lack of identified E-R associations may be due to the limited number of patients with both PK and efficacy data (n=26), the inclusion of only one dosage in the E-R dataset (1.8 mg/kg IV Q3W), or both.

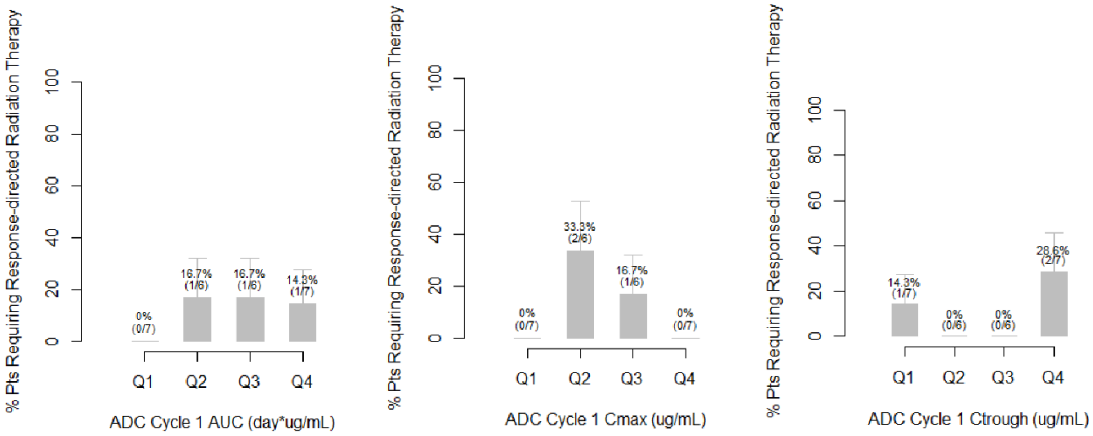
Figure 29 displays ERR according to Cycle 1 ADC exposure quartile. Figure 30 displays RTR according to Cycle 1 ADC exposure quartile. Figure 31 displays complete metabolic response rate according to Cycle 1 ADC exposure quartile. Cycle 1 ADC exposure quartiles are described in Table 49.

Figure 29: Observed Early Response Rate across Predicted Cycle 1 ADC Exposure Quartiles in Study AHOD1331 Patients with PK Data



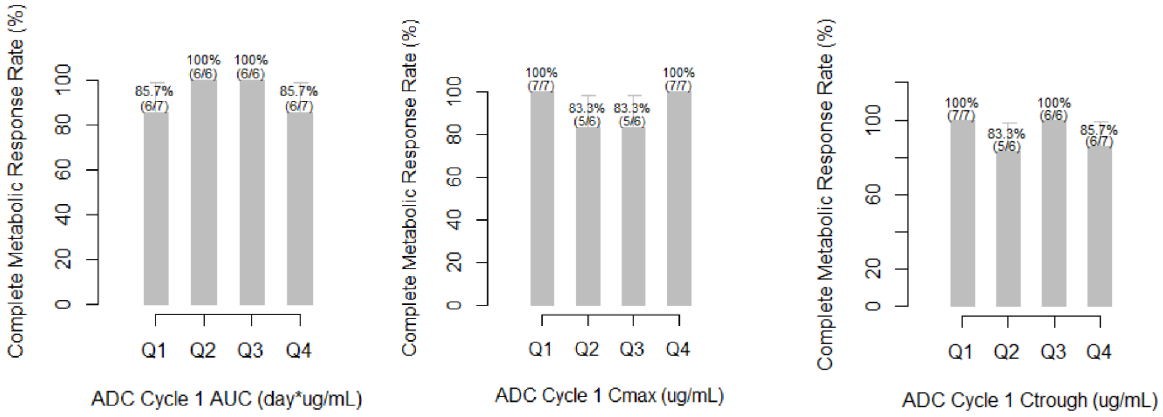
Q1 = lowest exposure quartile.
ADC=antibody-drug conjugate; AUC=area under the concentration-time curve; Cmax = maximum concentration; Ctrough = trough concentration; Q = quartile.
Source: Figure 1 in Applicant's 6 September 2022 response to 26 August 2022 information request.

