11 November 2021
EMA/754188/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

ADCETRIS

International non-proprietary name: brentuximab vedotin

Procedure No. EMEA/H/C/002455/II/0093

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Steps taken for the assessment	
Start of procedure	03 Aug 2021
CHMP Rapporteur Assessment Report	09 Sep 2021
PRAC Rapporteur Assessment Report	10 Sep 2021
PRAC endorsed relevant sections of the assessment report	28 Sep 2021
Start of written procedure	28 Sep 2021
Request for supplementary information	30 Sep 2021
Submission of MAH's responses	8 Oct 2021
Re-start of procedure	13 Oct 2021
CHMP Rapporteur Assessment Report	27 Oct 2021
CHMP members comments	03 Nov 2021
Updated CHMP Rapporteur Assessment Report	05 Nov 2021
Opinion	11 Nov 2021

Table of contents

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Takeda Pharma A/S submitted to the European Medicines Agency on 8 July 2021 an application for a variation.

The following changes were proposed:

Variation requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

Update of sections 4.2, 4.8, 5.1, 5.2, and 6.6 of the SmPC based on results from study C25004, an open-label study in order to assess the safety and tolerability, of brentuximab vedotin when combined with multiagent chemotherapy regimen for first-line treatment of advanced-stage Hodgkin lymphoma in paediatric patients. The RMP version 16 has also been submitted.

The requested variation proposed amendments to the Summary of Product Characteristics and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0013/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0013/2021 was completed.

2. Overall conclusion and impact on the benefit/risk balance

In support of this variation, the final study results of the paediatric clinical study C25004 and of a meta-analysis including published studies in which paediatric patients were treated with brentuximab vedotin (BV), were submitted. The MAH is proposing to include a limited selection of these data in SmPC Sections 4.2, 4.8, 5.1 and 5.2. The MAH is not seeking with this variation submission an extension of indication for the treatment of Hodgkin lymphoma in the paediatric population.

Study C25004

Study C25004 was an open-label, multicentre, phase 1/2 study of A+AVD in 59 paediatric patients with previously untreated Stage III or Stage IV cHL. Patient age at study entry ranged from 6 to 17 years. The median age was 14 years.

The study was the first to investigate body surface area (BSA)-based dosing of brentuximab vedotin in combination with adriamycin (doxorubicin), vinblastine, and dacarbazine (BV+AVD) combination in children. Patients (N=59) received 48 mg/m^2 of BV administered as an intravenous infusion over 30 minutes + doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2 every 2 weeks (Q2W) were analysed for overall response rate (ORR) per independent review facility (IRF) and other safety, efficacy, and pharmacokinetic (PK) endpoints.

The pharmacokinetics of brentuximab vedotin (antibody-drug conjugate [ADC] and monomethyl auristatin E [MMAE]) in paediatric patients was evaluated C25004 by non-compartmental analysis using PK rich data. Integrated population pharmacokinetic (PK) modelling of PK data from paediatric studies C25002 (BV monotherapy 1.8 mg/kg Q3W, procedure EMEA/H/C/002455/II/0049) and C25004

is performed to support the proposed dosing regimens and to compare exposure with exposure in adult patients.

Study C25004 enrolled 59 patients, eleven patients (19%) were between 6 and 11 years, and 48 patients (81%) were between 12 and 17 years.

Pharmacokinetics

Maximum concentrations of brentuximab vedotin were typically observed at the end of infusion or the sampling timepoint closest to the end of infusion. A multiexponential decline in ADC serum concentrations was observed with a terminal half-life of approximately 4 days. A 30% higher AUC exposure of ADC was observed with multiple doses at the every 2-week schedule, which is slightly higher than anticipated for a terminal half-life of 4 days. Typical Cmax and AUC of ADC after a single 48 mg/m^2 dose was approximately 23 µg/mL and 47 µg.day/mL, respectively. Mean Cmax and AUC of MMAE were 4.9 ng/mL, 27 ng.day/mL, respectively. MMAE exposures decreased after multiple doses of brentuximab vedotin with approximately 50% to 70% of the exposure of the first dose being observed at subsequent doses.

ADC and MMAE exposures were comparable for paediatric patients <12 and ≥12 years of age in study C25004, supporting the BSA-based dosing of brentuximab vedotin in paediatric patients treated with brentuximab vedotin in combination with chemotherapy.

Based on non-compartmental PK across study comparison, ADC and MMAE steady-state exposures were comparable in paediatric patients from Study C25004 administered 48 mg/m^2 Q2W in combination with chemotherapy AVD and in adult patients with advanced HL from Study C25003 administered 1.2 mg/kg Q2W in combination with chemotherapy AVD.

The popPK model for ADC and especially for MMAE shows overestimation of the variability, some bias for both paediatric studies, and while the objective function of the popPK improved by inclusion of the co-variates, the unexplained variability was not improved, and the co-variates had no significant effect. PopPK estimated an approximately 2-fold higher ADC clearance for patients on concurrent treatment with AVD. This is rather unexpected since non-compartmental analysis indicated only a 10-25% lower ADC exposure in paediatric patients with concurrent chemotherapy. In addition, in adults on concurrent treatment with AVD, pharmacokinetics of ADC was consistent with that of monotherapy. Therefore, the popPK models of ADC and MMAE are considered suitable for descriptive purposes only, not for simulation purposes and consequently comparison with adult exposures and exposure-effect analysis by means of popPK simulations are considered exploratory only.

Since there are sufficient pharmacokinetic data from the non-compartmental analysis to describe the pharmacokinetics of ADC and MMAE in paediatric patients from studies C25002 (brentuximab vedotin 1.8 mg/kg Q3W) and C25004 (brentuximab vedotin 48 mg/m^2 Q2W in combination with chemotherapy) in the SmPC section 5.2, no questions regarding the popPK model will be raised. A corrected Table with PK estimates of MMAE Cmax values was submitted as requested and the MAH is recommended for future applications to review the popPK model. The text in section 5.2 of the SmPC has been amended to report the pharmacokinetics of ADC and MMAE as determined by non-compartmental analysis.

Immunogenicity

Four patients (7%) were ADA positive at some time point post-baseline of which 1 patients was already ADA positive at baseline. All 4 patients were transiently ADA positive with a low (≤25) ADA titre. Two of 59 patients (3%) were Nab positive. The low immunogenicity is line with previous observations. Section 4.8 of the SmPC has accordingly been updated.

Efficacy

Results of the small, single arm clinical study C25004 show high response rates with brentuximab vedotin in paediatric patients with newly diagnosed HL. CR rate was above 76%. The high response rate indicates significant anti-tumour activity. The median PFS, EFS and OS were not reached yet, which is due to the good prognosis of (paediatric) patients with HL. However, the interpretation of the results of the time dependent endpoints is hampered due to the single arm study design of C25004. Additional long term follow up data is likely be obtained in the LTFU study of C25004.

Results of the C25004 study were not contextualized with historical efficacy results obtained with other available treatment regimens for newly diagnosed paediatric HL patients. Also, the applicant stated that the study C25004 results (including response rates) for newly diagnosed paediatric HL patients treated with brentuximab-vedotin+AVD produced were comparable to results in adults, while a thorough discussion on the concept of extrapolation of adult data to the paediatric population was not included. However, as no indication for newly diagnosed paediatric HL is currently requested, the absence of contextualization and the extrapolation exercise is acceptable.

Meta-analysis

To support the efficacy of brentuximab-vedotin in paediatric patients with HL, results of a meta-analysis were submitted. This meta-analysis was part of the modified Paediatric Investigation Plan. Study inclusion criteria were defined as that studies needed to include paediatric patients who were treated with brentuximab vedotin, studies needed to have relevant efficacy and safety outcome data and should be a RCTs, nRCTs or observational study. Twenty-three publications, reporting the findings of 12 unique studies, met the inclusion criteria. Of these, 11 studies were included in the meta-analysis, nine for the efficacy outcome analyses and 11 for the exploratory safety outcome analyses. The following efficacy outcomes were analyzed based on available data: OS (data available from 3 studies); ORR (data available from 6 studies); CR (c data available from 9 studies) and PR (data available from 3 studies). Exploratory safety analyses were also conducted.

The results showed an estimated 96.9% of patients were alive at 3 months; 91% at 12 months and 87% at 24 months. For response outcomes, an estimated 79% of patients achieved a response, with the majority of these experiencing a CR as best response outcome. A separate calculation for CR, based on more study data than was available for ORR, suggested that around 73% of patients achieve CR when treated with brentuximab vedotin. PR analysis suggested 14% of patients experience a PR, in addition to the >70% experiencing a CR.

It appears that most studies used in this meta-analysis include relapsed/refractory patients. Without further discussion on the impact of e.g. differences in study population, backbone therapy, etc, the results of the meta-analysis provide at this point limited support for the results obtained by study C25004.

For paediatric patients with previously untreated Stage III or Stage IV HL, long and healthy survivorship are the ultimate treatment goals. According to the applicant study C25004 is currently too early in its observation to determine if these treatment goals will be met. This is agreed. Two-year follow-up of PFS and EFS is ongoing, and 10-year follow-up of OS, cardiac toxicity, and second malignancies continues.

Safety

The safety population consisted of 59 patients who received at least 1 dose of any drug in the A+AVD regimen. All treated patients completed the maximum 6 cycles of protocol therapy (A+AVD).

At least 1 TEAE of any grade was reported for all 59 patients (100%) and at least 1 drug-related TEAE of any grade for 57 patients (97%) in the safety population. At least 1 Grade 3 or higher TEAE was reported for 54 patients (92%) and was considered drug-related for 51 patients (86%). At least 1 SAE was reported for 24 patients (41%) and was considered drug-related for 19 patients (32%). No AEs were reported that resulted in the premature and permanent discontinuation of study treatment, and no on-study deaths were reported in the study.

Most frequently reported TEAE were vomiting (85% of patients); nausea (75%); neutropenia (58%); pyrexia and WBC count decreased (42% each); abdominal pain (39%); constipation, neutrophil count decreased, and stomatitis (37% each); headache (32%); anaemia, decreased appetite, diarrhoea, and back pain (24% each); oropharyngeal pain and weight decreased (22% each); and fatigue (20%).

At least 1 SAE was reported for 24 patients (41%) in the safety population. Febrile neutropenia was the most commonly reported SAE, i.e. for 17% of patients. Neutropenia and vomiting were reported as SAE for 5% of patients each.

Peripheral Neuropathy (PN) is a well characterized adverse drug reaction for brentuximab vedotin. At least 1 PN (SMQ) event of any grade was reported for 14 patients (24%) in the safety population. A Grade 2 PN (SMQ) event (the highest severity reported in the study) was reported for 3 patients (5%), and a PN (SMQ) event led to dose reduction for 2 patients (3%). The PT, PMN was reported as an SAE for 1 patient (2%). Resolution of all PN events was reported for most patients for whom at least 1 PN (SMQ) event was reported during treatment. At the time of the last follow-up, resolution of all PN events was reported for 11 patients (79%) among the 14 patients for whom at least 1 PN event was reported. Resolution of at least 1 PN event was reported at a median of 1.57 weeks (range, 0.3-50.3 weeks).

Safety data for subgroups including patients 5-11 years of age and patients 12-17 years of age was provided. The toxicity profile of brentuximab-vedotin seemed to be similar for paediatric age groups from 5 years on. From the toxicity profile already known from adults study with A+AVD, no new adverse drug reactions were observed in the paediatric population receiving the A+AVD combination.

However, as stated above, the meta-analysis includes studies in which brentuximab is used in different combinational treatment regimens at different doses and in different patient populations (most patients with r/r disease). The sensitivity analysis that includes studies sharing specific characteristic with regard to treatment or patients population, generally involves only few studies. In general, the heterogeneity between the studies was high. The safety results from the meta-analysis are thus considered exploratory. Considering all above the value of this meta-analysis in support of the safety profile of brentuximab vedotin+AVD combination therapy in newly diagnosed paediatric HL patients, is limited without further discussion.

Long term safety data for brentuximab vedotin+AVD is not yet available.

In conclusion, with the currently submitted single arm study the benefit of brentuximab vedotin for the treatment of newly diagnosed paediatric HL patients, cannot be definitively determined. The efficacy results are not contextualized. Also similarity and differences between the efficacy results obtained in the paediatric HL population compared to those obtained in adult HL patients was not thoroughly discussed. Furthermore, the submitted meta-analysis without further discussion provides limited support.

Even so, the discussed limitations of the submitted data are not considered a concern for this variation with and the provided data package is sufficient for an update of the SmPC. However, in case the MAH wants to extend the indication to the first line HL paediatric patients in the future the following is recommended:

- further develop the popPK model;

- expand on the contextualisation of the single arm data by justifying that the meta-analyses can be used to support the C25004 data or focus on external data obtained in the first line;

- include a full extrapolation exercise as described in the EMA Reflection paper on the use of extrapolation in the development of medicines for paediatrics (EMA/189724/2018).

The benefit-risk balance of Adcetris, remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

Update of sections 4.2, 4.8, 5.1, 5.2, and 6.6 of the SmPC based on the final results from study C25004, an open-label study in order to assess the safety and tolerability, of brentuximab vedotin when combined with multiagent chemotherapy regimen for first-line treatment of advanced-stage Hodgkin lymphoma in paediatric patients, in order to complete the PIP (P/0013/2021) and in order to fulfil Article 46 of Regulation EC No 1901/2006. The RMP version 16 has also been submitted.

☒is recommended for approval.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0013/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex I and to the Risk Management Plan are recommended.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion EMEA/H/C/002455/II/0093.

For more information, please refer to the Summary of Product Characteristics.

Annex: Rapporteur's assessment on the type II variation

5. Introduction

On the dossier and regulatory background

The MAH is submitting with this variation application data from Study C25004, a single-arm study designed to assess PK, safety, and antitumour activity of brentuximab vedotin in combination with adriamycin (doxorubicin), vinblastine, and dacarbazine (A+AVD) in paediatric patients with previously untreated Stage III or IV classical Hodgkin lymphoma (cHL).

Also included in this submission is a meta-analysis of clinical studies for brentuximab vedotin in paediatric patients with Hodgkin lymphoma as supportive background data on paediatric cHL.

The MAH is not applying here for a paediatric extension of indication for the treatment of Hodgkin lymphoma within this procedure but proposes to update the SmPC sections 4.2, 4.8, 5.1 and 5.2 with data from study C25004. Information on paediatric use of brentuximab vedotin is already included in the SmPC. This was based on the results of Study C25002, that was assessed during variation EMEA/H/C/002455/II/0049 in order to fulfil article 46 of EC Regulation No 1901/2006.

On the product

ADCETRIS (Brentuximab vedotin (SGN-35)) is a CD30-directed antibody-drug conjugate (ADC) (recombinant chimeric immunoglobulin G1 [IgG1], produced by recombinant DNA technology in Chinese Hamster ovary cells) consisting of 3 components:

1) the chimeric IgG1 antibody cAC10, specific for human CD30;

2) the microtubule-disrupting agent monomethyl auristatin E (MMAE); and

3) a protease-cleavable linker that covalently attaches MMAE to cAC10.

Brentuximab vedotin is proposed to have a multi-step mechanism of action that is initiated by binding to CD30 on the cell surface and internalization of the ADC. Upon trafficking to lysosomes, MMAE is released from the conjugate through proteolytic degradation of the drug linker. Binding of released MMAE to tubulin disrupts the microtubule network, leading to G2/M phase cell cycle arrest and apoptosis.

Current indication

The currently approved indications for ADCETRIS are:

Hodgkin lymphoma

ADCETRIS is indicated for adult patients with previously untreated CD30+ Stage IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine and dacarbazine (AVD) (see sections 4.2 and 5.1).

ADCETRIS is indicated for the treatment of adult patients with CD30+ HL at increased risk of relapse or progression following autologous stem cell transplant (ASCT) (see section 5.1).

ADCETRIS is indicated for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL):

1. following ASCT, or

2. following at least two prior therapies when ASCT or multi agent chemotherapy is not a treatment option.

Systemic anaplastic large cell lymphoma

ADCETRIS in combination with cyclophosphamide, doxorubicin and prednisone (CHP) is indicated for

adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL) (see section 5.1).

ADCETRIS is indicated for the treatment of adult patients with relapsed or refractory sALCL.

Cutaneous T cell lymphoma

ADCETRIS is indicated for the treatment of adult patients with CD30+ cutaneous T cell lymphoma (CTCL) after at least 1 prior systemic therapy (see section 5.1).

Extract from Current posology

The recommended dose for monotherapy and in combination with chemotherapy (cyclophosphamide, doxorubicin and prednisone) is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks.

The recommended dose in combination with chemotherapy (doxorubicin [A], vinblastine [V] and dacarbazine [D] [AVD]) is 1.2 mg/kg administered as an intravenous infusion over 30 minutes on days 1 and 15 of each 28-day cycle for 6 cycles.

If the patient's weight is more than 100 kg, the dose calculation should use 100 kg.

6. Clinical Pharmacology aspects

The clinical pharmacology of brentuximab vedotin (antibody-drug conjugate [ADC] and monomethyl auristatin E [MMAE]) in paediatric patients was evaluated in Studies C25002 and C25004. Integrated population pharmacokinetic (PK) modelling of PK data from both studies is performed to support the proposed dosing regimens and to compare exposure with exposure in adult patients.

Results from study **C25002** have been evaluated in procedure EMEA/H/C/002455/II/0049. A summary of pharmacokinetic data of brentuximab vedotin monotherapy in paediatric patients from study **C25002** is presented here. Plasma PK parameters of brentuximab vedotin and MMAE following IV administration of 1.8 mg/kg brentuximab vedotin Q3W in paediatric patients for in Cycles 1 and 8 in are summarised in Table 1. Median brentuximab vedotin AUC in children adolescents from this study was approximately 14% and 3% lower than in adult patients, respectively, while MMAE exposures were 53% lower and 13% higher, respectively, than in adult patients. There was a trend observed for lower brentuximab vedotin exposures at lower ages/ body weights in the study population. Simulations of different dosing regimens showed that BSA based dosing results exposure approximately similar across different body weight ranges and similar to exposure. There was a trend of increased clearance of brentuximab vedotin in paediatric patients confirmed positive for anti-drug antibodies (ADAs). No patients aged <12 years and 2 patients aged ≥12 became persistently ADA positive.

Table 1 Plasma PK parameters of ADC and MMAE in paediatric patients following IV administration of 1.8 mg/kg brentuximab vedotin Q3W in Cycles 1 and 8 (study C25002, EMEA/H/C/002455/II/0049, non-compartmental analysis)

ADC					MMAE				
	Cycl 1 N	gMean (CV%)	Cycl 8 N	gMean (CV%)		Cycl 1 N	gMean (CV%)	Cycl 8 N	gMean (CV%)
Cmax (µg/mL)	30	31.8 (28)	14	33.7 (29.9)	Cmax (ng/mL)	32	4.4 (67.3)	13	2.0 (56.6)
AUC21d (day.µg/mL)	26	63.3 (31.3)	13	98 (48.2)	AUC21d (day.ng/mL)	27	27.0 (60.9)	10	14.9 (57.1)
T1/2 (days)	25	4.7 (34.1)			T1/2 (days)	22	3.2 (28.5)		

Because the pharmacokinetic data from study C25002 indicated that BSA based dosing would result in exposure approximately similar across different body weight ranges, dosing in study **C25004** was BSA based, i.e. 48 mg/m^2 Q2W. Immunogenicity was evaluated. Further, an exploratory exposure-response analysis was conducted using data from Study C25004 to evaluate relationships between steady-state ADC and MMAE exposure and selected safety and efficacy endpoints.

6.1. Methods – analysis of data submitted (study C25004)

Design of study C25004

Study C25004 was an open-label, multi-centre, phase 1/2 study of A+AVD in 59 paediatric patients with previously untreated Stage III or Stage IV cHL. Patient ages at study entry ranged from 6 to 17 years. The median age was 14 years.

The study was the first to investigate body surface area (BSA)-based dosing and the A+AVD combination in children. Patients (N=59) received 48 mg/m^{2}of brentuximab vedotin administered as an intravenous infusion over 30 minutes + doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m2 every 2 weeks (Q2W) were analysed for overall response rate (ORR) per independent review facility (IRF) and other safety, efficacy, and pharmacokinetic (PK) endpoints.

Design – PK sampling

In Study C25004, body surface area (BSA)-based doses of 48 mg/m^2 brentuximab vedotin given every 2 weeks (Q2W) were evaluated in combination with a multiagent chemotherapy regimen (adriamycin [doxorubicin], vinblastine, and dacarbazine [AVD]) in paediatric patients with advanced-stage (Ann Arbor Stage III or IV), newly diagnosed, CD30-positive (CD30+) classical HL. For patients with a BSA >2.5 mg/m^2, the dose was calculated based on a BSA of 2.5 mg/m^2, as the maximum dose of brentuximab vedotin that a patient could receive was 120 mg. AVD was administered first, and brentuximab vedotin was administered approximately 1 hour later by IV infusion. Blood samples for determination of serum concentrations of brentuximab vedotin and TAb and plasma concentrations of MMAE were collected at the following time points during phase 1:

- Cycles 1 through 6: On Day 1 and Day 15 within 4 hours before the start of the brentuximab vedotin infusion and at the end of the infusion (EOI).

- Cycle 1 and Cycle 3: Additional samples collected 24 hours (Day 2), 48 hours (Day 3), 72 hours (Day 4), and 168 hours (Day 8) from the start of the Day 1 brentuximab vedotin infusion and 24 hours (Day 16), 48 hours (Day 17), 72 hours (Day 18), and 168 hours (Day 22) from the start of the Day 15 brentuximab vedotin infusion.

The PK sampling schedule was revised during phase 2 to omit blood collection on Days 16, 17, 18, and 22 during Cycles 1 and 3 to reduce blood collection burden on patients.

Blood samples were collected at screening, pre-dose on Day 1 of Cycles 2, 4, and 6, and at EOT to evaluate serum ADA and for ADA-positive samples only, Nab status (negative or positive).

Population

In total, 59 (28 female, 31 male) paediatric patients were enrolled with a median age of 14 years (range, 6-17 years). Eleven patients (19%) were between 6 and 11 years, and 48 patients (81%) were between 12 and 17 years. Baseline characteristics of the paediatric patients from studies C25002 and C25004 are shown in Table 2.

Study	Geometric Mean	Median	Mean	SD	CV%	Minimum	Maximum
Age (yr)							
25002	12.7	14.0	13.1	3.2	24.0	7.0	18.0
25004	13.2	14.0	13.7	3.0	22.0	6.0	17.0
Height (cm)							
25002	157.1	158.5	158.0	17.5	11.0	123.7	188.0
25004	157.7	160.0	158.4	14.6	9.0	118.0	185.0
Weight (kg)							
25002	47.0	49.9	50.0	17.4	35.0	21.2	87.0
25004	46.6	49.0	49.4	16.0	32.0	18.8	81.0
Body Mass Index (kg/m^2)							
25002	19.1	18.7	19.6	4.7	24.0	12.9	32.4
25004	18.7	18.1	19.2	4.3	22.0	12.9	32.0
Body Surface Area (m^2)							
25002	1.44	1.52	1.48	0.32	22.00	0.89	2.03
25004	1.44	1.52	1.47	0.29	20.00	0.79	2.03
Albumin (g/L)							
25002	40.5	40.5	40.9	5.9	14.0	27.0	51.0
25004	37.7	39.0	38.1	5.3	14.0	23.0	46.0
Alkaline Phosphatase (U/L)							
25002	143.5	122.0	160.8	90.0	56.0	81.0	484.0
25004	164.8	167.0	191.1	128.5	67.0	47.0	862.0
Alanine Aminotransferase (U/L)							
25002	19.0	16.0	27.1	30.9	114.0	7.0	140.0
25004	18.4	15.0	26.2	30.6	117.0	5.0	170.0
Aspartate Aminotransferase (U/L)							
25002	22.5	22.5	25.8	15.6	60.0	8.0	75.0
25004	22.1	21.0	25.5	17.1	67.0	8.0	116.0
Bilirubin (umole/L)							
25002	5.50	5.15	6.60	4.15	63.00	1.71	20.00
25004	6.62	6.84	7.75	5.95	77.00	1.71	45.16
Creatinine (umole/L)							
25002	43.4	44.5	45.4	13.8	30.0	25.0	78.0
25004	47.7	46.9	49.2	12.3	25.0	18.6	90.2
Creatinine clearance (cockroft) (mL/min)							
25002	160.9	165.3	166.7	45.7	27.0	102.0	301.4
25004	140.4	132.3	144.5	35.9	25.0	85.5	251.2
Creatinine clearance where AGE <= 12(Schwartz) (mL/min/1.73m2)							
25002	205.0	197.5	208.7	40.4	19.4	149.6	278.1
25004	171.7	166.7	175.7	42.3	24.1	124.0	309.1
Sum of tumor area (mm2)							
25002	1615	1581	2158	1890	87.6	555	6515
25004	1817	1639	2317	2095	90.4	455	9792
Longest tumor diameter (mm)							
25002	32.9	31.0	36.1	16.4	44.4	17.0	74.0
25004	41.6	39.5	46.1	27.0	58.6	19.0	144.0

yr – year, kg – kilogram, m – meters, g – grams, L – liters, U - unit, umole – micromole, min –minutes, mL – milliliters, SD – standard deviation, N – number, mm – milliliters, cm – centimeters, CV – coefficient of variation
Notes: Creatinine Clearance based on Cockcroft formula [(140 - age) x weight in kg] (x 0.85 for females) / (creatinie x 72);
BSA was estimated using DuBois and DuBois [4]:
Source: All_continuous_cov.docx

Bioanalysis

Plasma concentrations of brentuximab vedotin total antibody (Tab, 2156 samples, 2146 evaluable) and ADC (2156 samples, 2152 evaluable) were measured using enzyme-linked immunosorbent assays

(ELISA) with a validated range between 12.5 and 400 ng/mL. Plasma concentrations of MMAE were measured after solid phase extraction using high performance liquid chromatography followed by tandem mass spectrometric detection with a validated analytical range between 25.0 to 1000 pg/mL. The methods have been previously validated at Covance Laboratories Inc.

Serum samples were tested for antidrug antibodies (ADA; previously described as antitherapeutic antibodies [ATA], 293 samples – 291 evaluable) to brentuximab vedotin using electrochemiluminescence with an assay sensitivity of 4 ng/mL. Serum samples were also evaluated for the presence of neutralizing antidrug antibodies (Nab; previously described as neutralizing antitherapeutic antibodies [nATA]) to brentuximab vedotin using an ELISA-based assay.

Since the method selectivity experiments were performed in the normal matrix during validation, additional selectivity testing was performed in Hodgkins Lymphoma serum samples for both the PK (CB-0202/CB-0203) and ADA (CB-1079/CB-1080a/CB-1823/CB-1824) assays.

In study performance of QC were in line with the validation, incurred sample reanalysis demonstrated acceptable reproducibility.

Pharmacokinetic analyses

PK parameters were calculated from individual plasma (MMAE) or serum ADC, TAb concentration-time data using noncompartmental methods using Phoenix WinNonlin (version 8.2, Certara, Princeton, NJ). Descriptive statistics were used to summarize PK parameters of ADC, TAb, and MMAE by dose group (as applicable), cycle, and day. Individual and mean serum and/or plasma concentration data were plotted over time by dose cohort and cycle/day.

Population PK analyses

Two population PK models were developed for this analysis one for ADC and one for MMAE. The ADC model was developed and finalized first, and then the model for MMAE was developed in which the MMAE formation was linked to ADC elimination using the individual parameter estimates from the ADC model to predict the ADC concentrations in the MMAE model. The models previously developed for brentuximab vedotin for Study C25002 were used a starting point (see assessment report of procedure EMEA/H/C/002455/II/0049).

The objectives of this POP PK analysis were to:

• Develop 2 POP PK models (ADC and MMAE) to describe concentration-time data arising from studies C25002 and C25004 of brentuximab vedotin in paediatric patients,

• Identify and characterize patient factors which influence the PK and PK variability of ADC and MMAE,

• Estimate the magnitude of unexplained variability in PK in paediatric patients,

• Evaluate the model performance of the 2 PK models developed, and use these models to summarize the systemic exposures of ADC and MMAE estimated in patients in studies C25002 and C25004.

Database

Dataset included 9479 records, 2608 from study C25002 and 6871 from study C25004 from 95 paediatric patients. There were 978 dosing records and 8501 concentration records. Of the concentration records, 2899 were ADC concentrations and 2748 were MMAE concentrations and 2854 were SGN35 concentrations. The SGN concentrations were not used in the analysis. Continuous baseline characteristics of the patients are summarised in Table 2.

For ADC, there were 95 ADC concentration records excluded from the analysis, 91 were predose concentrations, 2 did not have concentration values, 1 had a clock time issue, and 1 had an issue with

the time of the sample. There were 31 records excluded due to |CWRES| values greater than 5. Also, 21 BLQ samples were excluded from the analysis. As a result, 2752 ADC concentration records were included in the analysis.

For MMAE, there 87 MMAE concentration records excluded from the analysis all due to being predose concentrations. There was 1 record excluded due to CWRES values greater than 5. There was one record without a concentration. Also, 76 BLQ samples were excluded from the analysis. As a result, 2583 ADC concentration records were included in the analysis.

There were 0.7% ADC BLQ records (21 records out of 2773 total ADC records including the BLQ records) and 2.9% MMAE BLQ records (76 records out of 2659 total MMAE records including the BLQ records). As a result, all BLQ records were excluded (commented out) from the analysis dataset. Given the low percentage of BLQ records this is considered acceptable.

PopPK model

The model for ADC PK was a linear three-compartment model with zero-order input and first-order elimination. The pharmacokinetic model parameters are shown in Table 3. IIV was included on CL, Q2, and V3 and the %CV was high for these parameters at 65 or less; however, shrinkage for these terms was 13.4% or less indicating the individual parameter values were acceptable. The covariates on CL included an increasing CL with increasing BSA; decreasing CL with increasing ALB concentration; decreasing CL with increasing tumour size, a higher CL for ATA positivity although there were very few ATA positive records, and a higher CL for patients on concurrent AVD treatment. Non-Hodgkins lymphoma patients had approximately ½ smaller Q2 parameter values than the Hodgkins lymphoma patients. V3 increased with increasing BSA. Parameter precision had a 32.2% standard error (SE) or less. Residual variability was 32.1% and the condition number was 14.

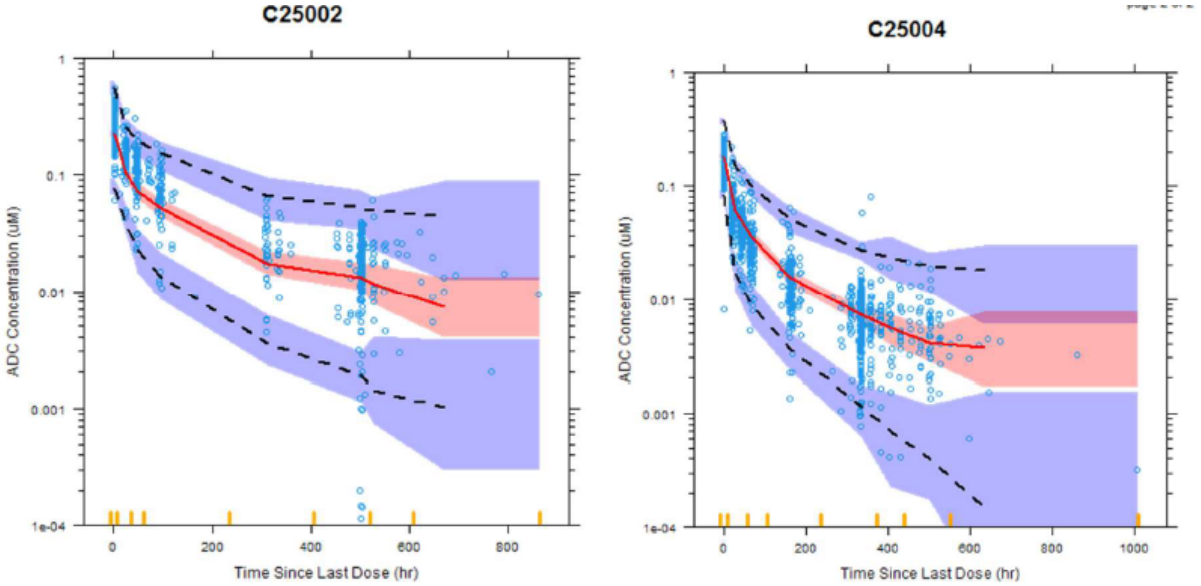
Table 3 ADC final pharmacokinetic model parameters

Parameter		Population Mean (SE%)	%CV IIV (shrinkage)
Clearance (L/hr)	Θ_1	0.0208 (16.3%)	48.4 (7.2%)
Central Volume (V1) (L)	Θ_2	2.54 (0.7%)	-
Inter-compartmental clearance 1 (Q2) (L/hr)	Θ_3	0.0192 (14.2%)	65.0 (13.4%)
Peripheral Volume 1 (V2) (L)	Θ_4	97.1 (18.9%)	-
Inter-compartmental clearance 2 (Q3) (L/hr)	Θ_5	0.0865 (7.3%)	-
Peripheral Volume 2 (V3) (L)	Θ_6	3.39 (15.8%)	60.3 (12.9%)
BSA effect on CL	Θ_8	1.38 (23.2%)	-
Albumin effect on CL	Θ_9	-0.776 (12.3%)	-
Tumor linear diameter size effect on CL	Θ_{10}	0.12 (17.3%)	-
Effect of non-HL Tumor Type on Q2	Θ_{11}	0.509 (32.2%)	-
BSA effect on V3	Θ_{12}	1.96 (20.8%)	-
ATA positivity effect on CL	Θ_{13}	2.6 (6.4%)	-
Concurrent chemotherapy treatment on CL	Θ_{13}	2.12 (18.7%)	-
Residual Variability	Θ_7	32.1%CV (0.7%)	-

ADC - antibody-drug conjugate, SE – standard error, CV – coefficient of variation, IIV – inter-individual variation, L – liters, hr – hour, BSA – body surface area, ATA – anti-therapeutic antibody
Source: adc_albLINDataDoxCL_bsaV3_nonhlQ2_cw3.smr

Bootstrap median parameter values, based on 2000 runs, were very similar to the final parameter values. Model evaluation by means of goodness of fit plots for population, individual, WRES, ETA distribution showed no trends for mis-specification and ETAs were normally distributed. VPC plots for studies C25002 and C25004 are shown in Figure 1.

Figure 1 ADC Final pharmacokinetic model visual predictive check for studies C25002 and C25004.



Source: Adcetris pop PK Report C25002 C25004 Figures 16 and 17.
ADC: antibody-drug conjugate.
The light blue circles are the observed concentration, the black dashed lines show the model predicted 90% intervals, and the red solid line shows the median predicted values. The blue shaded area around the black dashed lines is the 90% CI around the 90% prediction interval. The pink shaded area is the 90% CI around the median prediction. The short vertical lines on the x-axis show the edges of the binned concentrations used to calculate the other values.

MMAE is attached to the anti-CD30 antibody on ADC via a protease-cleavable linker, and as a result, the actual dose of MMAE is unknown. Therefore the PK model of MMAE is primarily descriptive. The PK model for MMAE included a link to ADC elimination using the individual parameter estimates from the ADC model to predict the ADC concentrations in the MMAE model. The PK of MMAE was described by a two-compartment model with first-order elimination and formation of MMAE both directly from ADC and through binding of ADC to a hypothetical target. The model had a lag compartment to describe the delay in the formation of MMAE both directly from ADC and through binding of ADC to the target. The fraction of MMAE formed directly from ADC is assumed to decrease following ADC administration, relative to TAD.

During the development of the MMAE model, it was initially determined that including IIV on CL, Vc, and the ADC to MMAE conversion rate (ALFM) resulted in the best model fit based on the OBJ value. Covariate effects were evaluated on this model. The covariates included in the model were ALB, ATA positivity, BSA and creatinine concentration on CL, non-HL tumour type, BSA on Vc and, non-HL tumour type on ALFM. Although creatinine concentration on CL did not decrease the OBJ by the needed amount, it was kept in the model based on previous modelling experience with brentuximab vedotin . After the completion of this stage of the model building, an ETA on Kd was added to the model due to a very significant decrease in the OBJ of 682 points. A visual inspection of the Kd ETA by covariate plots showed a trend with ALB and Kd. This effect was added to the model and resulted in a further decrease in the OBJ of 113 points. This model was selected as the final model.

The pharmacokinetic model parameters for MMAE are shown in Table 4. The final MMAE parameter precision SE% was acceptable at 27.5% or less. All the IIV parameter values had a high %CV with a range of 50.6 to 147. However, the shrinkage ranged from 4.2 to 18.8% indicating simulations with this model would result in acceptable individual parameter values of AUC, Cmax, and Cmin. Residual variability was moderate at 37.5%. The condition number was at 5.18. The covariates effects showed that MMAE CL decreases with increasing creatinine concentration and ALB concentration, and increases

with increasing BSA. MMAE CL is higher with ATA negativity compared to ATA positivity. MMAE central volume is larger for patients with HL compared to non-HL patients and Vc increases with increasing BSA. ALFM is comparable between patients with HL and ALCL. MMAE Kd decreases with increasing ALB concentration.

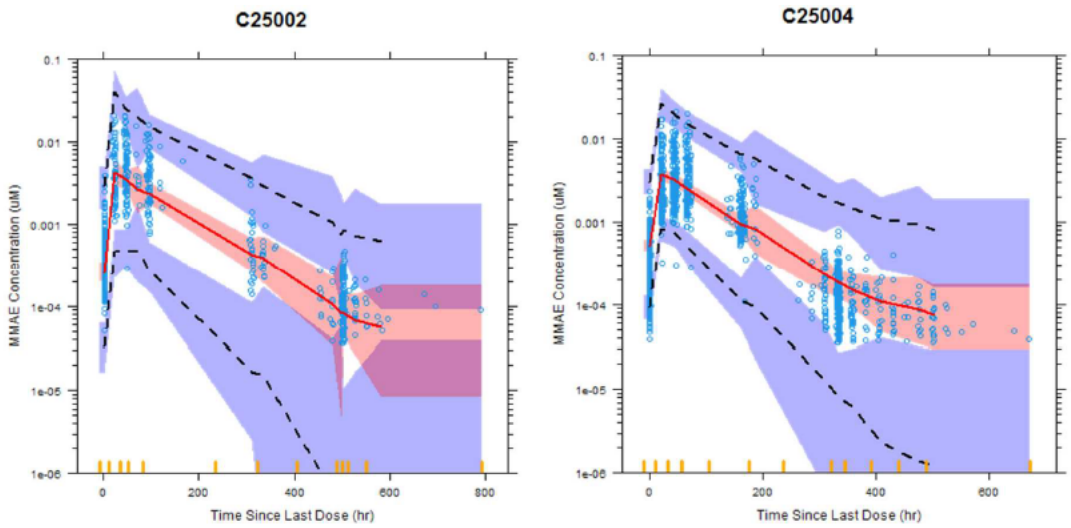
Table 4 MMAE final pharmacokinetic model parameter

Parameter		Population Mean (SE%)	%CV IIV (shrinkage)
Clearance (L/hr)	Θ_1	0.794 (2.0%)	50.6 (9.1%)
Central Volume (V1) (L)	Θ_2	20.1 (0.7%)	79.9 (4.2%)
Binding Rate Constant (Kd) (1/hr)	Θ_3	0.0186 (0.4%)	147 (7.8%)
Fraction Metabolized	Θ_4	1 FIX	-
ADC to MMAE Conversion Rate (ALFM) (1/hr)	Θ_5	0.00462 (0.7%)	88.8 (18.8%)
Lag Compartment Rate Constant (Klag) (1/hr) (Q64)	Θ_6	60.8 (1.3%)	-
Inter-compartmental clearance (Q2) (L/hr)	Θ_7	0.628 (1.2%)	-
Peripheral Volume (V2) (L)	Θ_8	2.74 (0.7%)	-
Creatinine Concentration on CL	Θ_9	-0.0952 (9.3%)	-
Albumin Concentration on CL	Θ_{10}	-0.0805 (27.5%)	-
Body Surface Area on CL	Θ_{11}	0.772 (8.4%)	-
Anti-drug Antibody Positive Status on CL	Θ_{12}	0.696 (5.3%)	-
Non-Hodgkin's Lymphoma Tumor Type on V1	Θ_{13}	0.296 (15.1%)	-
Body Surface Area on V1	Θ_{14}	0.546 (9.7%)	-
Not Hodgkin's Lymphoma Tumor Type on ALFM	Θ_{15}	0.884 (17.7%)	-
Albumin Concentration on Kd	Θ_{16}	-4.11 (3.3%)	-
Residual Variability	Θ_9	37.5% (1.2%)	-

MMAE - monomethyl auristatin E, SE – standard error, CV – coefficient of variation, IIV – inter-individual variability, L – liters, hr – hour, ADC - antibody-drug conjugate, ALFM - rate constant to describe the decline in direct conversion of ADC to MMAE following time after dose
Source: MMAE_iivKd_albKd.smr

Bootstrap median parameter values, based on 1000 runs, were reasonably similar to the final parameter values. Model evaluation by means of goodness of fit plots for population, individual, WRES plot showed some underprediction of MMAE 3-8 days and overprediction >2 weeks after administration, ETAs were normally distributed. VPC plots for studies C25002 and C25004 are shown Figure 2.

Figure 2 MMAE final pharmacokinetic model visual predictive check for studies C25002 and C25004.



Source: Adcetris pop PK Report C25002 C25004 Figures 41 and 42.
MMAE: monomethyl auristatin E.
The light blue circles are the observed concentration, the black dashed lines show the model predicted 90% intervals, and the red solid line shows the median predicted values. The blue shaded area around the black dashed lines is the 90% CI around the 90% prediction interval. The pink shaded area is the 90% CI around the median prediction. The short vertical lines on the x-axis show the edges of the binned concentrations used to calculate the other values.

Exposure-Response Analyses

Data from Study C25004 were used to conduct descriptive exposure-response analyses to describe relationships between brentuximab vedotin exposure and safety or efficacy outcomes. Exploratory analyses of relationships between ADC and MMAE steady-state exposures, and the following safety endpoints were evaluated: Grade 3 or higher neutropenia or neutrophil count decrease (NEU3), febrile neutropenia (FN), any grade of peripheral neuropathy (PN), and Grade 3 or higher treatment-emergent adverse events (TEAE3). Exploratory analyses of relationships between ADC and MMAE steady-state exposures, and the following efficacy endpoints were evaluated: overall response rate (ORR, CR+PR) and progression-free survival (PFS).

Graphical explorations for each of the safety and efficacy endpoints were conducted to evaluate whether a trend with ADC and/or MMAE exposures were evident. If there was an exposure-response trend, logistic regression for binary type data, or Cox proportional hazard regression for survival-type data, were used to further evaluate the exposure-response relationship. The exposure metrics and limited covariates were tested using a full model approach (i.e., add all covariates of interest, and remove one by one if not significant). All statistical analysis and data processing were performed using R Statistical Software (version 4.0.3).

Immunogenicity

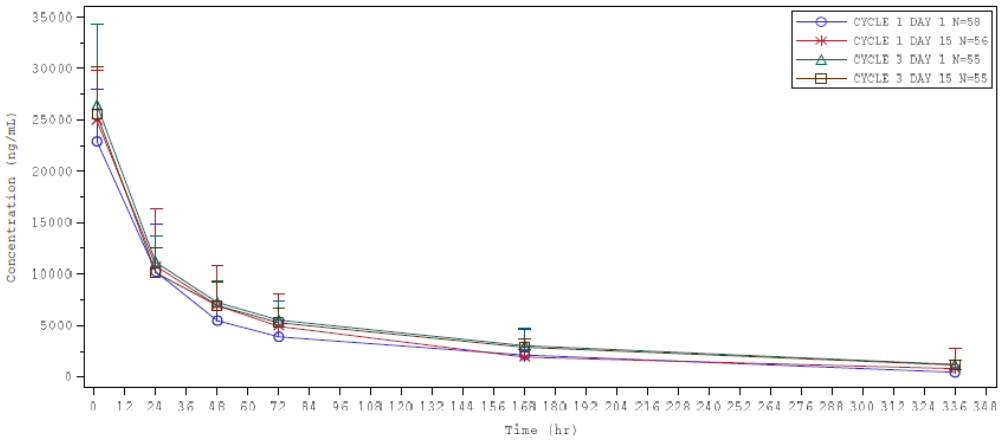
Immunogenicity data were summarized for patients in the immunogenicity population and presented using descriptive statistics into the following categories: ADA negative, transiently ADA positive, persistently ADA positive, low (≤25) and high (>25) ADA titer, and Nab status (negative or positive) as defined in the study protocol for ADA-positive patients only.

6.2. Results

Study C25004 – non-compartmental analysis

Following IV administration of brentuximab vedotin, ADC Cmax occurred approximately at the end of infusion (Figure 3). ADC serum concentrations declined in a multi-exponential manner with a t1/2z of approximately 4 days. Accumulation of ADC in serum was approximately 1.3 fold from Cycle 1 to Cycle 3 with a Q2W regimen of 48 mg/m^2 brentuximab vedotin.

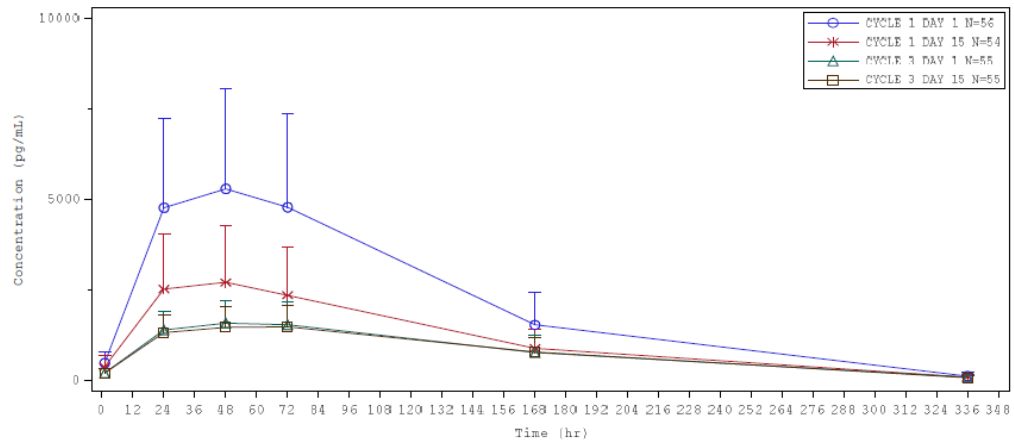
Figure 3 Mean (+SD) serum ADC concentration-time profiles following IV administration of 48 mg/m^2 brentuximab vedotin Q2W in combination with AVD in Cycle 1 and Cycle 3 (PK Population, study C25004)



Source: C25004 CSR Figure 11.i.
ADC: antibody-drug conjugate; IV: intravenously; PK: pharmacokinetic; Q2W: every 2 weeks.