Figure 30: Observed Rate of Response-Directed Radiation Therapy across Predicted Cycle 1 ADC Exposure Quartiles in Study AHOD1331 Patients with PK Data



Q1 = lowest exposure quartile.
ADC=antibody-drug conjugate; AUC=area under the concentration-time curve; Cmax = maximum concentration; Ctrough = trough concentration; Q = quartile.
Source: Figure 1 in Applicant's 6 September 2022 Response to 26 August 2022 Information Request.

Figure 31: Observed Complete Metabolic Response Rate across Predicted Cycle 1 ADC Exposure Quartiles in Study AHOD1331 Patients with PK Data



Q1 = lowest exposure quartile.
ADC=antibody-drug conjugate; AUC=area under the concentration-time curve; Cmax = maximum concentration; Ctrough = trough concentration; Q = quartile.
Source: Figure 1 in Applicant's 6 September 2022 Response to 26 August 2022 Information Request.

Table 49: Summary of Predicted Cycle 1 ADC Exposure Quartiles in Study AHOD1331 Patients with PK Data

Cycle 1 ADC	Q1 N=7	Q2 N=6	Q3 N=6	Q4 N=7	% Reduction from Q4 to Q1 *
Cavg (ug/mL)	2.22 (1.8,2.86)	3.06 (2.97,3.17)	3.52 (3.27,4.08)	4.6 (4.22,8.17)	51.74
AUC (day*ug/mL)	46.62 (37.75,60.15)	64.32 (62.28,66.67)	73.94 (68.76,85.71)	96.59 (88.59,171.56)	51.73
C_{max} (ug/mL)	22.93 (20.95,25.18)	26.11 (25.65,27.78)	28.98 (28.61,29.5)	33.32 (29.57,36.64)	31.18
C_{trough} (ug/mL)	0.42 (0.32,0.54)	0.58 (0.58,0.62)	0.67 (0.63,0.76)	1.03 (0.78,3.99)	59.22

Calculated as 100(Q4 median - Q1 median)/Q4 median. Q1 = lowest exposure quartile.
ADC=antibody-drug conjugate; AUC=area under the concentration-time curve; Cavg = average concentration; Cmax = maximum concentration; Ctrough = trough concentration; Q = quartile.
Source: Table 4 in Applicant's 6 September 2022 Response to 26 August 2022 Information Request.

Additional subgroup analyses of efficacy

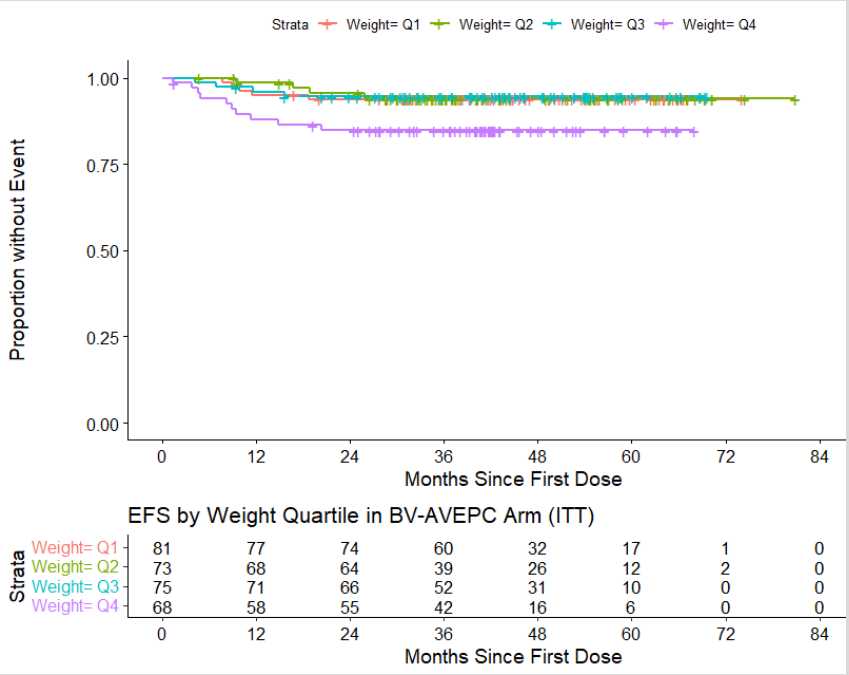
The E-R efficacy analysis was limited by the relatively small number of patients in Study AHOD1331 with PK data (n=26). However, because higher body weight was associated with higher exposure following 1.8 mg/kg IV Q3W (see Section 19.4.1.2), the reviewer compared efficacy in the Study AHOD1331 ITT population across body weight quartiles to evaluate whether lower weight was associated with differences in efficacy outcomes. No clear associations were identified between lower body weight and worse EFS, ERR, or RTR.