Following IV administration of brentuximab vedotin, median tmax of MMAE occurred in plasma approximately 2 days post-dose (Figure 4). MMAE plasma concentrations declined log-linearly, with a mean t1/2z of approximately 2 days. Following repeated doses of brentuximab vedotin at 48 mg/m^2 Q2W, MMAE concentrations in plasma decreased to approximately 40% of the values of the first administration.

Figure 4 Mean (+SD) serum MMAE concentration-time profiles following IV administration of 48 mg/m^2 brentuximab vedotin Q2W in combination with AVD in Cycle 1 and Cycle 3 (PK Population, study C25004)



Source: C25004 CSR Figure 11.k.
IV: intravenous; MMAE: monomethyl auristatin E; PK: pharmacokinetic; Q2W: every 2 weeks.

A summary of the PK parameters of ADC and MMAE in paediatric patients from study C25004 is presented in Table 5. Upon repeated Q2W dosing, ADC AUC exposure was 30% increase compared to the first dosing. MMAE AUC values were approximately by 70% decreased in the 3rd cycle compared to the first cycle.

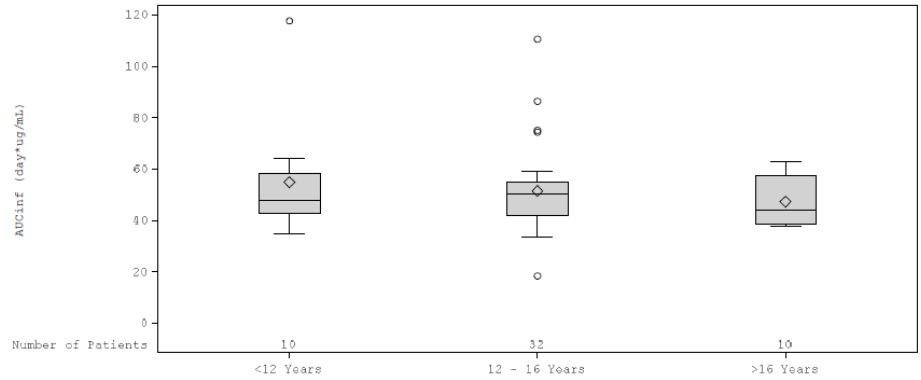
Table 5 Plasma PK parameters of ADC and MMAE in paediatric patients following IV administration of 48 mg/m^2 brentuximab vedotin Q2W in combination with AVD in Cycles 1 and 3 (study C25004, non-compartmental analysis)

ADC					MMAE				
	Cycl 1	gMean	Cycl 3	gMean		Cycl 1	gMean	Cycl 3	gMean

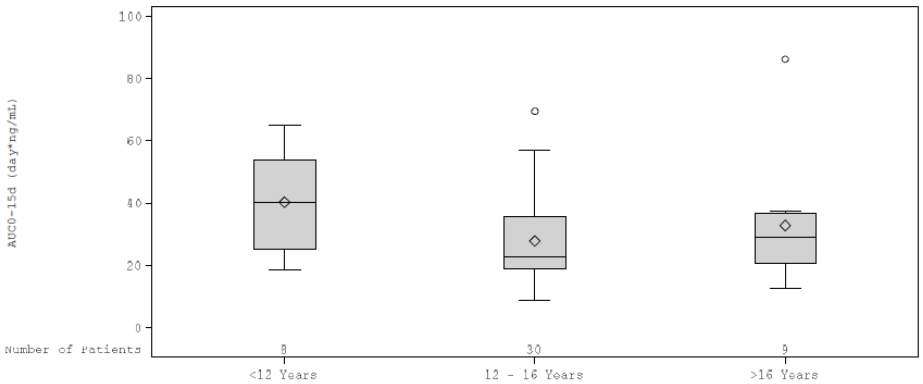
	N	(CV%)	N	(CV%)		N	(CV%)	N	(CV%)
Cmax (µg/mL)	57	22.5 (22.6)	55	26.4 (21.3)	Cmax (ng/mL)	54	4.9 (51)	53	1.6 (37.6)
AUC14d (day.µg/mL)	57	46.7 (33.5)	54	61.1 (29.2)	AUC14d (day.ng/mL)	47	27.2 (54.5)	48	10.1 (44.3)
T1/2 (days)	52	3.8 (28)			T1/2 (days)	42	2.1 (17.8)		

Figure 5 shows that ADC and MMAE exposures were comparable for the 3 age groups <12, 12-16, >16 years of age following the BSA-based dosing of brentuximab vedotin.

Figure 5 Box plots of ADC (top panel) and MMAE (bottom panel) exposures (AUCinf) by age group for the first dose of brentuximab vedotin 48 mg/m² (study C25004, non-compartmental analysis)



Source: C25004 CSR Figure 11.n.
ADC: antibody-drug conjugate; AUC_{inf}: area under the concentration versus time curve from time 0 to infinity; PK: pharmacokinetic.



Source: C25004 CSR Figure 11.o.
AUC_{15D}: area under the concentration versus time curve from time 0 to 15 days postdose; MMAE: monomethyl auristatin E.

PopPK analysis

The final popPK models for ADC and MMAE was used to simulate concentrations following 5 cycles of brentuximab vedotin administration using all patients in the dataset. One hundred fifty replicate simulations were performed. A summary of PK parameters derived from the simulations is presented in Table 6.

Table 6 PopPK model simulation of ADC (Top panel) and MMAE (Bottom panel, corrected Table) PK parameters for paediatric patients in studies C25002 and C25004

Parameter (Unit)	Study	Cycle	Median	Mean	Geometric Mean	Lowest 5th Percentile	Highest 95th percentile	SD	CV%
AUC_{21D} (µg*day/mL)	C25002	1	112.6	120.8	110.8	63.6	189.3	51.2	42.4
		5	138.1	149.7	138.3	83.4	232.0	61.4	41.0
AUC_{14D} (µg*day/mL)	C25004	1	51.7	55.1	51.4	31.7	82.5	20.9	37.9
		5	60.5	64.0	59.7	36.9	95.0	24.2	37.8
C_{max} (µg/mL)	C25002	1	30.8	34.7	30.8	13.7	69.1	17.9	51.6
		5	32.6	36.5	32.6	14.9	72.1	18.2	49.9
C_{max} (µg/mL)	C25004	1	25.3	26.6	24.0	10.6	47.2	11.3	42.5
		5	26.0	27.5	24.9	11.2	48.6	11.7	42.5
C_{min} (µg/mL)	C25002	1	1.0	1.3	1.0	0.3	3.3	1.0	76.9
		5	1.9	2.3	1.9	0.6	5.1	1.5	65.2
C_{min} (µg/mL)	C25004	1	0.4	0.5	0.4	0.1	1.2	0.4	80.0
		5	0.8	0.9	0.7	0.2	2.2	0.7	77.8

Source: Adcetris pop PK Report C25002 C25004 Tables 12, 13, 14, 15, 16, and 17.

ADC: antibody-drug conjugate; AUC_{14D}: area under the concentration versus time curve from time 0 to 14 days postdose; AUC_{21D}: area under the concentration versus time curve from time 0 to 21 days postdose; C_{max}: maximum observed concentration; C_{min}: minimum (trough) concentration; CV: coefficient of variation; PK: pharmacokinetic.

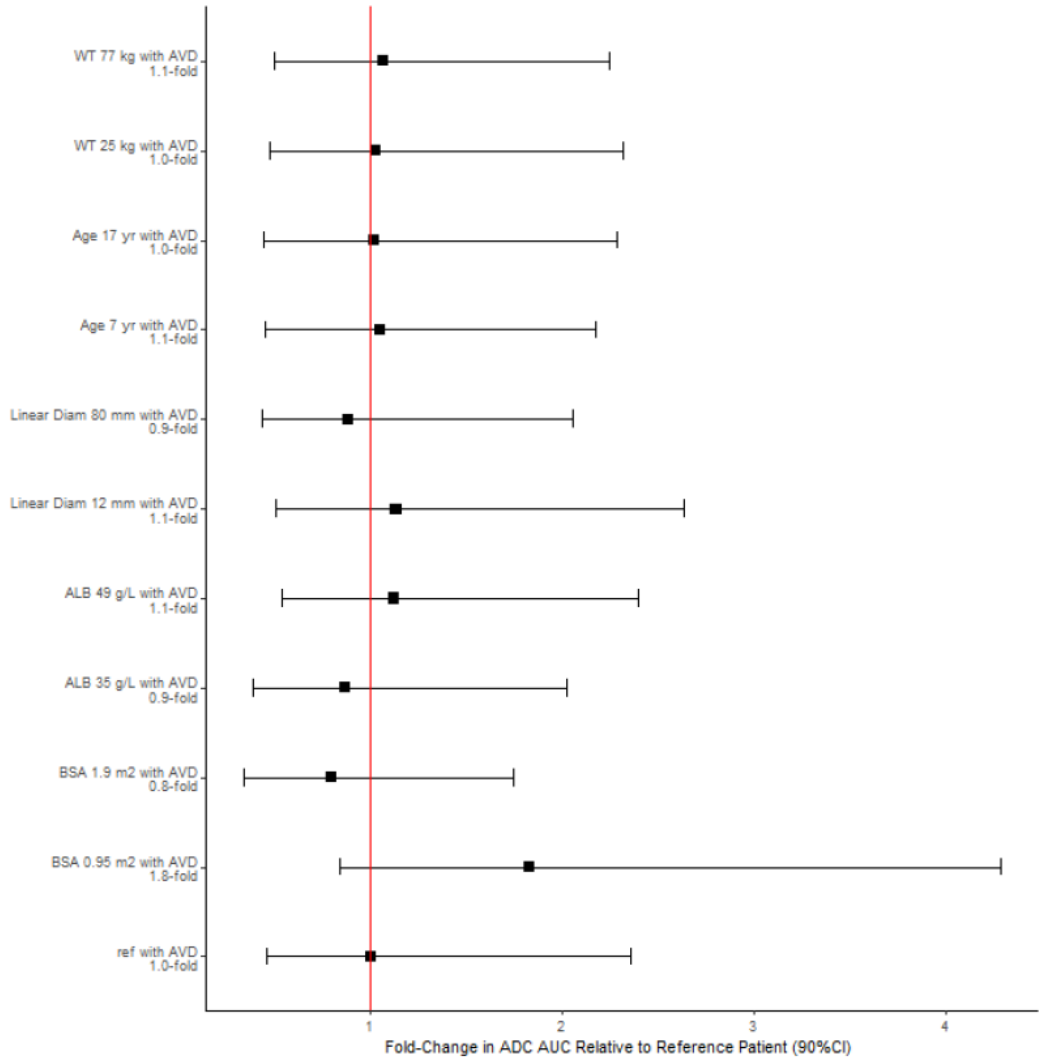
Parameter (Unit)	Study	Cycle	Median	Mean	Geometric Mean	Lowest 5th Percentile	Highest 95th percentile	SD	CV%
$AUC_{(0\text{-}21days)}$ (ng*day/mL)	C25002	1	36.3	45.1	34.1	11.9	89.5	34.7	76.9
		5	11.3	14.5	11.0	4.2	28.4	11.7	80.7
$AUC_{(0\text{-}14days)}$ (ng*day/mL)	C25004	1	26.7	35.5	26.3	9.4	72.1	30.0	84.5
		5	12.0	14.3	11.8	5.2	26.0	9.4	65.7
C_{max} (ng/mL)	C25002	1	**2.626**	**6.646**	**2.706**	**0.294**	**26.160**	**12.141**	**183**
		5	**0.702**	**1.367**	**0.758**	**0.166**	**4.904**	**2.263**	**166**
C_{max} (ng/mL)	C25004	1	**2.170**	**4.988**	**2.305**	**0.353**	**19.420**	**8.890**	**178**
		5	**1.012**	**1.318**	**0.993**	**0.272**	**3.366**	**1.111**	**84**
C_{min} (ng/mL)	C25002	1	0.102	0.198	0.077	0.004	0.688	0.316	159.6
		5	0.040	0.085	0.027	0.001	0.307	0.149	175.3
C_{min} (ng/mL)	C25004	1	0.173	0.352	0.168	0.021	1.294	0.565	160.5
		5	0.108	0.198	0.093	0.008	0.678	0.294	148.5

Source: Adcetris pop PK Report C25002 C25004 Tables 22, 23, 24, 25, 26, and 27.

AUC_{14D}: area under the concentration-time curve from time 0 to 14 days postdose; AUC_{21D}: area under the concentration-time curve from time 0 to 21 days postdose; C_{max}: maximum observed concentration; C_{min}: minimum observed concentration; CV: coefficient of variation; MMAE: monomethyl auristatin E; PK: pharmacokinetic.

Chemotherapy AVD resulted in approximately 2-fold higher ADC CL. Tumour linear diameter (ie, lymphoma volume), albumin, and BSA had impact on ADC CL and AUC. Age and weight were not identified as covariates in the final model and accordingly, the range of CL is similar. Forest plot is shown in Figure 6.

Figure 6 Forest plot of ADC AUC by covariate values for patients receiving concurrent chemotherapy



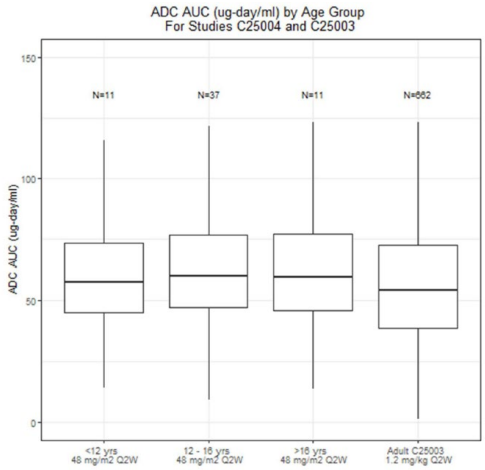
Source: Adcetris pop PK Report C25002 C25004 Figure 68.

ADC: antibody-drug conjugate; ALB: albumin; AUC: area under the concentration-time curve; AVD: Adriamycin (doxorubicin), vinblastine, dacarbazine; BSA: body surface area; Diam.: diameter; ref: reference; WT: weight.
The horizontal black lines and box display the fold change in the 5th, 95th quantiles, and the median, respectively, of ADC AUC values for the median, 5th, and 95th quantiles of various continuous covariate values. The fold increase was calculated by dividing the 5th, 95th quantiles, and the median AUC values for each covariate by the median AUC of the reference patient. The vertical red line shows the reference patient which is equal to 1. The reference patient is a virtual patient with median covariate values. The reference patient is a virtual patient with median covariate values.

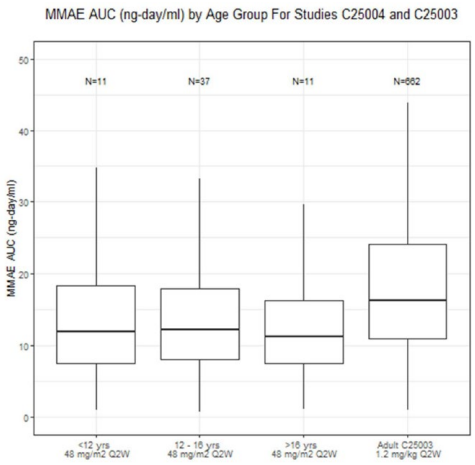
Comparison between paediatric patients and adult patients

Simulations were performed to evaluate ADC and MMAE exposure in order to compare dosing regimens between paediatric and adult patients (Figure 7). Simulations were performed to compare ADC and MMAE exposure in paediatric patients from Study C25004 administered 48 mg/m^2 Q2W in combination with chemotherapy AVD to adult patients with advanced HL from Study C25003 administered 1.2 mg/kg Q2W in combination with chemotherapy AVD. Boxplots of ADC and MMAE AUC are provided in Figure 7. ADC AUC for these dosing regimens overlap across the age groups indicating that administration of brentuximab vedotin to paediatric patients based on BSA results in similar exposure to adults administered doses based on body weight. A similar conclusion about consistent exposures in paediatric patients across age ranges can be made for MMAE AUC even though the range of the adult AUC is in the upper range of the paediatric AUC values.

Figure 7 Simulations of steady-state ADC (left panel) and MMAE (right panel) AUC following administration of 48 mg/m^2 Q2W brentuximab vedotin in paediatric subjects from Study C25004 compared with adult patients from Study C25003 administered 1.2 mg/kg Q2W by age group



Source: Adcetris pop PK Report C25002 C25004 Figure 62.
ADC: antibody-drug conjugate; AUC: area under the concentration versus time curve; Q2W: every 2 weeks.



Source: Adcetris pop PK Report C25002 C25004 Figure 63.
AUC: area under the concentration-time curve; BSA: body surface area; MMAE: monomethyl auristatin E; Q2W: every 2 weeks.

For the readers convenience non-compartmental pharmacokinetic parameters for ADC and MMAE in adult patients with advanced HL from Study C25003 administered 1.2 mg/kg Q2W in combination with chemotherapy AVD are shown in Table 7.

Table 7 Plasma PK parameters of ADC (top panel) and MMAE (bottom panel) in adult patients on C1D1 and C3D1 after IV administration of 1.2 mg/kg Brentuximab Vedotin Q2W + AVD (EPAR EMEA/H/C/002455/II/0055)

Parameter	Geometric Mean (%CV)			
	C1D1		C3D1	
	N	1.2 mg/kg Q2W	N	1.2 mg/kg Q2W
C_{max} (µg/mL)	55	22.9 (28.1)	52	23.6 (27.8)
t_{max} (day)	55	0.0278 (0.0208, 1.99) (a)	52	0.0403 (0.00347, 1.03) (a)
C_{eoi} (µg/mL)	24	22.2 (25.0)	19	19.9 (35.8)
AUC_{14D} (day*µg/mL)	55	43.2 (28.9)	50	56.1 (23.8)
AUC_{∞} (day*µg/mL)	53	46.0 (25.4)	NR	NR
$t_{1/2z}$ (day)	53	3.70 (19.8)	44	5.00 (16.9)
CL (L/day)	53	1.68 (28.4)	50	1.37 (28.2)
V_z (L)	53	8.96 (29.4)	49	9.96 (27.7)
$R_{ac(AUC14D)}$	NA	NA	46	1.27 (23.9)

Parameter	Geometric Mean (%CV)			
	C1D1		C3D1	
	N	1.2 mg/kg Q2W	N	1.2 mg/kg Q2W
C_{max} (ng/mL)	59	3.20 (73.6)	56	1.36 (51.7)
t_{max} (day)	59	1.86 (0.828, 6.94) (a)	56	1.88 (0.188, 7.01) (a)
AUC_{14D} (day*ng/mL)	59	18.8 (74.9)	54	9.46 (50.3)
AUC_{∞} (day*ng/mL)	49	20.1 (75.8)	NR	NR
$t_{1/2z}$ (day)	51	3.11 (35.0)	44	3.92 (21.9)
$R_{ac(AUC14D)}$	NA	NA	54	0.528 (68.6)

Exposure response

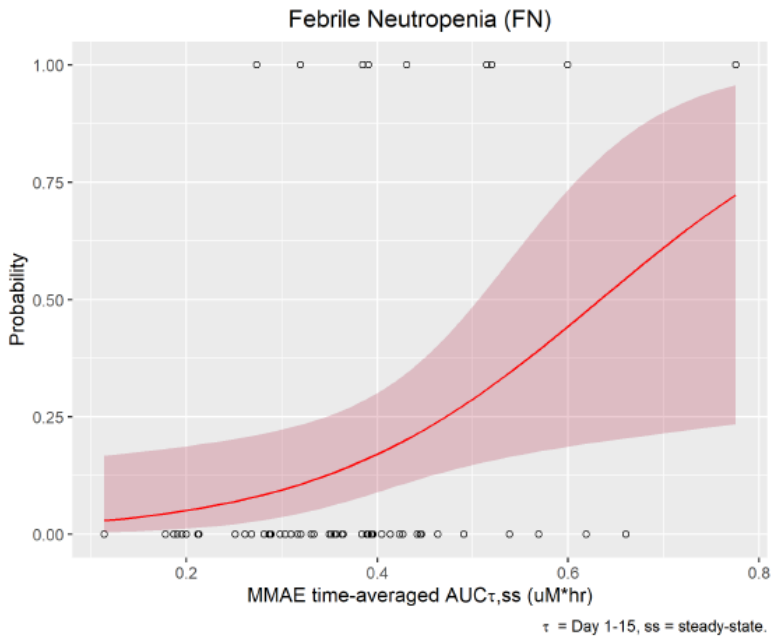
In total, 59 subjects from Study C25004 were included in the exposure-response (safety and efficacy) analyses. The time-averaged AUC for ADC and MMAE were used as exposure metrics, in which time-averaged AUC at steady state was calculated for the Q2W dose interval (AUCτ,SS). These exposure metrics were obtained from the individual predicted concentration-time profiles for 1 cycle (Day 1 to Day 15) at steady state, using individual post-hoc PK parameter estimates derived from the final population PK model.

Efficacy*:* PFS was the only efficacy endpoint that was evaluated in the exposure-efficacy analysis. All 59 subjects were alive and most responded to the treatment (either CR or PR) for the study duration, including treatment cycles and follow-up period. Therefore, overall survival analysis and ORR analysis were not conducted.

Kaplan-Meier plots of PFS by tertiles of time-averaged AUC exposure for both ADC and MMAE showed no apparent relationship between ADC or MMAE exposures and PFS. The exposures of ADC or MMAE were not significant based on a log-rank test. Therefore, no further evaluation with a statistical model was conducted.

Safety*:* The relationships between ADC and MMAE exposure and the following AEs were examined: NEU3, FN, PN, and TEAE3.

The relationships between exposure metrics (time-averaged AUCτ,ss with ADC and MMAE) and AEs of interest were evaluated using a logistic regression model. In this analysis, age and sex were also tested as potential covariates only if ADC or MMAE was a significant predictor of any of the AEs evaluated. No apparent relationships were identified between ADC exposures and the incidence of PN, NEU3, FN, or TEAE3. There was a significant increase ($p<0.05$) in the incidence of FN with increasing exposure of MMAE, consistent with what was observed in adults. The model predictions for the probability of FN events over the range of MMAE exposure is provided in Figure 8. There were no statistically significant relationships identified between MMAE exposure and PN, NEU3, or TEAE3.



Source: Exposure-Response Report Figure 2.
AUCτ,ss: area under the concentration versus time curve at steady state over the dosing interval; MMAE: monomethyl auristatin E.

Immunogenicity in Study C25004

All 59 patients (100%) had available immunogenicity data (received at least 1 dose of study drug and had at least 1 baseline and postbaseline immunogenicity assessment) for inclusion in immunogenicity analyses. All patients except 1 were ADA negative at baseline. The patient with a positive result at baseline had an ADA titre of <5.00 at baseline.

Overall, 55 of the 59 patients (93%) were ADA negative (not confirmed positive) at all postbaseline time points, and 4 patients (7%) were ADA positive at some time point postbaseline. ADA status is considered positive if both the screening and the confirmatory result are positive at a given cycle. All 4 patients were transiently ADA positive with a low (≤25) ADA titre. Among these 4 ADA-positive patients, 3 were ADA negative at baseline and developed ADA after administration of brentuximab vedotin. The patient who was ADA positive at baseline (baseline titre <5.00) also had positive ADA results postbaseline, but the titres did not increase, indicating that this patient had pre-existing ADA instead of the drug-induced ADA. No patients were persistently ADA positive. Two of 59 patients (3%) were Nab positive.

6.3. Discussion

Study C25004 was a single-arm study designed to assess PK, safety, and antitumour activity of brentuximab vedotin (ADC) in combination with adriamycin (doxorubicin), vinblastine, and dacarbazine (A+AVD) in paediatric patients with previously untreated Stage III or IV classical Hodgkin lymphoma (cHL). Previously, pharmacokinetic data from study C25002 (procedure EMEA/H/C/002455/II/0049) in paediatric patients treated with brentuximab vedotin 1.8 mg/kg monotherapy had indicated that BSA based dosing would result in exposure approximately similar across different body weight ranges. Therefore, dosing in study C25004 was BSA based, i.e. 48 mg/m^2 Q2W in combination with AVD in a 4-weeks cycle. PK rich data for ADC and MMAE, the unbound toxin, were collected in cycles 1 and 3. Pharmacokinetics was evaluated by non-compartmental analysis and by popPK analysis. Integrated population pharmacokinetic modelling of PK data from both studies is performed to support the proposed dosing regimens and to compare exposure with exposure in adult patients. An exploratory exposure-response analysis was conducted using data from Study C25004 to evaluate relationships between steady-state ADC and MMAE exposure and selected safety and efficacy endpoints. In addition, immunogenicity was evaluated.

Pharmacokinetics of ADC and MMAE in paediatric patients study C25004

Study C25004 enrolled 59 patients, eleven patients (19%) were between 6 and 11 years, and 48 patients (81%) were between 12 and 17 years.

Maximum concentrations of brentuximab vedotin ADC were typically observed at the end of infusion or the sampling timepoint closest to the end of infusion. A multiexponential decline in ADC serum concentrations was observed with a terminal half-life of approximately 4 days. A 30% higher AUC exposure of ADC was observed with multiple doses at the every 2-week schedule, which is slightly higher than anticipated for a terminal half-life of 4 days. Typical Cmax and AUC of ADC after a single 48 mg/m^2 dose was approximately 23 µg/mL and 47 µg.day/mL respectively. Mean Cmax and AUC of MMAE were 4.9 ng/mL, 27 ng.day/mL. MMAE exposures decreased after multiple doses of brentuximab vedotin with approximately 50% to 70% of the exposure of the first dose being observed at subsequent doses.

ADC and MMAE exposures were comparable for paediatric patients <12 and ≥ 12 years of age supporting the BSA-based dosing of brentuximab vedotin in paediatric patients.

Comparison of pharmacokinetics in the two paediatric studies C25002 and C25004

PopPK estimated an approximately 2-fold higher ADC clearance for patients on concurrent treatment with AVD. This is rather unexpected since non-compartmental analysis indicated only a 10-25% lower ADC exposure in paediatric patients with concurrent chemotherapy and in adults on concurrent treatment with AVD, pharmacokinetics of ADC was consistent with that of monotherapy. This apparent inconsistency in effect of concurrent AVD treatment between paediatric and adult patients needs to be clarified when the MAH wants to apply for an indication in paediatric patients. Mean MMAE exposures were comparable for the first administration for paediatric patients in studies C25002 and C25004 but were slightly lower for the combination therapy in cycle 3, although there was an overlap in exposures.

PopPK analysis - comparison with exposure in adult patients

For study C25004, mean AUC exposure estimates were comparable for non-compartmental and for popPK simulations for both ADC and MMAE in paediatric patients treated with brentuximab vedotin 48 mg/m^2 Q2W in combination with chemotherapy. For brentuximab vedotin 1.8 mg/kg Q3W, mean ADC AUC exposures estimates by popPK were ~30% higher than non-compartmental analysis. Remarkably, VPC plots (Figure 1) suggested an underprediction of the ADC serum concentrations for study C25002 and a overprediction of ADC plasma values for study C25004. Since these were not predicted corrected VPC plots, while there is some time variance these plots are difficult to interpret. The popPK model for ADC and especially for MMAE shows overestimation of the variability (Figure 1 and Figure 2), the intersubject variability of the simulated PK parameters was considerably higher than observed in the non-compartmental analysis (compare Table 1, Table 5, and Table 6). While the objective function of the popPK improved by inclusion of the co-variates, the unexplained variability was not improved compared to the base model, and apparently the co-variates had no significant effect (see Figure 6). Therefore, the popPK models of ADC and MMAE are considered suitable for descriptive purposes only, not for simulation purposes and consequently comparison with adult exposures and exposure-effect analysis are considered exploratory only.

Based on non-compartmental PK across study comparison (compare Table 5 and Table 7), ADC and MMAE steady-state exposures were comparable in paediatric patients from Study C25004 administered 48 mg/m^2 Q2W in combination with chemotherapy AVD and in adult patients with advanced HL from Study C25003 administered 1.2 mg/kg Q2W in combination with chemotherapy AVD.

There are sufficient pharmacokinetic data from the non-compartmental analysis to describe the pharmacokinetics of ADC and MMAE in paediatric patients from studies C25002 (brentuximab vedotin 1.8 mg/kg Q3W) and C25004 (brentuximab vedotin 48 mg/m^2 Q2W in combination with chemotherapy) in the SmPC section 5.2, therefore, no questions regarding the popPK model will be raised in this procedure. When the MAH wants to apply for an indication in paediatric patients with a difference dosing than used in the clinical study(ies), it is suggested to review the popPK model to reduce the observed bias and to reduce the overpredicted variability. The MAH is then kindly requested to include the output files, figures of individual predictions, and provide pcVPC with predicted and observed median and median 5% - 95% indicated.

Immunogenicity

Overall, 55 of the 59 patients (93%) were ADA negative at all postbaseline time points, and 4 patients (7%) were ADA positive at some time point postbaseline of which 1 patients was already ADA positive at baseline. All 4 patients were transiently ADA positive with a low (≤25) ADA titre. Two of 59 patients (3%) were Nab positive. The low immunogenicity is in line with previous observation, there are not sufficient data to draw a conclusion on the effect of ADAs on the pharmacokinetics of ADC. The text in the SmPC 4.8 has been adequately updated with the ADA incidence in paediatric patients from study C25004.

Conclusions

The MAH does not apply for a paediatric indication within this procedure, but proposes modification of the SmPC sections 4.2, 4.8, 5.1 and 5.2 with data from study C25004.

Since there are sufficient pharmacokinetic data from the non-compartmental analysis to describe the pharmacokinetics of ADC and MMAE in paediatric patients from studies C25002 (brentuximab vedotin 1.8 mg/kg Q3W) and C25004 (brentuximab vedotin 48 mg/m^2 Q2W in combination with chemotherapy) in the SmPC section 5.2, no questions regarding the popPK model will be raised. The MAH is recommended for future applications to review the popPK model. The text in section 5.2 of the SmPC has been amended to report the pharmacokinetics of ADC and MMAE as determined by non-compartmental analysis.

7. Clinical Efficacy aspects

As part of this type II variation, intended to update the paediatric data presented in the ADCETRIS Summary of Product Characteristics (SmPC), the final results of Study C25004 in paediatric patients with previously untreated Stage III or IV classical Hodgkin lymphoma (cHL)are submitted by the MAH. In addition a meta-analysis of clinical studies for brentuximab vedotin in paediatric patients with Hodgkin lymphoma were submitted.

Study C25004

Study C25004 was a global, multi-centre study conducted at 14 investigative sites, which included 2 US sites and 12 ex-US sites located in 3 countries (Brazil, Japan, Italy). Site initiation visits were conducted and study drug distributed at 12 additional investigative sites (1 site each in Italy, Hong Kong, and Singapore, 2 sites each in Japan, Taiwan, and the US, and 3 sites in Brazil) but no patients were enrolled at these sites.

Study C25004, an extension of the ongoing brentuximab vedotin development program in adult patients, was intended to investigate potential use in paediatric patients with newly diagnosed Stage III or IV classical Hodgkin lymphoma (cHL). Study C25004 was a phase 1/2, open-label, multi-agent, multicentre study of brentuximab vedotin given in combination with Adriamycin (doxorubicin), vinblastine, and dacarbazine (A+AVD) in paediatric patients with advanced-stage, newly diagnosed classical CD30+ first-line HL.

The study consists of 2 phases.

Primary Objective of phase 1 was to assess the safety and tolerability, and to identify the recommended dose of brentuximab vedotin when combined with multiagent chemotherapy regimen AVD for first-line treatment of advanced-stage HL in paediatric patients.

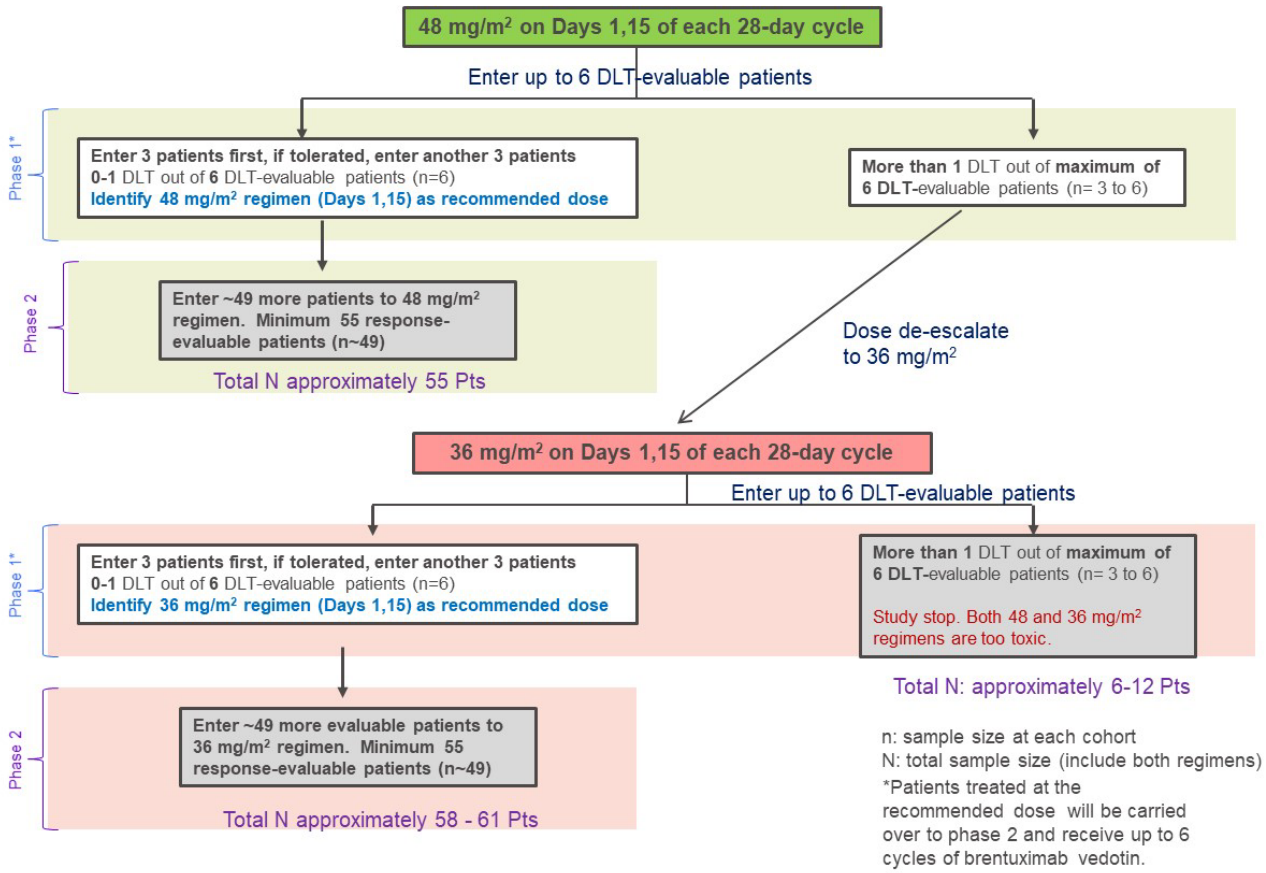
Primary Objective of phase 2 was**:**

- To evaluate the CR rate of paediatric patients with advanced-stage HL at the end of protocol therapy.
- To determine the percentage of patients who were PET-negative after 2 cycles of protocol therapy.
- To evaluate the PR rate of paediatric patients with advanced-stage HL at the end of protocol therapy.
- To evaluate the ORR of paediatric patients with advanced-stage HL at the end of protocol therapy.
- To determine the percentage of patients who were able to complete 6 cycles of protocol therapy at the recommended dose.

7.1. Methods – analysis of data submitted

Study C25004 was a phase 1/2, open-label, multiagent, multi-centre study of brentuximab vedotin given in combination with Adriamycin (doxorubicin), vinblastine, and dacarbazine (A+AVD) in paediatric patients with advanced-stage, newly diagnosed classical CD30+ first-line HL (see study design scheme Figure 9).

Figure 9 Study C25004: Dosing scheme



DLT: dose-limiting toxicity; Pts: patients.

The first 3 patients enrolled in the study were to be monitored for DLTs during the DLT observation period (Cycle 1 +28 days [from the first dose through Study Day 56]). If no or 1 DLTs occurred in the first 3 patients, 3 additional patients were to be enrolled and monitored for DLTs. If the first 6 patients completed the DLT observation with no patient or 1 patient experiencing a DLT, 48 mg/m² was to be the recommended dose of brentuximab vedotin, and approximately 49 additional patients were to be enrolled in the phase 2 study to further assess safety and efficacy for a total of at least 55 evaluable patients at the recommended dose in the study. Available PK data were to be reviewed along with the safety data to guide the final decision on the recommended dose.

Study population

The paediatric study population consisted of patients aged 5 to < 18 years with advanced-stage (Stage III or Stage IV), newly diagnosed CD30+ cHL who were treatment naïve and had a Karnofsky Performance Status or Lansky Play-Performance of ≥50. Patient eligibility was established before each patient enrolled in the study.

Maine inclusion criteria

1. Patients aged 5 to <18 years.

2. Histologically confirmed CD30+ cHL.

3. Advanced-stage (Stage III or Stage IV) newly diagnosed HL.

4. Treatment-naïve HL.

5. Had performance scores of ≥50 for Lansky Play-Performance or Karnofsky Performance Status.

6. Clinical laboratory values (ANC, Platelet count, total bilirubin, ALT, creatine clearance, serum creatine and haemoglobin) within 4 days before the first dose of protocol therapy as follows at predefined levels

Main exclusion Criteria

Patients who met any of the following exclusion criteria were not to be enrolled in the study:

1. Nodular lymphocyte predominant HL.

2. Known active cerebral/meningeal disease, including signs or symptoms of progressive multifocal leukoencephalopathy (PML) or any history of PML.

3. Any sensory or motor PN.

4. Symptomatic neurologic disease compromising normal activities of daily living or requiring medications.

5. Any active systemic viral, bacterial, or fungal infection requiring systemic antibiotics within 2 weeks before the first study protocol therapy.

6. Use of any strong or listed moderate cytochrome P450 (CYP) 3A4 inhibitors <2 weeks before the first dose of protocol therapy.

7. Any of the predefined cardiovascular conditions (shortening fraction, heart failure, uncontrolled cardiovascular conditions including cardiac arrhythmias, congestive heart failure, angina or electrocardiographic evidence of acute ischemia or active conduction system abnormalities) or values within 6 months before the first dose of protocol therapy.

Treatment

Study C25004 was an open-label, single-arm study with no reference therapy. Treatment group assignments were not applicable. No randomization scheme or codes were used in the study.

The components of A+AVD used in this study were considered investigational medicinal products and were supplied by the study sponsor. A+AVD consists of brentuximab vedotin 48 or 36 mg/m^2, plus doxorubicin, vinblastine, and dacarbazine .

A: Doxorubicin: 25 mg/m^2 was to be administered by intravenous (IV) infusion on Days 1 and 15 of each 28-day cycle.

V: Vinblastine: 6 mg/m^2 was to be administered by IV infusion on Days 1 and 15 of each 28-day cycle.

D: Dacarbazine: 375 mg/m^2 was to be administered by IV infusion on Days 1 and 15 of each 28-day cycle.

Brentuximab vedotin was to be administered after AVD:

A: brentuximab vedotin: 48 or 36 mg/m^2 was to be administered by IV infusion on Days 1 and 15 of each 28-day cycle, starting approximately 1 hour after the end of the dacarbazine administration.

Dosing was based on the patient's BSA according to the institutional standard. However, it was required that doses be adjusted for patients who experienced a ≥10% change in BSA from the most recent dose calculation. The dose was calculated based on a BSA of 2.5 m^2 for patients with a BSA of >2.5 m^2 to ensure that patients received no more than the maximum brentuximab vedotin dose of 120 mg. The dose was rounded to the nearest whole number milligrams. Recommended dosing of brentuximab vedotin could need to be modified in case of AE (Table 8)

Table 8 Study C25004: Recommended Brentuximab Vedotin Dose Modifications for Treatment-Associated Toxicity

Treatment-Associated Toxicity

Toxicity	Grade ≤2		Grade ≥3	
Nonhematologic (excluding neuropathy)	Continued at same dose level.		A+AVD dosing held until toxicity resolved to Grade ≤2 or returned to baseline [a, b, c].	
Hematologic	Continued at same dose level.		For neutropenia, managed with growth factors (G-CSF or GM-CSF) per institutional guidelines. G-CSF use was not permitted in the DLT observational period (Cycle 1 + 28 days in phase 1). For thrombocytopenia, platelet transfusion was to be considered and/or management according to institutional guidelines. For anemia, management per institutional guidelines.	
Peripheral neuropathy	**Grade 1** Continued at same dose level.	**Grade 2** Reduced brentuximab vedotin dose by 25% and resumed treatment; if already reduced by 25%, dosing continued at same dose.	**Grade 3** Brentuximab vedotin withheld until toxicity was Grade ≤2, then dose reduced by 25% and treatment resumed. If already reduced by 25%, consultation with sponsor. (AVD could be continued or held concurrently at physician's discretion.)	**Grade 4** Brentuximab vedotin discontinued.

Source: Protocol Table 8.a (Appendix 16.1.1).

A+AVD: brentuximab vedotin with Adriamycin (doxorubicin), vinblastine, and dacarbazine; AVD: Adriamycin (doxorubicin), vinblastine, and dacarbazine; DLT: dose-limiting toxicity; G-CSF: granulocyte colony stimulating factor; GM-CSF: granulocyte macrophage colony stimulating factor.

[a] Patients who developed clinically insignificant Grade 3 or 4 electrolyte laboratory abnormalities could continue study treatment without interruption.

[b] Dose modifications for nonhematologic toxicity could be considered after discussion with the medical monitor.

[c] In the case of dose delays >2 weeks, a discussion with the medical monitor should have occurred.

Study treatment was to be discontinued after completion of 6 cycles of protocol therapy, occurrence of unacceptable adverse event (AE), progressive disease (PD), patient withdrawal, or study termination. Patients could have discontinued protocol therapy at any time.

For patients who received radiation at EOT, ISRT recommendations consisted of 2100cGy in 14 fractions of 150cGy per day. Treatment was to be administered 5 days per week. All fields were to be treated once per day.

Endpoints

Phase 1 Primary Endpoints

- Determination of the recommended dose of brentuximab vedotin in combination with AVD in a pediatric population.
- Percentage of patients who experienced AEs from the first dose of protocol therapy through 30 days after administration of the last dose of protocol therapy.
- Percentage of patients who experienced SAEs from the first dose of protocol therapy through 30 days after administration of the last dose of protocol therapy.

Phase 1 Secondary Endpoints

- Mean Cmax and mean AUC15D of brentuximab vedotin, TAb, and MMAE.
- Median tmax of brentuximab vedotin, TAb, and MMAE.
- Percentage of patients who achieved a CR by IRF assessment at EOT per IWG criteria.
- Percentage of patients who achieved a PR by IRF assessment at EOT per IWG criteria.
- Percentage of patients who achieve an overall response by IRF assessment at EOT per IWG criteria.
- Percentage of patients whose disease was PET-negative after 2 cycles of protocol therapy by IRF assessment.
- Percentage of patients whose disease was PET-positive after 6 cycles of protocol therapy by IRF assessment.
- Percentage of patients who were ADA negative, ADA positive, persistently positive, or transiently positive; ADA titer and Nab positive at baseline, predose at Cycle 2 Day 1, Cycle 4 Day 1, Cycle 6 Day 1, or at treatment termination if treatment was terminated before Cycle 6, and at EOT.
- Impact of ADA and Nab on the safety, efficacy, and PK endpoints.

Phase 1 Exploratory Endpoints

Phase 1 exploratory endpoints include among others; PFS, EFS, OS, DOR.

Phase 2 Primary Endpoints

- Percentage of patients who achieved a CR by IRF assessment at EOT per IWG criteria.
- Percentage of patients whose disease was PET-negative after 2 cycles of protocol therapy by IRF assessment.
- Percentage of patients who achieved a PR by IRF assessment at EOT per IWG criteria.
- Percentage of patients who achieved an overall response by IRF assessment at EOT per IWG criteria.
- Percentage of patients who completed 6 cycles of protocol therapy at the recommended dose.

Phase 2 Secondary Endpoints

- PFS, EFS, OS, DOR.
- Percentage of patients receiving irradiation for HL following study treatment.
- Percentage of patients who experienced AEs from the first dose of protocol therapy through 30 days after administration of the last dose of protocol therapy.

- Percentage of patients who experienced SAEs from the first dose of protocol therapy through 30 days after administration of the last dose of protocol therapy.
- Percentage of patients who were ADA negative, ADA positive, persistently positive, or transiently positive; ADA titer and Nab positive at baseline, pre-dose Cycle 2 Day 1, Cycle 4
- Day 1, Cycle 6 Day 1, or at treatment termination if treatment is terminated before Cycle 6, and at EOT.
- Impact of ADA and Nab on the safety, efficacy, and PK endpoints.
- Percentage of patients who experienced PN, regardless of seriousness, from the first dose of protocol therapy through study closure.
- Time to onset and time to resolution for all PN events.
- Immune reconstitution baseline, EOT, and at 6, 12, and 18 months (±1 month) after last dose, until the start of subsequent anticancer therapy (except for radiotherapy administered as part of first-line therapy).

Phase 2 Exploratory Endpoints

Phase 2 exploratory endpoints include those related to the results of the PedsQL 4.0 Generic Core Scales and PedsQL 3.0 Cancer Module.