Event-free survival

The lowest weight quartile (Q1) did not appear to be associated with worse EFS in either arm (BV-AVEPC or ABVE-PC) compared to higher weight quartiles. However, it should be noted that only 18/300 (6.0%) patients weighed <30 kg and 5/300 (1.7%) patients weighed <20 kg in the BV-AVEPC arm. Therefore, it is still inconclusive if there are any differences in EFS between patients weighing <20 kg or <30 kg compared to patients with higher weights.

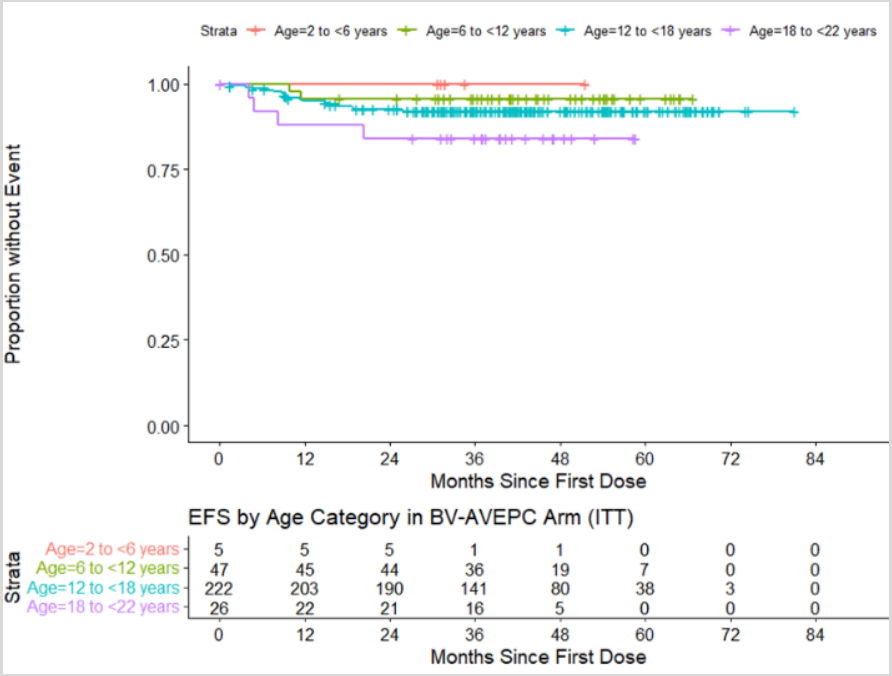
Younger age groups did not appear to have worse EFS compared to older age groups. The primary efficacy endpoint, EFS, is presented in patients randomized to receive BV according to body weight quartile in Figure 32 and according to age category in Figure 33.
Similarly, the FDA independently conducted subgroup analyses of EFS in the ITT population to determine hazard ratios in patients aged 2 to <12 years and in patients aged 12 to <18 years (see Section 8.1.2). This exploratory analysis did not identify worse EFS according to either age category. However, due to limited numbers of patients in multiple age categories, the current data cannot support any definitive conclusions on the association between EFS and age in pediatric patients aged 2 years and older.

Figure 32: Kaplan Meier Plots of Event-Free Survival According to Body Weight Quartile in Study AHOD1331 ITT Population Randomized to BV-AVEPC Arm



Note: data excluded for 3 patients in the BV-AVEPC arm without recorded baseline body weight. Efficacy data cutoff date of 31 December 2021. Weight Q1= 14.8 to <47.5 kg; weight Q2 = 47.5 to <58.7 kg; weight Q3 = 58.7 to <70.8 kg; weight Q4 = 70.8 to 178.5 kg.
BV-AVEPC = brentuximab vedotin, doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide; EFS = event-free survival; ITT = intent-to-treat; Q = quartile.
Source: FDA Reviewer analysis