Definitions of endpoints

ORR: the percentage of patients who achieved a CR or PR at EOT, by IRF assessment using PET, CT, MRI

PFS: PFS by IRF assessment was defined as the time from the first dose until disease progression by IRF assessment or death due to any cause, whichever occurred first.

EFS: EFS by IRF assessment was defined as the time from the first dose until any treatment failure: PD by IRF assessment including progression events during follow-up period, failure to complete 6 cycles of treatment for any reason, or death due to any cause, whichever occurred first.

DOR: DOR by IRF assessment in patients with a response (CR or PR per IRF) was defined as the time from start of the first objective tumour response (CR or PR per IRF) to the first subsequent PD or death due to any cause, whichever occurred first.

Response to treatment and disease status assessments were evaluated according to the International Working Group (IWG) Revised Criteria for Response Assessment for Malignant Lymphoma. These disease assessments were performed by investigators and an independent review facility (IRF) at times specified in the SOE. Evaluations were to be performed as defined in the SOE until PD was documented by the investigator, death occurred, or the study ended.

B symptoms (fever, night sweats, and/or weight loss) were to be recorded at screening, on Day 1 of each treatment cycle, at the EOT visit, and every 12 weeks during PTFU.

A bone marrow biopsy was to be collected at screening within 28 days of the first dose of protocol therapy. For patients with a positive bone marrow biopsy at screening, a second bone marrow biopsy was required to confirm response within 2 weeks after documentation of response at either Cycle 2 Day 25 or at the EOT visit. A repeat biopsy was not required once it was determined that the bone marrow sample was negative.

Patient-reported and parent proxy HRQOL assessments were scheduled to be performed at screening, on Day 1 of Cycle 1, at every other cycle thereafter, at the EOT visit, and during PTFU visits. The

PedsQL 4.0 Generic Core Scales is a 23-item questionnaire designed to measure HRQOL in children and adolescents aged 2 to 18 years, and the PedsQL 3.0 Cancer Module is a 27-item questionnaire designed to measure paediatric cancer-specific HRQOL.

Blood samples were scheduled to be collected at screening (baseline), on Day 1 of Cycles 2, 4, and 6 or at termination of treatment if treatment is terminated before Cycle 6, and at EOT to evaluate serum ADA and Nab. Blood samples for ADA and Nab assessment were scheduled to be collected before administration of study treatment. Nab assessment was performed for ADA-positive samples only. The incidence of ADA and Nab to brentuximab vedotin was determined and the effect of ADA and Nab on PK, efficacy, and safety was assessed.

AEs were assessed, and laboratory values and vital signs measurements were obtained to evaluate the safety and tolerability of protocol therapy. Toxicity was evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03, effective 14 June 2010.

DLT was defined as any of the following events with onset during the DLT observation period that were considered by the investigator to be at least possibly related to brentuximab vedotin therapy:

- Any nonhematologic Grade 3 or higher toxicity except for any Grade 3 or higher nonhematologic toxicity that occurred in the absence of optimal supportive therapy (eg, antiemetic, antidiarrheal) and lasted more than 5 consecutive days (such as vomiting, diarrhea, constipation, pyrexia, infection, or mucosal inflammation).

Grade 3 or higher nonhematologic toxicity (except Grade 3 alopecia) that was controllable to Grade 2 or lower with appropriate treatment was not to be considered DLT.

- Treatment delay of longer than 14 days.
- Asymptomatic laboratory abnormalities were not to be considered DLTs except for Grade 2 pancreatitis (enzyme elevation only without clinical and/or radiographic findings).

Patients were to be followed for survival until the sooner of death, study closure, or up to 2 years after enrollment of the last patient.

All study participants were to be offered the opportunity to participate in an optional LTFU for a least 10 years after the specific patient's enrollment to assess safety and survival annually. Patients participating in the optional LTFU were to start the first optional LTFU visit 2 years after the specific patient's EOT visit and continue with annual visits until at least 10 years from the date on which the patient enrolled. This optional LTFU is intended to assess long-term safety outcomes, including:

- Development of any secondary malignancies.
- Treatment-related SAEs.
- Cardiovascular function abnormalities.
- Ongoing PN assessment.
- Development assessment.
- Immune function abnormalities.
- Survival status.

Analysis

As of the 18 December 2020 cutoff for data analysis, all enrolled patients had completed the treatment period of the study; and the main study posttreatment follow-up (PTFU) and the LTFU periods were ongoing.

The endpoints that will be analysed for which study population and at which phase of the study are descript in the table below (Table 9).

The populations defined for analysis of the study data were:

- **Safety population**: included patients who received at least 1 dose of any drug in the A+AVD regimen. The safety population was used for analysis of safety data, and efficacy endpoints, PFS, EFS, OS, and the percentage of patients who received irradiation for HL.
- **Response-evaluable population (IRF and investigator)**: included patients who received at least 1 dose of A+AVD, had measurable disease at baseline, and at least 1 postbaseline IRF and/or investigator disease assessment. The response-evaluable population was defined separately for IRF and investigator assessments, and was used for the analysis of ORR, CR, and PR rates, DOR, PET negativity after Cycle 2, and PET negativity after Cycle 6.
- **PK Population**: included patients with sufficient data to enable calculation of at least 1 PK parameter. The PK population was used for PK analyses.
- **Immune reconstitution population**: included patients who received at least 1 dose of study drug and had a sufficient immune reconstitution blood sampling to allow for immune reconstitution evaluation. The immune reconstitution population was used to analyze immune reconstitution–related endpoints.
- **DLT-evaluable population**: included patients in the phase 1 study who received at least 1 dose of protocol therapy and experienced a DLT during the DLT observation period (Cycle 1+28 days [from first dose through Study Day 56]), and patients who received all planned doses of protocol therapy in Cycle 1 and completed all relevant study procedures/assessments during the DLT observation period without a DLT. Only patients used to determine the recommended dose were included in the DLT-evaluable population.Patients who received G-CSF during the DLT observation period were excluded from the DLT-evaluable population.
- **Immunogenicity population**: included patients who received at least 1 dose of study drug and had the baseline immunogenicity sample and at least 1 postbaseline immunogenicity sample assessment. The immunogenicity population was used for the immunogenicity analyses.

The efficacy analyses were performed for binary and time-to-event endpoints using either the response-evaluable or safety populations.

Table 9 Study C25004: Efficacy Endpoints Evaluated

Endpoint	Primary Analysis Population	Phase 1	Phase 2
Binary			
ORR, CR and PR rates at EOT	Response-evaluable	2nd	1st
PET- after Cycle 2 defined by Deauville score (1 or 2, and 1, 2, or 3)	Response-evaluable	2nd	1st
PET+ after Cycle 6 defined by Deauville score (3, 4, or 5 and 4 or 5)	Response-evaluable	2nd	
Radiation for HL after EOT	Safety	3rd	2nd
Time-to-event			
PFS, EFS, OS	Safety	3rd	2nd
DOR	Response-evaluable population with a response	3rd	2nd

CR: complete response (remission); DOR: duration of response; EFS: event-free survival; EOT: end of treatment; HL: Hodgkin lymphoma; ORR: overall response rate; OS: overall survival; PET: positron emission tomography; PET-: PET-negative; PET+: PET-positive; PFS: progression-free survival; PR: partial response (remission).
1st: primary endpoint; 2nd: secondary endpoint; 3rd: exploratory endpoint.

An interim analysis (IA) for futility was performed after 25 patients had completed 6 cycles of study treatment and had their EOT response assessment. The boundary for the futility IA was set to 80%. If the upper bound of the 80% CI would have been below 80%, this would mean that A+AVD had an inferior efficacy, in terms of ORR, compared with the known ORR rates of 80% to 90% for the standard of care therapies. In addition to the 80% CI, a conventional 95% CI was used for the IA. Following the results of the IA, the 80% exact CI of ORR at EOT by IRF assessment was 75%, 96%, while the 95% CI was 69%, 97%. Since the upper bounds of both CIs did not cross the predefined futility boundary of 80%, no futility was inferred and the study continued as planned. Because the study results are descriptive, no multiplicity adjustment was done in the final analysis.

7.2. Results

Patient disposition

A total of 63 subjects were screened to determine eligibility for study enrolment (Table 10). Four subjects were determined to be screen failures. One patient was not treatment-naïve (inclusion criterion 4), and 1 patient did not meet the prespecified clinical laboratory values within 4 days of the first dose of protocol therapy (inclusion criterion 10). Exclusion criteria that precluded enrollment for the other 2 subjects were an active systemic infection that required systemic antibiotic therapy within 2 weeks of protocol therapy (exclusion criterion 7), and a predefined cardiovascular condition or value within 6 months before the first dose of protocol therapy (exclusion criterion 13).

Fifty-nine patents were enrolled in the study from 4 geographic regions: North America, Latin America, Western Europe, and Asia. A total of 12 patients (20%) were enrolled at 2 investigative sites in the US, 30 patients (51%) at 6 investigative sites in Brazil, 15 patients (25%) at 4 investigative sites in Italy, and 2 patients (3%) at 2 investigative sites in Japan.

The primary reason for study treatment discontinuation was reported as completion of the maximum 6 cycles of protocol therapy for all 59 patients (100%). As of the 18 December 2020 data cut, the study was ongoing with patients participating in either PFSFU or overall survival follow-up (OSFU) of the main study, and/or the 10-year optional LTFU.

Table 10 Study C25004: Overall Disposition

Subject disposition, n (%)	Phase 1 N=8	Phase 2 N=51	Phase 1+Phase 2 N=59
Screened	9	54	63
Safety population	8 (100)	51 (100)	59 (100)
Response-evaluable population (INV)	8 (100)	51 (100)	59 (100)
Response-evaluable population (IRF)	8 (100)	51 (100)	59 (100)
PK population	8 (100)	51 (100)	59 (100)
Immune-reconstitution population	8 (100)	51 (100)	59 (100)
DLT-evaluable population	6 (75)	0	6 (10)
Immunogenicity population	8 (100)	51 (100)	59 (100)
Discontinued study drug	8 (100)	51 (100)	59 (100)
Primary reason to discontinue from study drug			
Completed maximum number of cycles per protocol	8 (100)	51 (100)	59 (100)
Adverse event	0	0	0
Progressive disease	0	0	0
Protocol violation	0	0	0
Study terminated by sponsor	0	0	0
Unsatisfactory therapeutic response	0	0	0
Withdrawal by patient	0	0	0
Participated in PFSFU	8 (100)	50 (98)	58 (98)
Participated in OSFU	0	6 (12)	6 (10)
Participated in LTFU	7 (88)	0	7 (12)
Discontinued from the study	0	0	0

Source: Table 15.1.1.1.

DLT: dose-limiting toxicity; INV: investigator; IRF: independent review facility; LTFU: long-term follow-up; OSFU: overall survival follow-up ; PFSFU: progression-free survival follow up ; PK: pharmacokinetic.

Percentages are based on the number of patients calculated relative to the total number of patients in the safety population for each phase.

According to the predefined criteria outlined in the ICH E3 guidance, protocol deviations were identified for 2 patients. One patient was enrolled and allowed to continue participation in the study after the use of an excluded CYP3A inhibitor was reported within 2 weeks before the first dose of protocol therapy. One patient was enrolled in the study despite an elevated bilirubin value higher than 1 allowed.

A total of 55 protocol deviations were documented related to the COVID-19 pandemic. Remote source data verification for at least 1 study visit accounted for the highest proportion (37 deviations [67%]) of deviations related to COVID-19. Other COVID-19 deviations pertained to study visits conducted remotely, outside the protocol-defined window, or not conducted altogether. In some instances, PET imaging was not performed, and in some instances, the procedure was performed outside the protocol-defined window.

Demographic Characteristics

Table 11 Study C25004: Demographics (Safety Population)

	Phase 1 N=8	Phase 2 N=51	Phase 1+Phase 2 N=59
Sex, n (%)			
Male	4 (50)	27 (53)	31 (53)
Female	4 (50)	24 (47)	28 (47)
Race, n (%) [a]			
White	8 (100)	26 (51)	34 (58)
Black or African American	0	12 (24)	12 (20)
Other [a]	0	9 (18)	9 (15)
Asian	0	3 (6)	3 (5)
Not reported	0	1 (2)	1 (2)
Ethnicity, n (%)			
Hispanic or Latino	2 (25)	21 (41)	23 (39)
Not Hispanic or Latino	6 (75)	26 (51)	32 (54)
Not reported	0	4 (8)	4 (7)
Age (years) [b]			
n	8	51	59
Mean (std dev)	12.4 (3.81)	13.9 (2.88)	13.7 (3.03)
Median	13.0	14.0	14.0
Minimum, maximum	6, 17	6, 17	6, 17
Age group, n (%) [b]			
5-11 years	3 (38)	8 (16)	11 (19)
12-17 years	5 (63)	43 (84)	48 (81)
Baseline body surface area, (m^2) [c]			
n	8	49	57
Mean (std dev)	1.38 (0.377)	1.48 (0.287)	1.47 (0.299)
Median	1.35	1.51	1.50
Minimum, maximum	0.8, 1.9	0.8, 2.0	0.8, 2.0

Source: Table 15.1.1.3.

std dev: standard deviation.

Baseline was defined as the value closest to but before the start of study drug administration.

Percentages are based on the number of patients calculated relative to the total number of patients in the relevant analysis set for each phase with non-missing values reported for the corresponding parameter.

[a] 'Other' reported races were mulatto (n=3) and brown (n=6).

[b] Age on the date of assent (not calculated based on local restriction of data collection).

[c] Calculated body surface area (m^2)=square root (height (cm)×weight (kg)/3600) based on Mosteller formula.

Baseline Disease Characteristics

Nodular sclerosis cHL was reported for 48 patients (81%). At the time of initial diagnosis, Ann Arbor Stage III disease was reported for 32 patients (54%) and Stage IV disease for 27 patients (46%) (Table 12).

At the time of study entry, evidence of bone marrow involvement was reported for 9 patients (15%). Extranodal involvement was reported for 35 patients (59%), and among these 35 patients, involvement of 1 extranodal site was reported for 12 patients (34%) and at least 2 extranodal sites for 23 patients (66%).

A median Lansky or Karnofsky performance score of 90 (range, 70-100) was reported for the patient population at baseline, and a Lansky/Karnofsky score of >90 was reported for 24 patients (41%).

At least 1 B symptom was reported at baseline for 23 patients (39%), including unexplained weight loss of at least 10% of body weight for 12 patients (20%); unexplained, persistent, or recurrent fever for 16 patients (27%); and recurrent drenching night sweats for 15 patients (25%). All 3 B symptoms were reported for 6 patients (10%).

Patients received the first dose of study treatment at a median of 2.71 weeks (range, 0.7-12.1 weeks) after the initial cHL diagnosis.

Table 12 C25004: Baseline Disease Characteristics (Safety Population)

	Phase 1 N=8	Phase 2 N=51	Phase 1+Phase 2 N=59
Primary diagnosis, n (%)			
Classical Hodgkin lymphoma	8 (100)	51 (100)	59 (100)
Nodular sclerosis classical	6 (75)	42 (82)	48 (81)
Lymphocyte-rich classical	1 (13)	2 (4)	3 (5)
Mixed-cellularity classical	1 (13)	5 (10)	6 (10)
Lymphocyte-depleted classical	0	0	0
Hodgkin lymphoma	0	2 (4)	2 (3)
Time since initial diagnosis (weeks) [a]			
n	8	51	59
Mean (standard deviation)	2.57 (1.360)	3.37 (2.423)	3.26 (2.315)
Median	2.43	2.71	2.71
Minimum, maximum	0.7, 4.9	0.9, 12.1	0.7, 12.1
Ann Arbor Stage, n (%)			
III	5 (63)	27 (53)	32 (54)
IV	3 (38)	24 (47)	27 (46)
Lansky/Karnofsky performance score, n (%)			
>90	4 (50)	20 (39)	24 (41)
50 to 90	4 (50)	26 (51)	30 (51)
<50	0	0	0
Median	95.0	90.0	90.0
Minimum, maximum	80, 100	70, 100	70, 100

	Phase 1 N=8	Phase 2 N=51	Phase 1+Phase 2 N=59
Evidence of bone marrow involvement, n (%)			
Yes	1 (13)	8 (16)	9 (15)
No	7 (88)	43 (84)	50 (85)
Evidence of extranodal involvement, n (%)			
Yes	4 (50)	31 (61)	35 (59)
No	4 (50)	20 (39)	24 (41)
Number of extranodal sites, n (%)			
1	0	12 (39)	12 (34)
≥2	4 (100)	19 (61)	23 (66)
Not applicable	4	20	24
Any baseline B symptom, n (%)			
Yes	2 (25)	21 (41)	23 (39)
No	6 (75)	28 (55)	34 (58)
Missing	0	2	2
All three baseline B symptoms, n (%)			
Yes	0	6 (12)	6 (10)
No	8 (100)	43 (84)	51 (86)
Missing	0	2	2
Unexplained weight loss >10% of body weight, n (%) [b]			
Yes	0	12 (24)	12 (20)
No	8 (100)	37 (73)	45 (76)
Missing	0	2	2
Unexplained, persistent, or recurrent fever >38°C, n (%) [b]			
Yes	2 (25)	14 (27)	16 (27)
No	6 (75)	35 (69)	41 (69)
Missing	0	2	2
Recurrent drenching night sweats, n (%) [b]			
Yes	1 (13)	14 (27)	15 (25)
No	7 (88)	35 (69)	42 (71)
Missing	0	2	2

Source: Table 15.1.1.4.

Baseline was defined as the value closest to but before the start of study drug administration.

Percentages are based on the number of patients calculated relative to the total number of patients in the relevant analysis set for each phase with non-missing values reported for the corresponding parameter. For Lansky and Karnofsky performance scores, the percentages are based on the number of patients in the relevant analysis set for each phase with results for the given score.

[a] Time since initial diagnosis (weeks)=(first dose date of study drug - date of initial diagnosis)/7.

[b] Unexplained weight loss; unexplained, persistent, or recurrent fever; and recurrent drenching night sweats are the 3 individual B symptoms.

Efficacy endpoints

Phase 1 primary objective; Determination of the recommended dose of brentuximab vedotin in combination with AVD in a paediatric population.

The DLT-evaluable population consisted of 6 patients treated at the starting dose of brentuximab vedotin 48 mg/m^2 in combination with AVD during phase 1. No patient met the protocol-defined DLT criteria The MTD of brentuximab vedotin was not reached and brentuximab vedotin 48 mg/m2 was determined to be the RP2D in this paediatric population.

Phase 1 Secondary Endpoints

Among the 8-patient phase 1 response-evaluable population, 7 patients (88%) achieved a CR by IRF assessment per IWG criteria. One patient (13%) achieved a PR by IRF assessment per the IWG criteria. Every patient (100%) achieved an objective response (either CR or PR) (Table 13). A total of 7 of 8 patients (88%) in the phase 1 response-evaluable population achieved a return to normal or a reduction of their disease's PET positivity as assessed by Deauville score ≤3 by the end of Cycle 2.

All patients in the phase 1, response-evaluable population received 6 cycles of protocol therapy and had their EOT visit occur after 6 cycles of therapy.

All 8 patients (100%) in the phase 1, response-evaluable population achieved a return to normal (7 patients, 88%) or a reduction in Deauville score (1 patient Deauville 5→4, 13%) by their EOT visit.

Table 13 Study C25004: Response Assessment, Deauville Score, and PET per IWG Criteria as Assessed per IRF Assessment (Phase 1 Subset, Response-Evaluable Population)

	Phase 1 N=8		
	n (%)	(80% CI)	(95% CI)
ORR at Cycle 2	8 (100)	(75, 100)	(63, 100)
ORR at EOT	8 (100)	(75, 100)	(63, 100)
Clinical response at Cycle 2			
Complete remission	6 (75)	(46, 93)	(35, 97)
Partial remission	2 (25)	(7, 54)	(3, 65)
Stable disease	0		
Progressive disease	0		
Clinical response at EOT			
Complete remission	7 (88)	(59, 99)	(47, 100)
Partial remission	1 (13)	(1, 41)	(<1, 53)
Stable disease	0		
Progressive disease	0		
Deauville score after Cycle 2			
1	0		
2	7 (88)		
3	0		
4	0		
5	1 (13)		
NE	0		
Deauville score at EOT			
1	2 (25)		
2	5 (63)		
3	0		
4	1 (13)		
5	0		
NE	0		
PET− after Cycle 2			
Deauville score of 1 or 2 [a]	7 (88)	(59, 99)	(47, 100)
Deauville score of 1 or 2 or 3 [b]	7 (88)	(59, 99)	(47, 100)

	Phase 1 N=8		
	n (%)	(80% CI)	(95% CI)
PET+ after Cycle 6			
Deauville score of 3 or 4 or 5 [a]	1 (13)	(1, 41)	(<1, 53)
Deauville score of 4 or 5 [b]	1 (13)	(1, 41)	(<1, 53)

Source: Table 15.2.1.1A.

EOT: end of treatment; IRF: independent review facility; IWG: International Working Group; NE: not estimable; ORR: overall response rate; PET: positron emission tomography; PET−: PET-negative; PET+: PET-positive. Clinical response summaries are based on EOT assessments. CIs are based on exact binomial distribution (Clopper-Pearson method).

ORR: complete remission and partial remission rates.

[a] Sensitivity analysis of PET− after Cycle 2 defined as an IRF Deauville score of 1 or 2, and PET+ after Cycle 6, defined as IRF Deauville scores of 3 or 4 or 5, respectively.

[b] PET− after Cycle 2 defined as an IRF Deauville score of (1 or 2 or 3). PET+ after Cycle 6 defined as an IRF Deauville score of (4 or 5).

Phase 1 Exploratory Endpoints

Median PFS follow-up was 30.03 months (range, 7 [censored]-32 [censored] months) for phase 1 safety population patients. The median PFS by IRF assessment for the phase 1 safety population was not reached (95% CI, 8.97 months–not estimable [NE]), with 2 of 8 patients in the population having experienced a PFS event by IRF assessment.

As all phase 1 (and indeed all study) patients completed 6 cycles of treatment, results for EFS are identical to those for PFS, which captured events of disease progression or death.

No phase 1 patient had died as of the 18 December 2020 data cut-off for this report. The median OS follow-up for the phase 1 safety population patients was 32.28 months (range, 29 [censored]-38 [censored] months), with all patients alive and remaining in OS follow-up.

Median DOR follow-up was 28.06 months (range, 5 [censored]-30 [censored] months) for phase 1 response-evaluable population patients. The median DOR by IRF assessment for the phase 1 response-evaluable population was not reached (95% CI, 7.26 months-NE), with 8 patients (100%) having experienced a response , and 2 patients (25%) having experienced a subsequent disease progression event.

Phase 2 Primary Endpoint

Of the 51-patient phase 2 response-evaluable population, 38 patients (75%) had achieved a CR at EOT by IRF assessment using IWG criteria (95% CI, 60%-86%) (Table 14). Furthermore, 46 patients (90%) were PET-negative by IRF assessment (Deauville score ≤3) at the end of Cycle 2. Because 21 patients (41%) had a Deauville score of 3 at the end of Cycle 2, results differed between the primary analysis and sensitivity analysis, with 25 patients (49%) considered PET negative by IRF assessment when patients with Deauville scores of 3 were excluded.

Six patients (12%) had a clinical response of PR at EOT by IRF assessment using IWG criteria (95% CI, 4%-24%). In total 44 patients (86%) achieved an objective response (CR or PR) at EOT by IRF assessment using IWG criteria (95% CI, 74%-94%).