Figure 33: Kaplan Meier Plots of Event-Free Survival According to Age Category in Study AHOD1331 ITT Population Randomized to BV-AVEPC Arm



Efficacy data cutoff date of 31 December 2021.
BV-AVEPC = brentuximab vedotin, doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide; EFS = event-free survival; ITT = intent-to-treat; Q = quartile.
Source: FDA Reviewer analysis

Early Response Rate and Rate of Response-directed Radiation Therapy

Although patients who weighed 70.8 kg and over in the BV-AVEPC arm had a numerically higher ERR (88% in Q4 compared to 82%, 71%, and 80% in Q1, Q2, and Q3, respectively), there were no clear differences in ERR or RTR across body weight quartiles in either treatment arm. There were also no clear differences in ERR or RTR identified by age subgroup, although this exploratory comparison is limited due to the relatively small number of patients in the 2 to <6 year, 6 to <12 year, and 18 to <22 year age groups.

Observed ERR and RTR in the ITT population are summarized according to body weight quartile in Table 50 and according to age category in Table 51.

Table 50: Early Response Rate and Rate of Response-Directed Radiation Therapy According to Body Weight Quartile in Study AHOD1331 ITT Population

Efficacy Endpoint	Planned Treatment	Weight Q1: 14.8 to <47.5 kg	Weight Q2: 47.5 to <58.7 kg	Weight Q3: 58.7 to <70.8 kg	Weight Q4: 70.8 to 178.5 kg
Early Response Rate	BV-AVEPC	66/81 (81.5%)	52/73 (71.2%)	60/75 (80%)	60/68 (88.2%)
	ABVE-PC	56/68 (82.4%)	57/75 (76%)	59/73 (80.8%)	65/80 (81.2%)
Response-directed Radiation Therapy Rate	BV-AVEPC	10/81 (12.3%)	11/73 (15.1%)	9/75 (12%)	7/68 (10.3%)
	ABVE-PC	8/68 (11.8%)	10/75 (13.3%)	10/73 (13.7%)	11/80 (13.8%)

Note: data excluded for 3 patients in the BV-AVEPC arm without recorded baseline body weight and for 4 patients in the ABVE-PC arm without recorded baseline body weight. Efficacy data cutoff date of 31 December 2021.
ABVE-PC= doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide;
BV-AVEPC = brentuximab vedotin, doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide;
ITT = intent to treat.
Source: FDA Reviewer analysis

Table 51: Early Response Rate and Rate of Response-Directed Radiation Therapy According to Age Category in Study AHOD1331 ITT Population

Efficacy Endpoint	Planned Treatment	2 to <6 years	6 to <12 years	12 to <18 years	18 to <22 years
Early Response Rate	BV-AVEPC	4/5 (80%)	38/47 (80.9%)	177/222 (79.7%)	19/26 (73.1%)
	ABVE-PC	4/4 (100%)	31/34 (91.2%)	176/226 (77.9%)	26/36 (72.2%)
Response-directed Radiation Therapy Rate	BV-AVEPC	1/5 (20%)	5/47 (10.6%)	28/222 (12.6%)	6/26 (23.1%)
	ABVE-PC	0/4 (0%)	2/34 (5.9%)	34/226 (15%)	7/36 (19.4%)

Efficacy data cutoff date of 31 December 2021. ABVE-PC= doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide; BV-AVEPC = brentuximab vedotin, doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide; ITT = intent to treat.
Source: FDA Reviewer analysis

Although higher body weight was associated with higher ADC exposure following 1.8 mg/kg IV Q3W, the subgroup analysis of the ITT population did not identify any associations between body weight and EFS, ERR, or RTR. The exploratory comparison of EFS, ERR, and RTR across age subgroups also did not identify any concerns with the 1.8 mg/kg IV Q3W dosage. These findings are congruent with the limited E-R analysis in 26 patients with PK data, which did not identify any associations between predicted Cycle 1 ADC exposure and ERR, RTR, or complete metabolic response rate. The E-R efficacy analysis and additional subgroup analyses support the proposed dosage of 1.8 mg/kg (up to 180 mg) IV Q3W due to lack of identifiable concerns about efficacy and exposure.

19.4.2.3. E-R Safety Executive Summary

The FDA's Assessment:

No associations were identified between ADC or MMAE exposure and Grade ≥2 peripheral neuropathy, Grade ≥3 neutrophil count decrease, Grade ≥3 febrile neutropenia, BV dose modification, or any drug dose modification.