Table 14 Study C25004: Response Assessment, Deauville Score, and PET per IWG Criteria per IRF Assessment (Phase 2 Subset, Response-Evaluable Population)

	Phase 2 N=51		
	n (%)	(80% CI)	(95% CI)
PET− after Cycle 2			
Deauville score of 1 or 2 [a]	25 (49)	(39, 59)	(35, 63)
Deauville score of 1 or 2 or 3 [b]	46 (90)	(83, 95)	(79, 97)
PET+ after Cycle 6			
Deauville score of 3 or 4 or 5 [a]	22 (43)	(34, 53)	(29, 58)
Deauville score of 4 or 5 [b]	10 (20)	(13, 29)	(10, 33)

Source: Table 15.2.1.1A.

EOT: end of treatment; IRF: independent review facility; IWG: International Working Group; NE: not estimable; ORR: overall response rate; PET: positron emission tomography; PET+: PET-positive; PET−: PET-negative.

Clinical response summaries are based on EOT assessments. CIs are based on exact binomial distribution (Clopper-Pearson method).

ORR: complete remission and partial remission rates.

[a] Sensitivity analysis of PET− after Cycle 2 defined as an IRF Deauville score of 1 or 2, and PET+ after Cycle 6 defined as IRF Deauville scores of 3 or 4 or 5, respectively.

[b] PET− after Cycle 2 defined as an IRF Deauville score of (1 or 2 or 3). PET+ after Cycle 6 defined as an IRF Deauville score of (4 or 5).

	Phase 2 N=51		
	n (%)	(80% CI)	(95% CI)
ORR at Cycle 2	47 (92)	(85, 97)	(81, 98)
ORR at EOT	44 (86)	(78, 92)	(74, 94)
Clinical response at Cycle 2			
Complete remission	39 (76)	(67, 84)	(63, 87)
Partial remission	8 (16)	(9, 24)	(7, 29)
Stable disease	4 (8)	(3, 15)	(2, 19)
Progressive disease	0		
Not evaluable	0		
Clinical response at EOT			
Complete remission	38 (75)	(65, 82)	(60, 86)
Partial remission	6 (12)	(6, 20)	(4, 24)
Stable disease	0		
Progressive disease	7 (14)	(8, 22)	(6, 26)
Not evaluable	0		
Deauville score after Cycle 2			
1	2 (4)		
2	23 (45)		
3	21 (41)		
4	2 (4)		
5	3 (6)		
NE	0		
Deauville score at EOT			
1	4 (8)		
2	25 (49)		
3	12 (24)		
4	7 (14)		
5	3 (6)		
NE	0		

All patients in the 51-patient phase 2 safety population (100%) completed 6 cycles of protocol therapy. However, 2 patients (4%) in the phase 2 safety population had brentuximab vedotin dose decrements, 1 of which was due to PN. Thus, 49 of the 51 patients (96%) in the phase 2 safety population completed 6 cycles of protocol therapy at the recommended dose.

Phase 2 Secondary Endpoints

The 18 December 2020 data cut-off date for this primary analysis was chosen to correspond to a minimum of 15 months PFS follow-up for the majority of patients. At a median PFS follow-up of 17.25 months, 11 patients (22%) had experienced an event of disease progression; no patient experienced a PFS event of death.

The median duration of PFS was not estimable at this time, with PFS durations ranging from 6 months to a censored duration of 28 months (Table 15). As of this analysis, the PFS duration for 9 patients (18%) was censored due to receipt of radiotherapy or non-protocol antitumor treatment as frontline therapy, as might be expected in this patient population with higher-risk Stage III or IV HL; all other patients were either still being followed for PFS or had a PFS event.

Table 15 Study C25004: PFS per IWG Criteria as Assessed per IRF (Phase 2 Subset, Safety Population)

	Phase 2 N=51
PFS (months)	
Number with events, n (%)	11 (22)
Number censored, n (%)	40 (78)
25th percentile (95% CI)	12.7 (6.70, NE)
Median (95% CI)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)
Minimum, maximum	6, 28*
Median follow-up (months)	17.25
Estimated progression-free rate (%) at	
6 months (95% CI)	96.1 (85.22, 99.00) [n=48]
12 months (95% CI)	77.2 (61.42, 87.11) [n=27]
15 months (95% CI)	74.2 (57.87, 84.97) [n=22]
18 months (95% CI)	74.2 (57.87, 84.97) [n=9]
24 months (95% CI)	74.2 (57.87, 84.97) [n=1]

	Phase 2 N=51
Reasons for event, n (%)	
PD	11 (22)
Death	0
Reasons for censoring, n (%)	
Lack of evaluation of tumor response	0
Received antitumor treatment other than SCT or radiotherapy as part of frontline treatment	9 (18)
Loss to follow-up	0
Withdrawal	0
No documented PFS event	31 (61)

Source: Table 15.2.2.1A.

IRF: independent review facility; IWG: International Working Group; NE: not estimable; PD: progressive disease; PFS: progression-free survival; SCT: stem cell transplantation.

Median follow-up (months) is calculated based on the reverse Kaplan-Meier method, switching patients' event and censored status.

Probability of being event-free [n=number of patients at risk].

PFS per IRF is defined as the time from the first dose until disease progression per IRF or death due to any cause, whichever occurs first. For patients who do not have an objective PD, did not die, and are either still on study follow-up at the time of the analysis, or were removed from the study before documentation of PD, PFS is censored on the date of last adequate disease assessment. In addition, for patients who were given antitumor treatment, other than SCT or radiotherapy as part of the frontline treatment, censoring was at the last adequate disease assessment before initiation of such alternative treatment. It should be noted that if a patient experienced disease progression per IRF or died after the initiation of the antitumor treatment, other than SCT or radiotherapy, such patients are censored, and have not been considered to have a PFS event. Patients lacking an evaluation of tumor response after their first dose have their PFS censored at the day of first dose.

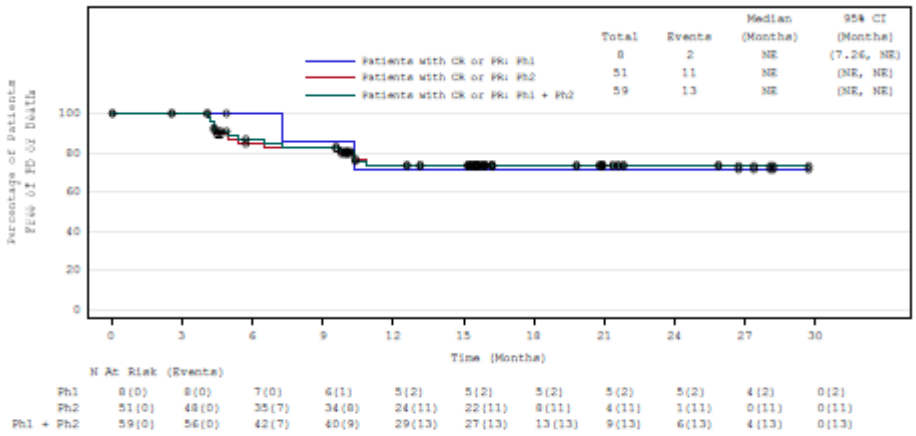
* Denotes a censored observation.

Because all phase 2 patients completed 6 cycles of treatment, results for EFS are identical to those for PFS.

No phase 2 patient had died as of the 18 December 2020 data cut-off for this report. As of that time the median duration of OS follow-up for the phase 2 safety population patients was 17.71 months (range, 13 [censored] to 28 [censored] months).

With a median follow-up of 15 months for phase 2 response-evaluable population patients for DOR, the median DOR per IRF for the phase 2 response-evaluable population was not estimable (95% CI, NE) (Figure 10), with 51 patients (100%) having experienced a response per IRF and 11 patients (22%) having experienced a subsequent disease progression event.

Figure 10 Study C25004: Kaplan-Meier Plot of Duration of Response per IWG Criteria as Assessed per IRF (Response-Evaluable Population, Subset of Patients With Response)



Source: Figure 15.2.3.1A.
CR: complete remission; IRF: independent review facility; IWG: International Working Group; NE: not estimable; PD: progressive disease; Ph: phase; PR: partial remission.
Symbols on the plot indicate censored patients.

Receipt of Irradiation After Cycle 6

A total of 13 patients (22%) (95% CI, 12%-35%) in the safety population were reported to have received irradiation after Cycle 6. According to the applicant the rate of irradiation in this paediatric study exceeded that observed in adults in study C25003 but is lower than that reported for 3 recently reported paediatric studies.

Resolution of B Symptoms

Resolution was reported for all 23 patients (100%) during treatment for whom at least 1 B symptom was reported at baseline. Resolution was reported at a median of 5.14 weeks (range, 0.3-10.1 weeks).

PRO Results

HRQOL as measured by the PedsQL 4.0 Generic Core Scales and the PedsQL 3.0 Cancer Module was an exploratory endpoint in both phase 1 and phase 2. The child and parent completed the questionnaires independently.

Compliance rates for PRO assessments over the course of the study for phase 1 and phase 2 combined were high overall for both the child and the parent. This also was true during phase 1 and phase 2. During PFSFU, compliance rates for the PedsQL 4.0 Generic Core Scales and the PedsQL 3.0 Cancer Module ranged from 81% to 100% for both child and parent. There were too few patients at OSFU to make a meaningful assessment of compliance.

PedsQL 4.0 Generic Core Scale scores generally showed a slight decrease (unfavourable change) from baseline to Cycle 5, but returned to baseline levels or higher at EOT, and continued to increase during PFSFU, indicating improvement.

Mean PedsQL 3.0 Cancer Module scores generally decreased slightly during the treatment period but returned to baseline levels or higher at EOT and PFSFU.

When PRO was analysed by clinical response (CR or PR), there was a trend of higher mean scores (indicating improvement) during the study period through EOT among patients who achieved CR or PR than among those who did not.

When PRO was analysed by selected AEs of special interest (febrile neutropenia and neutropenia) and non–AEs of special interest, in general, there was a pattern of a decrease in mean scores from baseline to EOT in patients who experienced febrile neutropenia, reflecting an unfavorable effect. Mean scores generally returned to baseline levels during the PTFU visits. Mean scores for patients with neutropenia or non–AEs of special interest generally appeared to remain more constant from baseline to EOT.

Immunogenicity

See section 1.2; Results of the pharmacology aspects.

7.3. Meta-analysis

The goal of this meta-analysis is to support the efficacy of brentuximab vedotin in paediatric patients with HL as part of the modified Paediatric Investigation Plan.

The objective of the targeted literature review (TLR) was to identify studies meeting the eligibility criteria for inclusion in a meta-analysis to assess the efficacy and safety of brentuximab vedotin in paediatric patients with HL.

Methods – analysis of data submitted

The identification of studies for inclusion in the meta-analysis (MA) was conducted in three phases with the outputs from each phase used to inform subsequent phases of the project. In an initial review of potentially relevant trials agreed between Takeda and the European Medicines Agency (EMA)/Paediatric Committee (PDCO), a review and extraction of studies reporting eligible data for efficacy and safety of BV in paediatric patients with HL was conducted. An additional electronic search was conducted to identify any publications associated with the list of trials. The final step was a TLR to identify any additional interventional or observational studies meeting the eligibility criteria for inclusion in the meta-analysis.

Electronic database searches were conducted on 28th September 2020 via the OVID platform, using a predefined search strategy:

The following electronic databases were searched via the Ovid platform:

- MEDLINE®, incorporating:
- MEDLINE®, 1946 to present day
- MEDLINE® In Process & Other Non-Indexed Citations
- MEDLINE® Epub Ahead of Print and MEDLINE® Daily
- Embase 1996 to 2020

The search is designed to identify any interventional (phase II-IV) trials with a paediatric (aged 5-21 years) HL population including BV as an intervention in at least one treatment arm.

Hand searching was used as a supplementary measure to identify further relevant studies. Hand searching of selected conference proceedings between 2017–2020 was carried out to identify relevant abstracts and posters, which may not have yet been published as a full journal article. The following conferences were searched via their respective online platforms or published abstract handbooks:

- European Society for Medical Oncology (ESMO)
- American Society of Clinical Oncology (ASCO)
- American Society of Haematology (ASH)c
- European Haematology Association (EHA)
- International Society of Paediatric Oncology (SIOP)

An electronic search was conducted via the OVID platform to identify publications of studies associated with the NCT numbers or trial names from the list agreed with PDCO. This electronic search was conducted on July 6th, 2020.

All studies included in the meta-analysis include paediatric patients treated with brentuximab vedotin, should have relevant efficacy and safety outcome data and should be a RCTs, nRCTs or observational study (Table 16).

Table 16 Eligibility criteria

Criteria	Include
Population	Paediatric patients with HL‡.
Intervention/comparators	All included studies should report data for BV
Outcomes	Relevant efficacy and safety outcome data
Setting/study design	RCTs, nRCTs, or observational cohort studies
Language of publication	No restriction
Conference date	No restriction§
Countries	No restriction

Abbreviations: BV, brentuximab vedotin, HL, Hodgkin Lymphoma; nRCT, non-randomised controlled trial; RCT, randomised controlled trial

‡ The primary population of interest for this review was paediatric however some studies recruiting both paediatrics and young adults were included and steps were taken to identify the data limited to the paediatric population, if possible

§ Conference abstracts were not excluded based on publication date, however additional hand searching of conferences were restricted to 2017 – 2020.

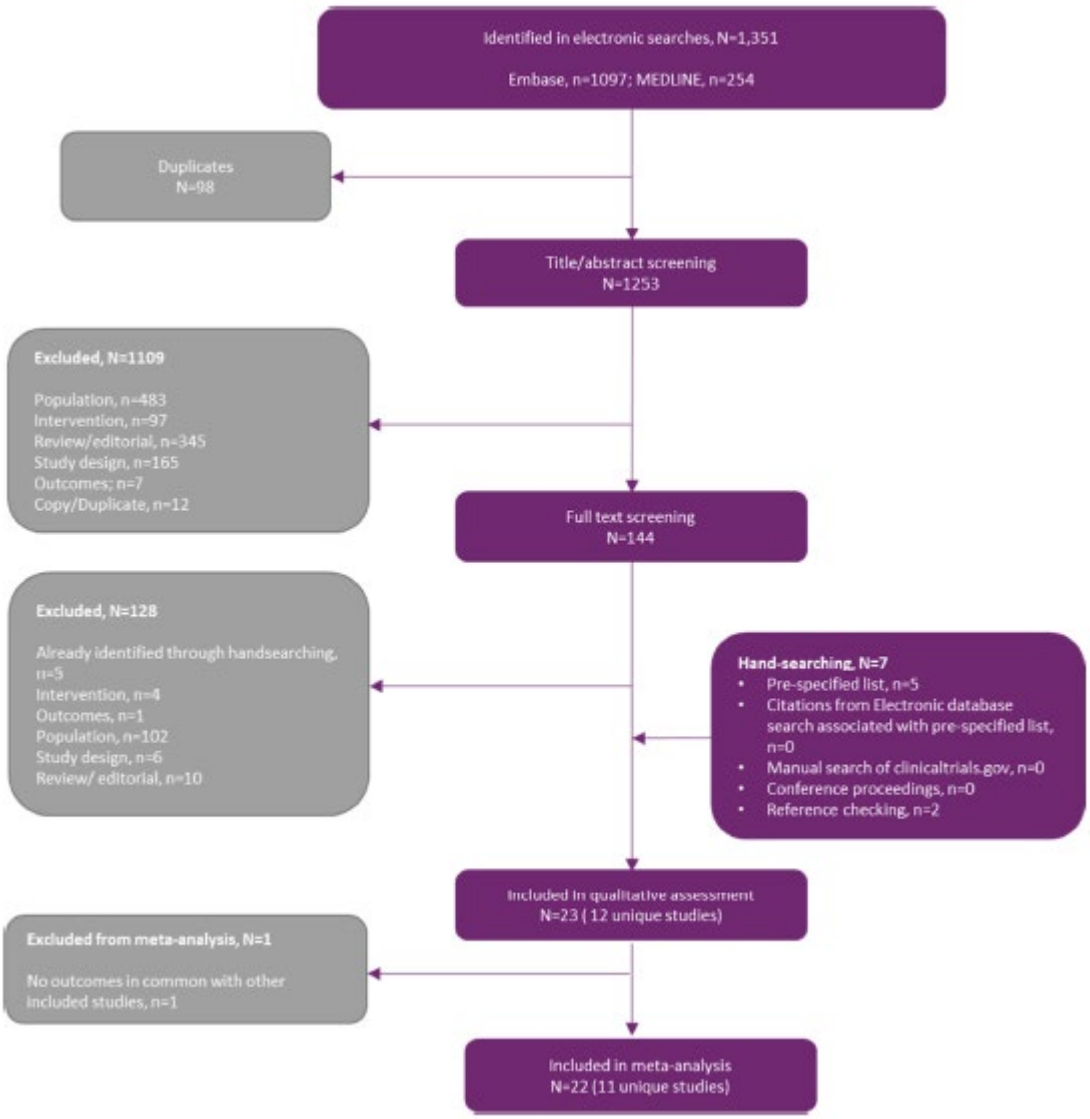
Data from eligible studies were extracted and used to assess the suitability of each study for inclusion in the meta-analysis.

- Data extraction was conducted by a single analyst, and quality checked by a senior analyst or project lead

Efficacy Results

Included studies

Figure 11 Flow diagram



Out of 23 identified publications (12 unique studies) from the electronic database search, four publications were retrospective cohort studies (22-25) and seven studies (18 publications) were phase 1 or 2 open-label non-randomised trials (either single-arm or dual-arm) (Table 17).

One further publication was a retrospective series reporting on consecutive patients (no other study design details were reported).

Two non-randomised controlled trials (nRCTs) (Hochberg, 2017a, 2017b, 2017c) and Franklin 2018, 2019) included newly diagnosed/ untreated patients, while a single study included a mixed patient population undergoing their first diagnosis or relapse and all remaining studies included patients with relapsed or refractory (R/R) disease.

The median age of recruited patients ranged from 14 years to 17 years and in nine studies a median age was not reported. Five studies enrolled young adults as well as paediatric patients but did not report findings separately for patients <18 years and those ≥18 years old (Cole, 2018; Harker-Murray 2019; Hochberg, 2017a, Korsantya, 2020 and McMillan, 2020), and these studies have been excluded in a sensitivity analysis, where possible.

In three studies reporting a monotherapy regimen, the dose of BV was 1.8 mg/kg administered once in a 21-day cycle. It was also noted that in a fourth study, monotherapy at a 1.8 mg/kg dose was

administered following combination treatment and stem cell transplant (SCT). The dose of BV for combination treatment regimens were also similar across studies.

- The most common BV dose and schedule was 1.8 mg/kg every three weeks (5/10 combination therapy studies);
- Two studies reported a 1.2 mg/kg dose of BV every two weeks 4;
- One study reported a cumulative dose of 7.8 mg/kg, but not the number of cycles for each patient;
- Two studies did not report BV dose.

The majority of studies reported between 30% and 70% of patients were male. There were three studies lying outside of this range with a particularly high proportion of males reported by Gulati, 2017 and Tacyilidiz, 2019 at 80% and 88%, respectively and a low proportion reported by Faulk 2018 at 14%. All three studies were observational in design, with very small sample sizes (between five and eight patients).

Table 17 Study and patient characteristics for evaluated publications, n=23 (n=12 unique studies)

Study name, Author year	Population (HL sample size)	Study design	Median age in years (range)	Male	Disease stage	SCT
Interventional studies (n=7)						
NCT01492088 Locatelli, 2018 (7), 2017 (38), 2013 (39)	HL, ALCL (n=19)	Single-arm, open label, dose escalation, phase 1/2	14 (7-18)	69%	I-IV	13/19 (68%) pts received SCT prior to study treatment
NCT01780662/ AHOD1221 Cole, 2018 (4), 2017 (3), 2015 (31)	HL (n=45)	Cole, 2015: Phase I Cole, 2017 & 2018: Open label, dose escalation, phase ½	17.6 (5.4-28.7)^	47%	IA-IVB	Prior SCT patients excluded; pts were removed from protocol tx if they elected to undergo SCT
NCT02398240 Hochberg, 2017a, 2017b & 2017c (18, 19, 28)	HL (n=23)	Open label, non-randomised, phase 2	15 (4-23)^	35%	I-IV	Tx naïve

Study name, Author year	Population (HL sample size)	Study design	Median age in years (range)	Male	Disease stage	SCT
Cohort from NCT02927769 Harker-Murray, 2019 (32), 2018 (34); Kelly 2019 (35), Mauz-Korholz, 2020 (33)	HL (n=44)	Open-label, phase 2, multicohort	16 (9-30)^	66%	IIIB or IV	NR
NCT02979522 Franklin, 2019 (30) & 2018 (37)	HL (n=6)	Single-arm, phase 1/2	NR (6-17)	50%	III or IV	Tx naïve
Koga, 2020a & 2020b (26, 29)	HL, ALCL (n=4)	Single-arm, open label, phase I	11.5 (5.0, 14.0)	33.3%	II-IV	No pts received SCT prior to study tx
Korsantya, 2020 (27)	HL (n=54)	Single-arm, open label	NR (4-25)+^ Mean 13.8 (SD 4.4)	44.4%	NR	NR
Observational studies (n=5)						
Faulk, 2018 (22)	HL (n=7)	Retrospective cohort	16.1 (13.4 - 17.2)	14%	IIA-IVB	NR
Gulati, 2017 (23)	HL (n=5)	Retrospective cohort	16.5 (12.2-17.9)	80%	NR	Pts went on to SCT after achieving CR or best response on comb tx. Pts resumed post-transplant tx with BV as monotherapy
McMillan, 2020 (36)	HL (n=19)	Retrospective series of consecutive patients	NR (9-27)^	NR	NR	4/19 (21%) pts received SCT prior to study tx
Tacyilidiz, 2019 (24)	HL	Retrospective cohort	14 (6–18)	88%	IIIB or IVB	1/8 (12.5%) pts

Study name, Author year	Population (HL sample size)	Study design	Median age in years (range)	Male	Disease stage	SCT
	(n=8)					received SCT prior to study tx
Titapiwatanakun, 2019 (25)	HL (n=9)	Retrospective cohort	16 (12-18)+*	30%	IIB-IVB	Unclear how many pts received SCT prior to or during BV tx

Abbreviations: ALCL, Anaplastic large cell lymphoma; BV, brentuximab vedotin; comb, combination; CR, complete response; HL, Hodgkin lymphoma; NR, not reported; pts, patients; SCT, stem cell transplant; SD, standard deviation; tx, treatment

†Age at diagnosis; *Calculated from individual ages reported; ^ As noted in Table 4, the Cole, 2018 (4), Hochberg, 2017a, 2017b & 2017c (18, 19, 28), Harker-Murray, 2019 (32), Korsantya, 2020 (27) and McMillan, 2020 (36) studies all enrolled young adult patients, as well as paediatric (≤18 years old)

Feasibility for meta-analysis

As described in this report, 12 studies from 23 publications were considered suitable to be considered for inclusion in MA. Of the 12 studies identified, 11 were included in the analysis, with some caveats:

- Six studies (from 12 publications) were only available as conference abstracts and therefore, an extensive comparison of baseline characteristics and study quality assessment could not be conducted
- There were insufficient studies to use meta-regression to explore whether the difference between the studies with respect to the balance of R/R patients will have a significant impact on outcomes. Other potential differences between the studies were explored in sensitivity analyses.