Although the E-R safety analysis was limited by the relatively small number of patients (n=26) and safety events, the E-R safety analysis generally supports the proposed dosage of 1.8 mg/kg IV Q3W for pediatric patients aged 2 and older.

19.4.2.4. E-R Safety Assessment Summary

The Applicant's Position:

As mentioned above, due to the limited PK population (N=26) in the randomized pivotal AHOD1331 study, and since the PK population primarily consisted of ages <13 years by design, age-specific analysis in the treated population was generated to supplement exposure-response analysis for safety. Additional body weight subgroup analyses were performed for safety parameters to delineate potential age-specific or body weight-specific risk factors.

There was no indication of differential safety with exposure in the AEs evaluated; the incidence rates of Grade 2 and higher peripheral neuropathy (PN), Grade 3 and higher PN, Grade 3 and higher neutrophil count decrease, and Grade 3 and higher febrile neutropenia did not appear to trend with age or body weight.

General Information		
Goal of ER analysis		To confirm that 1.8 mg/kg Q3W brentuximab vedotin provides positive benefit-risk to pediatric subjects with previously untreated high-risk cHL and that no subgroup, such as pediatric subjects aged <12 years, will require a dose adjustment.
Study Included		AHOD1331
Population Included		Pediatric subjects with high-risk previously untreated cHL
Endpoint		Peripheral neuropathy, febrile neutropenia and neutrophil count decreased
No. of Patients (total, and with individual PK)		Total patients=296, Patients having PK=26
Population Characteristics	General	*Age median: 15 yrs. (range 3-21 yrs.)* *Weight median: 57.4 kg (range: 15.4-178.4 kg)* *159 (53.7%) male* *221 (74.7%) White; 34 (11.5%) Black or African American; 7 (2.4%) Asian; 8 (2.7%) Others; 26 (8.7%) Unknown/Not reported*
	Organ impairment	*N/A*
	Pediatrics (if any)	*Age median: 15 (3-21 yrs., 1.7% < 6 yr, 15.8% 6 to < 12 yrs., 74.3% 12 to <18 yrs.)*

Geriatrics (if any)	N/A	
Dose(s) Included	1.8 mg/kg Q3W	
Exposure Metrics Explored (range)	Cave	
Covariates Evaluated	Not applicable	
Final Model Parameters	**Summary**	**Acceptability [FDA's comments]**
Model Structure	N/A	
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	m2.7.2 Figures 21 and Figure 24	No associations were identified between ADC or MMAE exposure and Grade ≥2 peripheral neuropathy, Grade ≥3 neutrophil count decrease, Grade ≥3 febrile neutropenia, BV dose modification, or any drug dose modification. Although the E-R safety analysis was limited by the relatively small number of patients (n=26) and safety events, no E-R safety concerns were identified.
Overall Clinical Relevance for ER	No apparent relationship between exposure and safety endpoints evaluated	
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	N/A	N/A

The FDA's Assessment:

The E-R safety dataset contained data from 26 pediatric patients with PK data aged 3 and older in Study AHOD1331 who were scheduled to receive 1.8 mg/kg IV Q3W of BV for treatment of previously untreated high risk cHL. Baseline patient demographics are summarized in Table 43.

No clear trends were identified between steady state exposure (ADC C_{max}, ADC AUC, MMAE C_{max}, and MMAE AUC) and incidence of Grade ≥2 peripheral neuropathy, Grade ≥3 neutrophil count decrease, or Grade ≥3 febrile neutropenia. Table 52 summarizes incidence according to ADC exposure quartile and Table 53 summarizes incidence according to MMAE exposure quartile. The rates of Grade ≥2 peripheral neuropathy, Grade ≥3 neutrophil count decrease, and Grade ≥3 febrile neutropenia across exposure quartiles were similar for MMAE Cycle 1 AUC and Cycle 1 C_{max} compared to MMAE AUC_{ss} and $C_{max,ss}$.

No clear trends were identified between steady state ADC or MMAE exposure and dose modification of BV, vincristine, or any drug (see Table 54). Dose modification is defined as dose reduction, dose interruption, dose delay, or drug discontinuation.

The E-R analysis is limited by the relatively small number of patients and safety events in the E-R safety dataset. However, no safety concerns were identified and the E-R safety analysis generally supports the proposed dosage of 1.8 mg/kg IV Q3W for pediatric patients aged 2 years and older.

Table 52: Incidence of TEAEs of Interest by ADC Steady State Exposure Quartile in Patients with PK Data

Exposure Metric	TEAE	Q1 (N=7) n (%)	Q2 (N=6) n (%)	Q3 (N=6) n (%)	Q4 (N=7) n (%)
ADC Cmax,ss	Grade ≥2 Peripheral neuropathy	2 (28.6)	0 (0)	1 (16.7)	2 (28.6)
	Grade ≥3 Febrile neutropenia	4 (57.1)	1 (16.7)	4 (66.7)	4 (57.1)
	Grade ≥3 Neutrophil count decreased	3 (42.9)	3 (50.0)	4 (66.7)	5 (71.4)
ADC AUCss	Grade ≥2 Peripheral neuropathy	2 (28.6)	1 (16.7)	0 (0)	2 (28.6)
	Grade ≥3 Febrile neutropenia	5 (71.4)	2 (33.3)	3 (50.0)	3 (42.9)
	Grade ≥3 Neutrophil count decreased	3 (42.9)	5 (83.3)	3 (50.0)	4 (57.1)

Steady state Cmax and AUC = predicted AUC and Cmax during Cycle 4 of 1.8 mg/kg IV every 3 weeks where 1 cycle is 21 days. Q1 = lowest exposure quartile.
ADC=antibody-drug conjugate; AUC=area under the concentration-time curve; Cmax=peak or maximum concentration; IV = intravenously; Q=quartile; ss = steady state; TEAE=treatment-emergent adverse event.
Source: Tables 1 and 2 in Applicant's 9 September 2022 Response to 26 August 2022 Information Request.

Table 53: Incidence of TEAEs of Interest by MMAE Steady State Exposure Quartile in Patients with PK Data

Exposure Metric	TEAE	Q1 (N=7) n (%)	Q2 (N=6) n (%)	Q3 (N=6) n (%)	Q4 (N=7) n (%)
MMAE Cmax,ss	Grade ≥2 Peripheral neuropathy	1 (14.3)	1 (16.7)	2 (33.3)	1 (14.3)
	Grade ≥3 Febrile neutropenia	4 (57.1)	3 (50)	2 (33.3)	4 (57.1)
	Grade ≥3 Neutrophil count decreased	2 (28.6)	5 (83.3)	4 (66.7)	4 (57.1)
MMAE AUCss	Grade ≥2 Peripheral neuropathy	1 (14.3)	1 (16.7)	2 (33.3)	1 (14.3)
	Grade ≥3 Febrile neutropenia	4 (57.1)	2 (33.3)	3 (50)	4 (57.1)
	Grade ≥3 Neutrophil count decreased	3 (42.9)	4 (66.7)	4 (66.7)	4 (57.1)

Steady state Cmax and AUC = predicted AUC and Cmax during Cycle 4 of 1.8 mg/kg IV every 3 weeks where 1 cycle is 21 days. Q1 = lowest exposure quartile.
AUC=area under the concentration-time curve; Cmax=peak or maximum concentration; IV = intravenously; MMAE = monomethyl auristatin E; Q=quartile; ss = steady state; TEAE=treatment-emergent adverse event.
Source: Tables 3 and 4 in Applicant's 9 September 2022 Response to 26 August 2022 Information Request.

Table 54: Summary of Incidence of TEAEs Leading to Dose Modifications According to Exposure Quartile in Patients with PK Data

Exposure Metric	TEAE Leading to Dose Modification	Q1 (N=7) n (%)	Q2 (N=6) n (%)	Q3 (N=6) n (%)	Q4 (N=7) n (%)
ADC AUCss	Dose Modification of Any Drug	1 (14.3%)	4 (66.7%)	1 (16.7%)	2 (28.6%)
	Dose Modification of Brentuximab Vedotin	1 (14.3%)	1 (16.7%)	1 (16.7%)	0
	Dose Modification of Vincristine	1 (14.3%)	0	1 (16.7%)	0
MMAE AUCss	Dose Modification of Any Drug	3 (42.9%)	3 (50%)	0	2 (28.6%)
	Dose Modification of Brentuximab Vedotin	1 (14.3%)	1 (16.7%)	0	1 (14.3%)
	Dose Modification of Vincristine	1 (14.3%)	1 (16.7%)	0	0