There may still be inherent bias in the findings because of the single arm study design of all the included studies and that this can limit the inferences made from the MA results. However, the analysis was a comprehensive pooling of the available data.

Analysis of outcomes in the combined treatment naïve and relapsed / refractory populations Overall survival (N=3 studies)

Overall survival was reported in three of the 11 studies for the combined treatment naïve and R/R populations. One study treated patients with monotherapy BV, one study treating patients with BV plus gemcitabine and the third study treated high risk patients with BV with doxorubicin, vincristine, prednisone and darcarbazine (BV-AVPD), and low risk patients with doxorubicin, vinblastine, darcarbazine and rituximab (BV-AVD-R). Patient characteristics were similar between studies, and though there were more males recruited in the Locatelli 2018 study (69%) and fewest recruited to Hochberg 2017a (35%), the differences may be due to small sample sizes within each study. Overall survival at 3, 12 and 24 months was pooled from these studies.

Overall response rate (N=6 studies)

Overall response rate was reported in six of the 11 studies and was defined as the sum of complete response (CR) and partial response (PR) in two of the studies; with 100% of patients experiencing a CR in 1 study and no specific definition given in the remaining studies. As with OS, the BV treatment regimens varied between these studies and this may undermine the validity of any pooled findings, patients were treated with,

- BV monotherapy in Locatelli 2018 and Koga 2020b
- BV + gemcitabine in Cole 2018
- High risk patients were treated with BV-AVPD / low risk patients with BV-AVD-R in Hochberg
- 2017a
- BV + bendamustine in McMillan 2020

- BV + nivolumab, followed by BV + bendamustine in the NCT02927769 study

Complete response (N=9 studies)

Complete response was reported in nine out of the 11 studies. One of the studies reported complete metabolic remission, and the Tacyilidiz 2019 abstract only defined the outcome as "remission". These were both assumed to be equivalent to CR reported in the other seven studies in order to include as much data as possible.

Partial response (N=3 studies)

Partial response was reported in three studies. One study treated patients with BV monotherapy (7), one study treating patients with BV plus gemcitabine, while patients in McMillan, 2020 were treated with BV plus bendamustine.

Adverse events

A wide variety of different adverse events are reported across the studies and thus limited analyses for a small number of these were conducted, where feasible.

Efficacy results

Table 18 Overview of available data for efficacy outcomes

	Survival			Response		
Study name, Author year	**EFS**	**OS**	**PFS**	**ORR**	**CR**	**PR**
NCT01492088 Locatelli, 2018 (7) 2017 (38), 2013 (39)	Median time to event (IRC)	Median NE; % of pts alive at 3, 12 and 24 mths	Median time to event (IRC)	√ (IRC)	√ (IRC)	√ (IRC)
NCT01780662/ AHOD1221 Cole, 2018 (4), 2017 (3), 2015 (31)	N/A	Median NE; % of pts alive at 12 mths; additional data available from K-M graph	N/A	√ (IRC)	√ (IRC)	√ (IRC)
NCT02398240 Hochberg, 2017a (19), 2017b (18) & 2017c (28)	Median follow up time of 915 days (30 mths) 100% surviving without event			√	√	N/A
Cohort from NCT02927769 Harker-Murray, 2019 (32), 2018 (34); Kelly 2019 (35), Mauz-Korholz, 2020 (33)	N/A	N/A	N/A	√ (IRC / INV)	√ (IRC / INV)	N/A
NCT02979522 Franklin, 2019 (30), 2018 (37)	N/A	N/A	N/A	N/A	N/A	N/A
Gulati, 2017 (23)	All patients are alive with no evidence of disease a median of 11.3 months since beginning salvage therapy (range 1.2-15 mths)			N/A	CR prior to SCT	N/A
Koga, 2020a (29), 2020b (26)	K-M curves available, but median time	N/A	K-M curves available, but median time	√ (IRC)	√ (IRC)	N/A
	to event NE		to event NE			
Korsantya, 2020 (27)	N/A	N/A	N/A	N/A	• Overall • BB regimen • BV	N/A
McMillan, 2020 (36)	N/A	N/A	N/A	√	√	√
Tacyilidiz, 2019 (24)	N/A	Median NE; 1 pt died after 6th BV cycle due to relapse/ refractory disease	N/A	N/A	√	N/A
Titapiwatanakun, 2019 (25)	N/A	N/A	N/A	N/A	N/A	N/A

Abbreviations: BB, sequential BV, bendamustine + DM; BV, bendamustine vedotin; CR, complete response; EFS, event-free survival; INV, investigator assessed; IRC, independent review committee assessment; K-M, Kaplan-Meier; mths, months; N/A, not applicable; NE, not evaluable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; pts, patients; SCT, stem cell transplant

Overall survival

Table 19 Overall survival rate data used in the meta-analysis

Study	Indication	Study design	Setting	BV Treatment	Timepoint	Total (N)	Alive (n)	%
Cole 2018 (NCT01780662)	HL	OL, Ph I/II	R/R	Combination	3 months	45	45	100
Hochberg 2017a (NCT02398240)	HL	OL, Ph II	Tx naïve	Combination	3 months	21	21	100
Locatelli 2018 (NCT01492088)	HL	OL, Ph I/II	R/R	Mono	3 months	16	15	93.8
Cole 2018 (NCT01780662)	HL	OL, Ph I/II	R/R	Combination	12 months	45	43	95
Hochberg 2017a (NCT02398240)	HL	OL, Ph II	Tx naïve	Combination	12 months	21	21	100
Locatelli 2018 (NCT01492088)	HL	OL, Ph I/II	R/R	Mono	12 months	16	11	68.2
Cole 2018 (NCT01780662)	HL	OL, Ph I/II	R/R	Combination	24 months	45	41	90
Hochberg 2017a (NCT02398240)	HL	OL, Ph II	Tx naïve	Combination	24 months	21	21	100
Locatelli 2018 (NCT01492088)	HL	OL, Ph I/II	R/R	Mono	24 months	16	10	61.4

Abbreviations: BV, brentuximab vedotin; HL, Hodgkin lymphoma; OL, open label; R/R, relapsed/refractory; tx, treatment.

Table 20 Comparison of basecase and sensitivity analysis log transform model results for OS

OS analysis	Basecase*	Include prospective (nRCT) studies only	Include studies enrolling R/R patients only^	Include BV combination tx studies only^	Include studies reporting BV dose of 1.8 mg/kg/q3w only	Include studies enrolling paediatric patients only
Number of studies included in analysis	3	3	2	2	2	1
3 months						
Odds of being alive (95% CI)	31.2 (7.6, 128.3)	Identical to basecase	28.0 (5.4, 143.8)	62.7 (8.7, 452.6)	Identical to exclude tx-naive analysis	NA
Proportion of patients alive (95% CI)	96.9% (88.3%, 99.2%)		96.5% (84.5%, 99.3%)	98.4% (89.7%, 99.8%)		
12 months						
Odds of being alive (95% CI)	10.1 (1.5, 67.7)	Identical to basecase	5.0 (2.1, 11.6)	24.8 (7.0, 87.7)	Identical to exclude tx-naive analysis	NA
Proportion of patients alive (95% CI)	91.0% (60.0%, 98.5%)		83.2% (68.0%, 92.1%)	96.1% (87.5%, 98.9%)		
24 months						
Odds of being alive (95% CI)	6.6 (1.3, 34.6)	Identical to basecase	4.1 (2.0, 8.4)	12.1 (4.6, 31.8)	Identical to exclude tx-naive analysis	NA
Proportion of patients alive (95% CI)	86.8% (55.8%, 97.2%)		80.3% (66.5%, 89.3%)	92.4% (82.2%, 97.0%)		

Abbreviations: BV, brentuximab vedotin; CI, confidence interval; FE, fixed effect; NA, not applicable; OS, overall survival; q3w, every 3 weeks; RE, random effects; tx, treatment
*Based on RE model (D+L in the figures); ^Based on FE model (I-V in the figures).

Overall response rate

Six studies reported data for overall response rate

Table 21 Overall response rate reported in the included studies

Study	Indication	Study design	Setting	BV Treatment	Assessment	Total (N)	ORR (n)	%
Cole 2018 (NCT01780662)	HL	OL, Ph I/II	R/R	Combination	IRC	42	31	74
Harker-Murray 2019 (NCT02927769)	HL	OL, Ph II	R/R	Combination	IRC - any time before consolidation*	43	42	98
Hochberg 2017a (NCT02398240)	HL	OL, Ph II	Tx naïve	Combination	NR	21	21	100
Koga 2020b	HL	OL, Ph I	R/R	Mono	IRC	4	2	50
Locatelli 2018 (NCT01492088)	HL	OL, Ph I/II	R/R	Mono	IRC	15	7	47
McMillan, 2020	HL	Observational	R/R	Combination	NR	19	15	79

Abbreviations: BV, brentuximab vedotin; HL, Hodgkin lymphoma; IRC, independent review committee assessment; NR, not reported; OL, open label; R/R, relapsed/refractory; tx, treatment.
* Investigator assessed ORR data also reported in the study

Table 22 Comparison of basecase and sensitivity analysis RE log transform model results for ORR

ORR analysis	Basecase	Include prospective studies (nRCTs) only	Include studies enrolling R/R patients only	Include BV combination tx studies only	Include studies reporting BV dose of 1.8 mg/kg/q3w only	Include studies enrolling paediatric patients only*
Number of studies included in analysis	6	5	5	4	4	2
Odds of achieving ORR (95% CI)	3.7 (1.3, 10.1)	3.9 (1.1, 14.5)	2.9 (1.1, 7.6)	7.4 (2.2, 24.9)	2.0 (0.98, 4.0)	0.90 (0.4, 2.2)
Proportion of patients achieving ORR (95% CI)	78.6% (57.3%, 91.0%)	79.8% (51.8%, 93.5%)	74.1% (51.8%, 88.4%)	88.1% (68.9%, 96.1%)	66.4% (49.5%, 80.0%)	47.4% (26.8%, 68.9%)

Abbreviations: BV, brentuximab vedotin; CI, confidence interval; ORR, overall response rate; q3w, every 3 weeks; RE, random effects
*FE model (only 2 included studies).

Complete response

Nine studies reported data for this outcome.

Table 23 Complete response rate reported in the included studies

Study	Indication	Study design	Setting	BV Treatment	Assessment	Total (N)	CR (n)	%
Cole 2018 (NCT01780662)	HL	Prospective	R/R	Combination	IRC	42	24	57
Gulati, 2017	HL	Observational	R/R	Combination	NR	5	5	
Harker-Murray 2019 (NCT02927769)	HL	Prospective	R/R	Combination	IRC - any time before consolidation*	43	38	88
Hochberg 2017a (NCT02398240)	HL	Prospective	Tx naïve	Combination	NR	21	21	100
Koga 2020b	HL	Prospective	R/R	Monotherapy	IRC	4	2	50
Korsantya, 2020	HL	Prospective	R/R	Combination /monotherapy	NR	54	44	81.4
Locatelli 2018 (NCT01492088)	HL	Prospective	R/R	Monotherapy	IRC	15	5	33
McMillan, 2020	HL	Observational	R/R	Combination	NR	19	14	74
Tacyildiz, 2019	HL	Observational	R/R	Combination	NR	8	6	75
Alternative data used for sensitivity analysis excluding BV monotherapy studies								
Korsantya, 2020	HL	Prospective	R/R	Combination	NR	42	37	88

Abbreviations: BV, brentuximab vedotin; HL, Hodgkin Lymphoma; IRC, independent review committee assessment; NR, not reported; R/R, relapsed/refractory; tx, treatment

*Investigator assessed CR data also reported in the study.

Table 24 Comparison of base case and sensitivity analysis RE log transform model results for CR

CR analysis	Basecase	Include prospective (nRCT) studies only	Include studies enrolling R/R patients only	Include BV combination tx studies only	Include studies reporting BV dose of 1.8 mg/kg/q3w only	Include studies enrolling paediatric patients only
Number of studies included in analysis	9	6	8	7	7	5
Odds of achieving CR (95% CI)	2.8 (1.4, 5.6)	2.5 (0.98, 6.6)	2.4 (1.2, 4.8)	4.4 (2.0, 9.7)	1.9 (0.98, 3.9)	2.0 (0.7, 6.3)
Proportion of patients achieving CR (95% CI)	73.4% (57.6%, 84.9%)	71.8% (49.4%, 86.9%)	70.6% (54.6%, 82.7%)	81.5% (66.7%, 90.7%)	66.1% (49.6%, 79.4%)	67.2% (39.8%, 86.4%)

Abbreviations: BV, brentuximab vedotin; CI, confidence interval; CR, complete response; q3w, every 3 weeks; RE, random effects.

Partial response results

Only three studies reported data for this outcome (Table 25)

The odds and proportion of patients achieving PR have been calculated.

Table 25 Partial response rate reported in the included studies

Study	Indication	Study design	Setting	BV Treatment	Assessment	Total (N)	PR (n)	%
Cole 2018 (NCT01780662)	HL	Prospective	R/R	Combination	IRC	42	7	16.7
Locatelli 2018 (NCT01492088)	HL	Prospective	R/R	Mono	IRC	15	2	13
McMillan, 2020	HL	Observational	R/R	Combination	NR	19	1	5.3

Abbreviations: BV, brentuximab vedotin; HL, Hodgkin Lymphoma; IRC, independent review committee assessment; NR, not reported; R/R, relapsed/refractory.

PR analysis	Basecase*	Include prospective studies (nRCTs) only	Include studies enrolling R/R patients only	Include BV combination tx studies only^	Include studies reporting BV dose of 1.8 mg/kg/q3w only	Include studies enrolling paediatric patients only
Number of studies included in analysis	3	2	3	2	3	1
Odds of achieving PR (95% CI)	0.16 (0.08, 0.32)	0.19 (0.09, 0.38)	Identical to basecase	0.17 (0.08, 0.36)	Identical to basecase	NA
Proportion of patients achieving PR (95% CI)	14.1% (7.7%, 24.4%)	15.8% (8.4%, 27.7%)		14.3% (7.3%, 26.2%)		

Abbreviations: CI, confidence interval; FE, fixed effect; PR, partial response; q3w, every 3 weeks; RE, random effects
*Based on RE model (D+L in the figures); ^Based on FE model (I-V in the figures)

7.4. Discussion Efficacy

As part of this type II variation, intended to update the paediatric data presented in the ADCETRIS Summary of Product Characteristics (SmPC), results of Study C25004 in paediatric patients with previously untreated Stage III or IV classical Hodgkin lymphoma (cHL) are submitted by the MAH. In addition a meta-analyses of published clinical studies for brentuximab vedotin in paediatric patients with Hodgkin lymphoma was submitted.

Paediatric study C25004

Study design

Study C25004 was a phase 1/2, open-label, multiagent, multi-centre study of brentuximab vedotin given in combination with Adriamycin (doxorubicin), vinblastine, and dacarbazine (A+AVD) in paediatric patients with advanced-stage, newly diagnosed classical CD30+ first-line HL. The in this study used bretuximab dose was, 48 or 36 mg/m^2, to be administered by IV infusion on days 1 and 15 of each 28 day cycle.

The use of AVD as back-bone chemotherapy was agreed during a modification of the PIP by the PDCO in August 2014. This modification of the PIP was based on positive results obtained in adults with this back-bone therapy. Extrapolation of adult data to children in support of results of the paediatric clinical study in front line HL was considered easier when the same back-bone chemotherapy for adults and the paediatric population would be used.

ABVD is used in paediatric, adolescent and adult front-line HL setting with similar efficacy and safety of other treatment options like BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone), OEPA (vincristine, etoposide, prednisone, doxorubicine) or OPPA (vincristine, procarbazine, prednisone, prednisone, doxorubicin). Replacing bleomycin with brentuximab vedotin in ABVD therapy could provide clinical benefit to paediatric patients with advanced-stage, newly diagnosed cHL when it proofs to decrease the risks of pulmonary toxicity (due to bleomycin treatment) and late undesirable effects associated with radiotherapy because it is expected that less patients need RT after treatment with brentuximab vedotin than after other available treatment regimens.

The planned dose of brentuximab vedotin in this study was 48 mg/m^2 administered Q2W. A BSA-based dose of brentuximab vedotin was chosen based on results from the C25002 study and the dose level of 48 mg/m^2 was chosen to match the observed PK exposures in ECHELON-1 for adults. ECHELON-1 (ClinicalTrials.gov: NCT01712490) was a pivotal phase 3, open-label, randomized, 2-arm, global, multicenter study, which was designed with the primary objective of comparing the modified PFS obtained with A+AVD versus that obtained with ABVD in adult patients with Stage III or Stage IV cHL.

The study consisted of 2 phases. Primary Objective of phase 1 was to assess the safety and tolerability, and to identify the recommended dose of brentuximab vedotin in combination with the

multiagent chemotherapy regime AVD, in treatment naïve paediatric HL. Secondary endpoints of this study phase include PK assessment, and efficacy endpoints like CR, PR ORR, PET negative after 2 and 6 treatment cycles, and development of ADA. Exploratory endpoints include PFS, EFS, OS and DOR.

Primary Objective of phase 2 was to determine efficacy including CR rate, percentage of patients who were PET negative after cycle 2, to evaluate PR and OR rate at the end of protocol therapy and to determine the percentage of patients who were able to complete 6 cycles of protocol therapy. Secondary endpoints include among others, PFS, EFS, OS, DOR, development of ADA and safety.

The paediatric study population consisted of patients aged 5 to < 18 years with advanced-stage (Stage III or Stage IV), newly diagnosed CD30+ cHL who were treatment naïve and had a Karnofsky Performance Status or Lansky Play-Performance of ≥50.

Primary and secondary endpoints were in accordance with what was agreed by PDCO, and are commonly used endpoints for oncology studies. However, given the single arm design of study C25004, interpretation of time dependent endpoints like PFS, EFS and OS is hampered. The single arm clinical study in children with newly diagnosed high risk HL was agreed by the PDCO, as it was believed that the paediatric indication could be supported by extrapolation of adult data to children. Although some differences between paediatric and adults HL were acknowledged (for instance differences in prevalence), the treatment strategy does not differ, and extrapolation of efficacy should be attempted.

In the current variation, the concept of extrapolation of adults data to children was not discussed. Also the efficacy results have not been contextualized e.g. using external and/or historical controls. For the purpose of this variation, noting that the MAH does not seek a paediatric indication, this can be agreed. If in the future the applicant applies for a paediatric indication the extrapolating of adult data to children needs to be attempted, and contextualising study data with historical controls needs to be performed.

Results

In total 59 patients were included in study C25004, 8 in phase 1 and 51 in phase 2 of the study. This is only a limited number of patients. In principle, the preformed meta-analysis could provide support for observations of this study in treatment naïve paediatric HL. However, the MAH did not discuss to what extent results of the meta-analysis are relevant for the C25004 study. If in the future the applicant applies for a paediatric indication, a discussion on how the meta-analyses data compare to the C25004 study results, taking into account impact of differences in patient population and treatment, should be included.

The DLT-evaluable population consisted of 6 patients treated at the starting dose of brentuximab vedotin 48 mg/m^2 in combination with AVD during phase 1. No patient met the protocol-defined DLT criteria. The MTD of brentuximab vedotin was not reached and brentuximab vedotin 48 mg/m^2 was determined to be the RP2D in this paediatric population.

Among the 8-patient phase 1 response-evaluable population, 7 patients (88%) achieved a CR by IRF assessment per IWG criteria. One patient (13%) achieved a PR by IRF assessment per the IWG criteria. Every patient (100%) achieved an objective response (either CR or PR). A total of 7 of 8 patients (88%) in the phase 1 response-evaluable population achieved a return to normal or a reduction of their disease's PET positivity as assessed by Deauville score ≤3 by the end of Cycle 2.

After a median PFS follow-up was 30.03 months, the median PFS was not reached. Two of the 8 patients in the population have experienced a PFS event. After a median OS follow of 32.28 months, no patient had died.

Of the 51-patient phase 2 response-evaluable population, 38 patients (75%) had achieved a CR. Furthermore, 46 patients (90%) were PET-negative by IRF assessment (Deauville score ≤3) at the end of Cycle 2. Six patients (12%) had a clinical response of PR. In total 44 patients (86%) achieved an objective response (CR or PR). With a median follow-up of 15 months the median DOR was not estimable.

A total of 13 patients (22%) (95% CI, 12%-35%) in the safety population were reported to have received irradiation after Cycle 6. According to the applicant the rate of irradiation in this paediatric study exceeded that observed in adults in study C25003, but is lower than that reported for 3 recently reported paediatric studies. However, the number of patients included in C25004 is small, by which no definitive conclusion can be drawn regarding the exact percentage of patients who need of RT after brentuximab-vedotin+AVD treatment.

At a median PFS follow up of 17.25 months, the median duration of PFS was not estimable, reported PFS durations ranged from 6 months to a censored duration of 28 months. Eleven patients (22%) had experienced an event of disease progression; no patient experienced a PFS event of death. At 12 months about 74% of the patients had not had a PFS event. Available PFS data suggest that the PFS curve reached a plateau after 15 months of follow up, however longer follow up would be needed for confirmation.

The single arm study design hampers the interpretation of the study results which is especially true for the time dependent efficacy endpoints like PFS, EFS and OS. Given the generally good prognosis and long survival of paediatric HL patients treated with currently available chemotherapeutic options, the follow-up time is too short to draw any conclusion. The high response rate indicates significant anti-tumour activity and the percentage of patients who had no PFS, EFS or OS event at specific time points might give point towards a clinically relevant effect of treatment, however for this the results should be contextualized and supported by extrapolation of adult efficacy data to children. Of note, given the prognosis, updated data would be needed. Potentially this will be provided by the optional LTFU in Study C25004 that provides an opportunity for patients to participate in a longer duration of PTFU monitoring for assessment of long-term safety endpoints and survival status. However, patients can choose to enter the LTFU study, this might introduce bias in the long-term follow up data, when patients with PD appear to be less likely to enter the LTFU study in comparison to patients who have no PD.

While in the agreed PIP it is noted that the A+AVD indication for peadiatric treatment naïve cHL might be supported by extrapolation from adult data, a general statement that response rates, PFS, EFS and OS were generally consistent between adult patients (study C25003 [ECHELON-1]) and paediatric patients with previously untreated Stage III or IV cHL (study C25004) is not sufficient for this purpose.

Meta-analysis

The identification of studies for inclusion in the meta-analysis (MA) an electronic database search was conducted via the Ovid platform. Followed by hand searching to identify further relevant studies which had not yet been published as a full journal article (e.g. conferences were searched via their respective online platforms or published abstract handbooks). Finally, data from eligible studies were extracted and used to assess the suitability of each study for inclusion in the meta-analysis.

Inclusion criteria for the meta-analysis were; studies needed to include paediatric patients who were treated with brentuximab vedotin and studies needed to have relevant efficacy and safety outcome data and should be a RCTs, nRCTs or observational study.

Twenty-three publications, reporting the findings of 12 unique studies, met the inclusion criteria. Of these, 11 studies were included in the meta-analyses, nine for the efficacy outcome analyses and 11 for the exploratory safety outcome analyses.