TEAE leading to dose modification refers to dose reduction, dose interruption, dose delay, or drug discontinuation. Any drug dose modification refers to dose modification of brentuximab vedotin, doxorubicin, vincristine, etoposide, prednisone, or cyclophosphamide. Per protocol guidance, dose modification for vincristine preceded that for brentuximab vedotin to preserve the dose intensity of brentuximab vedotin. Steady state AUC = predicted AUC during Cycle 4 of 1.8 mg/kg IV every 3 weeks where 1 cycle is 21 days. Q1 = lowest exposure quartile.
ADC=antibody-drug conjugate; AUC=area under the concentration-time curve; IV = intravenously; MMAE=monomethyl auristatin E; Q = quartile; SS = steady state; TEAE = treatment emergent adverse event.
Source: FDA Reviewer Analysis of Study AHOD1331 adec.xpt Dataset

19.4.2.5. Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position:

No apparent relationships between exposure and efficacy endpoints were found. Consistent EFS benefit was observed in pediatric subjects aged 2 to <12 and 12 to <18 years with previously untreated, high-risk cHL receiving 1.8 mg/kg Q3W brentuximab vedotin in combination with AVEPC in the AHOD1331 study. While the ADC exposure was lower in subjects aged 2 to <12 years, similar EFS rates were observed between pediatric subjects aged 2 to <12 and 12 to <18 years. Within the pediatric subjects that were randomized and received the 1.8 mg/kg Q3W dose, there were no clear relationships between exposure and incidence rates of PN, neutrophil count decrease or febrile neutropenia in the pediatric population based on age and body weight subgroup analyses and E-R analyses. Collectively, these results support the recommended 1.8 mg/kg Q3W brentuximab vedotin dose in combination with AVEPC for the proposed indication in pediatric subjects 2 years and older with previously untreated high-risk cHL.

The FDA's Assessment:

Due to the limited number of patients aged 2 to <12 (n=52), no meaningful conclusions can be drawn from the comparison of EFS rates in patients aged 2 to <6 years, 6 to <12 years, and 12 to <18 years. No conclusions can be drawn regarding the relationships between EFS and ADC exposure because patients with PK data (n=26) did not experience any EFS events. However, the lower ADC and MMAE exposure in pediatric patients aged 2 to <6 years did not appear to have a clinically significant impact on secondary efficacy endpoints. Refer to Section 19.4.2.2 for details.

The FDA generally agrees with the Applicant's conclusions regarding safety according to ADC and MMAE exposure, age subgroups, and body weight subgroups.

Overall, the efficacy, safety, PK, and PD data indicate a favorable benefit-risk profile and support the proposed dosage of 1.8 mg/kg IV Q3W for pediatric patients aged 2 and older with previously untreated high risk cHL.

19.5. Modified ("BALIS") Pediatric Scale of Peripheral Neuropathies

Peripheral Motor Neuropathy:

- Grade 1: Subjective weakness, but no deficits detected on neurological exam, other than abnormal deep tendon reflexes.
- Grade 2: Weakness that alters fine motor skills (buttoning shirt, coloring, writing or drawing, using eating utensils) or gait without abrogating ability to perform these tasks.
- Grade 3: Unable to perform fine motor tasks (buttoning shirt, coloring, writing or drawing, using eating utensils) or unable to ambulate without assistance.
- Grade 4: Paralysis.

Peripheral Sensory Neuropathy:

- Grade 1: Paresthesias, pain, or numbness that do not require treatment or interfere with extremity function.
- Grade 2: Paresthesias, pain, or numbness that are controlled by non-narcotic medications (without causing loss of function), or alteration of fine motor skills (buttoning shirt, writing or drawing, using eating utensils) or gait, without abrogating ability to perform these tasks.
- Grade 3: Paresthesias or pain that are controlled by narcotics, or interfere with extremity function (gait, fine motor skills as outlined above), or quality of life (loss of sleep, ability to perform normal activities severely impaired).
- Grade 4: Complete loss of sensation, or pain that is not controlled by narcotics.

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/s/

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