Two trials (Hochberg, 2017a, 2017b, 2017c and Franklin 2018, 2019) included newly diagnosed/ untreated patients, while a single study included a mixed patient population undergoing treatment following their first diagnosis or relapse (Titapiwatanakun, 2019) and all remaining studies included patients with relapsed or refractory (R/R) disease.

The following efficacy outcomes were analysed based on available data: OS (data available from 3 studies); ORR (data available from 6 studies); CR (data available from 9 studies) and PR (data available from 3 studies). Exploratory safety analyses were also conducted.

The efficacy analyses results for brentuximab vedotin, showed an estimated 96.9% of patients were alive at 3 months; 91% at 12 months and 87% at 24 months in the meta-analysis (corresponding to basecase results (of all studies combined) in the provided tables and figures).

For response outcomes, an estimated 79% of patients achieved a response, with the majority of these experiencing a CR as best response outcome. A separate calculation for CR, based on more study data than was available for ORR suggested that around 73% of patients achieve CR when treated with BV. PR was only reported in three studies (a subgroup of those reporting CR) and the analysis suggested 14% of patients experience a PR, in addition to the >70% experiencing a CR. [Note that ORR is not equal to CR+PR because not all studies reported PR].

As most of the studies included in the meta-analysis include relapsed/refractory patients, the value of this analysis to support the efficacy data of study C25004 in patients that includes previously untreated high risk HL patients, is not immediately evident. Only 2 of the studies included in the meta-analysis newly diagnosed/ untreated patients. The applicant did not discuss whether efficacy results of these studies were comparable to the efficacy results obtained with study C25004, or whether even it would be feasible to compare the study results given the treatment including the back bone chemotherapy, and the patient populations included in the studies.

Conclusion

Results of the small clinical study C25004 show high response rates with brentuximab vedotin in paediatric patients with newly diagnosed HL.CR rate was above 75%. The discussed limitations of the submitted data (i.e. lack of contextualisation of the single arm C25004 trial data, no discussion regarding extrapolation from adults data and no discussion on how the meta-analysis data can support the C25004 results) are not a concern for this variation aiming to include a limited selection of the available paediatric data in SmPC Sections 4.2, 4.8, 5.1 and 5.2.

However, if in the future the applicant intends to apply for a paediatric (first line) indication, these above mentioned limitations need to be addressed.

8. Clinical Safety aspects

Exposure

The safety population consisted of 59 patients who received at least 1 dose of any drug in the A+AVD regimen. All treated patients completed the maximum 6 cycles of protocol therapy. Patients treated in this study received a median of 6 cycles (range, 6-6 cycles) of each of the 4 components of the protocol therapy (A+AVD), administered over a median of 25.29 weeks (range, 23.7-31.1 weeks).

Median RDI for each component of the A+AVD regimen was 99.9% (range, 87.89%-103.18%) for

brentuximab vedotin, 99.9% (range, 74.65%-103.11%) for doxorubicin, 99.7% (range, 78.07%-102.88%) for vinblastine, and 99.9% (range, 91.92%-108.28%) for dacarbazine.

A dose delay was the most frequently reported treatment modification for patients in the safety population. At least 1 dose delay for each component of the A+AVD regimen was reported for 43 patients (73%) in the safety population. A brentuximab vedotin dose reduction and dose interruption were reported for 3 patients each (5%), and a dose hold was reported for 1 patient 2%). Within the AVD regimen, a dose reduction for doxorubicin was reported for 1 patient (2%), for vinblastine for 4 patients (7%), and for dacarbazine for 3 patients (5%). A dose interruption for dacarbazine was reported for 2 patients (3%).

Summary of AEs

At least 1 TEAE of any grade was reported for all 59 patients (100%) and at least 1 drug-related TEAE of any grade for 57 patients (97%) in the safety population (Table 26). At least 1 Grade 3 or higher TEAE was reported for 54 patients (92%) and was considered drug related for 51 patients (86%). At least 1 SAE was reported for 24 patients (41%) and was considered drug related for 19 patients (32%). No AEs were reported that resulted in the premature and permanent discontinuation of study treatment, and no on-study deaths were reported in the study.

Table 26 Study C25004: Overview of AE and Safety Profile (Safety Population)

	Phase 1 N=8	Phase 2 N=51	Phase 1+Phase 2 N=59
Any TEAE	8 (100)	51 (100)	59 (100)
Any drug-related TEAE	8 (100)	49 (96)	57 (97)
Grade 3 or higher TEAE	8 (100)	46 (90)	54 (92)
Drug-related grade 3 or higher TEAEs	8(100)	43 (84)	51 (86)
AEs resulting in study drug discontinuation	0	0	0
SAEs	1 (13)	23 (45)	24 (41)
Drug-related SAEs	1 (13)	18 (35)	19 (32)
On-study deaths	0	0	0
Follow-up deaths	0	0	0

Source: Table 15.3.1.1.

AE: adverse event; SAE: serious adverse event; TEAE: treatment-emergent adverse event.

A TEAE was defined as any AE that occurred after administration of the first dose of study treatment and up through 30 days after the last dose of study treatment.

Percentages are based on the number of patients in each category calculated relative to the total number of patients in the relevant analysis set for each phase.

On-study death was defined as a death that occurred between the first dose of protocol treatment and 30 days after the last dose of protocol treatment.

Follow-up death was defined as a death that occurred after 30 days of the last dose of protocol treatment.

TEAEs: Any Grade

The TEAE PTs of any grade reported for at least 20% of patients in the safety population were vomiting (85% of patients); nausea (75%); neutropenia (58%); pyrexia and WBC count decreased (42% each); abdominal pain (39%); constipation, neutrophil count decreased, and stomatitis (37% each); headache (32%); anaemia, decreased appetite, diarrhoea, and back pain (24% each); oropharyngeal pain and weight decreased (22% each); and fatigue (20%) (Table 27).

PT, n (%)	Phase 1 N=8	Phase 2 N=51	Phase 1+Phase 2 N=59
Any TEAE	8 (100)	51 (100)	59 (100)
Vomiting	8 (100)	42 (82)	50 (85)
Nausea	8 (100)	36 (71)	44 (75)
Neutropenia	5 (63)	29 (57)	34 (58)
Pyrexia	4 (50)	21 (41)	25 (42)
White blood cell count decreased	5 (63)	20 (39)	25 (42)
Abdominal pain	2 (25)	21 (41)	23 (39)
Constipation	4 (50)	18 (35)	22 (37)
Neutrophil count decreased	4 (50)	18 (35)	22 (37)
Stomatitis	4 (50)	18 (35)	22 (37)
Headache	5 (63)	14 (27)	19 (32)
Anaemia	1 (13)	13 (25)	14 (24)
Back pain	2 (25)	12 (24)	14 (24)
Decreased appetite	2 (25)	12 (24)	14 (24)
Diarrhoea	4 (50)	10 (20)	14 (24)
Oropharyngeal pain	3 (38)	10 (20)	13 (22)
Weight decreased	1 (13)	12 (24)	13 (22)
Fatigue	3 (38)	9 (18)	12 (20)
Abdominal pain upper	3 (38)	8 (16)	11 (19)
Alopecia	0	11 (22)	11 (19)
Febrile neutropenia	1 (13)	9 (18)	10 (17)
Rhinitis	3 (38)	7 (14)	10 (17)
Arthralgia	1 (13)	8 (16)	9 (15)
Cough	1 (13)	8 (16)	9 (15)
Asthenia	5 (63)	3 (6)	8 (14)
Bone pain	0	8 (16)	8 (14)
Oral pain	1 (13)	7 (14)	8 (14)
Pain in extremity	2 (25)	6 (12)	8 (14)
Dizziness	1 (13)	6 (12)	7 (12)
Lymphocyte count decreased	0	7 (14)	7 (12)
Nasal congestion	2 (25)	5 (10)	7 (12)
Pruritus	0	7 (14)	7 (12)
Conjunctivitis	2 (25)	4 (8)	6 (10)
Leukopenia	1 (13)	5 (10)	6 (10)
Myalgia	1 (13)	5 (10)	6 (10)
Pain	0	6 (12)	6 (10)
Pain in jaw	0	6 (12)	6 (10)
Rash maculopapular	2 (25)	4 (8)	6 (10)
Upper respiratory tract infection	1 (13)	5 (10)	6 (10)

Source: Table 15.3.1.3.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; TEAE: treatment-emergent adverse event.

A TEAE was defined as any AE that occurred after administration of the first dose of study treatment and up through 30 days after the last dose of study treatment.

Patients with 1 or more AEs within a level of MedDRA term are counted only once for each PT.

Percentages are based on the number of patients in each category calculated relative to the total number of patients in the relevant analysis set for each phase.

AEs are coded using the MedDRA Version 23.0.

TEAEs by Age Group: Any Grade

Patients aged 5 to 11 years constituted 19%, and those aged 12 to 17 years, 81% of patients in the safety population. The TEAE PTs of any grade reported for at least 30% of patients aged 5 to 11 years were vomiting (91% of patients), pyrexia (82%), nausea (73%), neutropenia (64%), WBC count

decreased (45%), and rhinitis (36%).

The TEAE PTs reported for at 30% of patients aged 12 to 17 years were vomiting (83% of patients); nausea (75%); neutropenia (56%); constipation (44%); abdominal pain and WBC count decreased (42% each); headache, neutrophil count decreased, and stomatitis (40% each); and pyrexia (33%).

Grade 3 or Higher TEAEs

At least 1 Grade 3 or higher TEAE was reported for 54 patients (92%) in the safety population. The Grade 3 or higher TEAE PTs reported for at least 10% of patients were neutropenia (56% of patients), WBC count decreased (41%), neutrophil count decreased (37%), febrile neutropenia (17%), and anaemia and lymphocyte count decreased (10% each) (Table 28).

Table 28 Study C25004: Grade 3 or Higher TEAEs by MedDRA PT (Safety Population)

PT, n (%)	Phase 1 N=8	Phase 2 N=51	Phase 1+Phase 2 N=59
Patients with at least 1 Grade 3 or higher TEAE	8 (100)	46 (90)	54 (92)
Neutropenia	5 (63)	28 (55)	33 (56)
White blood cell count decreased	5 (63)	19 (37)	24 (41)
Neutrophil count decreased	4 (50)	18 (35)	22 (37)
Febrile neutropenia	1 (13)	9 (18)	10 (17)
Anaemia	1 (13)	5 (10)	6 (10)
Lymphocyte count decreased	0	6 (12)	6 (10)
Leukopenia	1 (13)	4 (8)	5 (8)
Vomiting	2 (25)	3 (6)	5 (8)
Lymphopenia	0	2 (4)	2 (3)
Weight decreased	0	2 (4)	2 (3)
Nausea	0	2 (4)	2 (3)
Gastrointestinal disorder	0	2 (4)	2 (3)
Sepsis	0	2 (4)	2 (3)
Back pain	0	2 (4)	2 (3)
Headache	1 (13)	0	1 (2)
Hepatotoxicity	1 (13)	0	1 (2)
Stomatitis	1 (13)	0	1 (2)
Haemoglobinaemia	0	1 (2)	1 (2)
Leukocytosis	0	1 (2)	1 (2)
Polymerase chain reaction positive	0	1 (2)	1 (2)
Gamma-glutamyltransferase increased	0	1 (2)	1 (2)
Colitis	0	1 (2)	1 (2)
Diarrhoea	0	1 (2)	1 (2)
Lip infection	0	1 (2)	1 (2)
Herpes zoster	0	1 (2)	1 (2)
Catheter site infection	0	1 (2)	1 (2)
Device related infection	0	1 (2)	1 (2)
Skin infection	0	1 (2)	1 (2)

PT, n (%)	Phase 1 N=8	Phase 2 N=51	Phase 1+Phase 2 N=59
Hypoxia	0	1 (2)	1 (2)
Acute respiratory distress syndrome	0	1 (2)	1 (2)
Pulmonary embolism	0	1 (2)	1 (2)
Mucosal inflammation	0	1 (2)	1 (2)
Pain	0	1 (2)	1 (2)
Hepatic function abnormal	0	1 (2)	1 (2)
Decreased appetite	0	1 (2)	1 (2)
Dehydration	0	1 (2)	1 (2)
Posterior reversible encephalopathy syndrome	0	1 (2)	1 (2)
Peau d'orange	0	1 (2)	1 (2)
Decubitus ulcer	0	1 (2)	1 (2)
Intracardiac thrombus	0	1 (2)	1 (2)

Source: Table 15.3.1.5.1; 15.3.1.5.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; TEAE: treatment-emergent adverse event.

A TEAE was defined as any AE that occurred after administration of the first dose of study treatment and up through 30 days after the last dose of study treatment.

Patients with 1 or more AEs within a level of MedDRA term are counted only once for each PT.

Percentages are based on the number of patients in each category calculated relative to the total number of patients in the relevant analysis set for each phase.

AEs are coded using the MedDRA Version 23.0.

At least 1 Grade 4 TEAE reported for 44 patients (75%). Grade 4 neutropenia was the most commonly reported Grade 4 TEAE PT. Grade 4 neutropenia was reported for 30 patients (51%), Grade 4 neutrophil count decreased for 16 patients (27%), and Grade 4 WBC count decreased for 12 patients (20%). Grade 4 lymphocyte count decreased was reported for 2 patients (3%). Grade 4 febrile neutropenia, leukopenia, mucosal inflammation, sepsis, and decubitus ulcer were reported for 1 patient each (2%).

SAEs

At least 1 SAE was reported for 24 patients (41%) in the safety population. Febrile neutropenia was the most commonly reported SAE. Febrile neutropenia was reported for 17% of patients, and neutropenia and vomiting were reported for 5% of patients each (Table 29).

Table 29 Study C25004: Treatment-Emergent SAEs by PT (Safety Population)

PT, n (%)	Phase 1 N=8	Phase 2 N=51	Phase 1+Phase 2 N=59
Patients with at least 1 serious TEAE	1 (13)	23 (45)	24 (41)
Febrile neutropenia	1 (13)	9 (18)	10 (17)
Neutropenia	0	3 (6)	3 (5)
Vomiting	0	3 (6)	3 (5)
Constipation	0	2 (4)	2 (3)
Gastrointestinal disorder	0	2 (4)	2 (3)
Nausea	0	2 (4)	2 (3)
Pyrexia	0	2 (4)	2 (3)
Sepsis	0	2 (4)	2 (3)
Abdominal pain	0	1 (2)	1 (2)
Abdominal pain upper	0	1 (2)	1 (2)
Acute respiratory distress syndrome	0	1 (2)	1 (2)
Anaemia	0	1 (2)	1 (2)
Bacteraemia	0	1 (2)	1 (2)
Colitis	0	1 (2)	1 (2)
Dehydration	0	1 (2)	1 (2)
Device-related infection	0	1 (2)	1 (2)
Dyspnoea	0	1 (2)	1 (2)
Herpes zoster	0	1 (2)	1 (2)

PT, n (%)	Phase 1 N=8	Phase 2 N=51	Phase 1+Phase 2 N=59
Hyperuricaemia	0	1 (2)	1 (2)
Hypoxia	0	1 (2)	1 (2)
Ileus	0	1 (2)	1 (2)
Intracardiac thrombus	0	1 (2)	1 (2)
Lip infection	0	1 (2)	1 (2)
Mucosal inflammation	0	1 (2)	1 (2)
Neutrophil count decreased	0	1 (2)	1 (2)
Peripheral motor neuropathy	0	1 (2)	1 (2)
Pneumonia	0	1 (2)	1 (2)
Pneumothorax	0	1 (2)	1 (2)
Posterior reversible encephalopathy syndrome	0	1 (2)	1 (2)
Pulmonary embolism	0	1 (2)	1 (2)
Skin infection	0	1 (2)	1 (2)
Venous thrombosis	0	1 (2)	1 (2)
White blood cell count decreased	0	1 (2)	1 (2)

Source: Table 15.3.1.7.1.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; SAE: serious adverse event; TEAE: treatment-emergent adverse event.

A TEAE was defined as any AE that occurred after administration of the first dose of study treatment and up through 30 days after the last dose of study treatment.

Patients with 1 or more AEs within a level of MedDRA term is counted only once for each PT.

Percentages are based on the number of patients in each category calculated relative to the total number of patients in the relevant analysis set for each phase.

AEs are coded using MedDRA Version 23.0.

Other SAEs by Age Group

Treatment-emergent SAEs are presented for patients by age group. Febrile neutropenia was the most commonly reported SAE for both age groups.

At least 1 treatment-emergent SAE was reported for 3 patients (27%) in the patient cohort aged 5 to 11 years. Febrile neutropenia was reported as an SAE for 2 patients (18%), and anaemia, pyrexia, pneumothorax, and GI disorder were reported as an SAE for 1 patient each in this patient cohort (9%).

At least 1 treatment-emergent SAE was reported for 21 patients (44%) in the patient cohort aged 12 to 17 years. Febrile neutropenia was reported as an SAE for 8 patients (17%), vomiting and neutropenia were reported as an SAE for 3 patients each (6%), and sepsis, constipation, and nausea were reported as SAEs for 2 patients each (4%) in this patient cohort.

AEs That Resulted in Dose Modification

At least 1 dose reduction was reported for 3 patients (5%), at least 1 dose delay for 43 patients (73%), and at least 1 dose interruption for 2 patients (3%).

The AE PTs that led to dose reduction were peripheral sensory neuropathy (2 patients), and weight decreased (1 patient).

Neutropenia was the most commonly reported TEAE PT that led to dose delay, followed by neutrophil count decreased, vomiting, WBC count decreased, pyrexia, and febrile neutropenia, and stomatitis, leukopenia, and herpes zoster.

An AE led to dose interruption for 2 patients (3%). Grade 3 hypoxia, and Grade 1 dyspnoea and vomiting were reported for 1 patient each.

AEs of special interest

Neutropenia

Treatment-emergent neutropenia, defined by the PTs of neutropenia and neutrophil count decreased,

was reported for 52 patients (88%) in the safety population. Grade 4 neutropenia was reported for 44 patients (75%) and Grade 3 neutropenia for 7 patients (12%). Neutropenia was reported as an SAE for 4 patients (7%).

Febrile Neutropenia

Grade 3 or Grade 4 febrile neutropenia was reported for 10 patients (17%) in the safety population.

A dose delay for febrile neutropenia was reported for 4 patients (7%).

The use of CSFs as a prophylactic strategy can reduce both the severity and duration of neutropenia, and the risk of febrile neutropenia associated with chemotherapy.

Onset of febrile neutropenia was reported for the safety population at a median of 46.5 days (range, 9-158 days) after the first dose of protocol therapy, and resolution at a median of 4 days (range, 0-13 days) after onset.

The administration of G-CSFs was allowed in this study, except during the DLT observation period in phase 1 because the assessment of DLTs and determination of the RP2D could be confounded by G-CSF usage.

G-CSF administration was reported for 37 patients (63%) in the safety population with the first G-CSF dose administered at a median of 17 days (range, 8-149 days) after the first dose of protocol therapy.

G-CSF usage was reported for 7 patients (64%) in the patient cohort aged 5 to 11 years and for a total of 30 patients (63%) aged 12 to 17 years.

Peripheral Neuropathy (PN)

A comprehensive review of PTs under the PN (SMQ) (MedDRA Version 23.0) broad was performed to assess the frequency and severity of PN reported in the study. The PN (SMQ) included PTs for both sensory and motor neuropathy and terms that had both sensory and motor components. An SSQ was performed to categorize treatment-emergent PN events into peripheral sensory neuropathy and PMN PTs.

At least 1 treatment-emergent PN (SMQ) event of any grade was reported for 14 patients (24%), and was considered drug related for 12 patients (20%) in the safety population.

At least 1 peripheral sensory neuropathy (SSQ) event of any grade was reported for 11 patients (19%) and at least 1 PMN (SSQ) event for 5 patients (8%). Peripheral sensory neuropathy, reported for 5 patients (8%), was the most commonly reported PT in the peripheral sensory neuropathy (SSQ). Muscular weakness and PMN, reported for 3 patients each (5%), were the most commonly reported PTs in the PMN (SSQ).

At least 1 PN (SMQ) event of any grade was considered drug related for 12 patients (20%) in the safety population.

Among patients for whom at least 1 treatment-emergent PN (SMQ) event of any grade was reported, onset of the first PN event was reported at a median of 5.93 weeks (range, 0.9-19.9 weeks), and onset of a Grade 2 PN event (the highest grade) at a median of 6.86 weeks (range, 0.9-19.9 weeks) after the first dose of protocol therapy.

Resolution of all PN events was reported for 9 patients (64%) at EOT, and for 11 patients (79%) the time of last follow-up for the 14 patients for whom at least 1 PN (SMQ) event was reported during treatment. Resolution of at least 1 PN event was reported at a median of 1.57 weeks (range, 0.3-50.3 weeks) for the 14 patients for whom at least 1 PN (SMQ) event was reported in the study.

Clinical Laboratory Evaluations

Serum Chemistry

A postbaseline shift from CTC Grade 0 to Grade 4 hypercalcemia was reported for 4 patients (7%), hyperuricemia for 3 patients (5%), hypocalcemia for 2 patients (3%), and hypoglycemia and increased creatinine for 1 patient each (2%). A postbaseline shift from CTC Grade 0 to Grade 3 increased ALT, AST, and hypophosphatemia was reported for 3 patients each (5%), and to hyponatremia for 1 patient (2%) in the safety population.

Hematology

A postbaseline shift from CTC Grade 0 to Grade 4 neutrophil count decreased was reported for 44 patients (75%), WBC count decreased for 15 patients (25%), platelet count decreased for 4 patients (7%), and lymphocyte count decreased for 2 patients (4%) in the safety population.

Post baseline shift from CTC Grade 0 to Grade 3 WBC count decreased was reported for 19 patients (32%), neutrophil count decreased for 9 patients (15%), lymphocyte count decreased for 5 patients (9%), and leukocytosis, platelet count decreased, and lympocyte count increased for 1 patient each (2%).

8.1. Meta-analysis Safety

Six studies reported treatment-related adverse events. Korsantya 2020 (27) reported that 3 patients experienced haematological toxicity and 1 patient experienced infection-related complications, but it is unclear whether these were the only adverse events experienced by the study patients. Thus, this study has been excluded from the analysis of this outcome, due to the lack of clarity. A summary of total AEs data reported in the five included studies is presented in Table 30.

Table 30 Treatment-related AEs reported in the included studies

Study	Indication	Study design	Setting	BV Treatment	Total (N)	trAEs (n)	%
Franklin 2019 (NCT02979522)	HL	Prospective	Tx naïve	Combination	8	8	100
Harker-Murray 2019 (NCT02927769)	HL	Prospective	R/R	Combination	44	31	70
Koga 2020b	HL	Prospective	R/R	Monotherapy	4	4	100
Locatelli 2018 (NCT01492088)	HL	Prospective	R/R	Monotherapy	16	13	81
Titapiwatanakun, 2019	HL	Observational	Mixed	Combination /monotherapy	9*	5	56
Alternative data used for sensitivity analysis excluding treatment naïve patients							
Titapiwatanakun, 2019	HL	Observational	R/R	Combination	7	4	57

Abbreviations: AE, adverse event; BV, brentuximab vedotin; HL, Hodgkin Lymphoma; R/R, relapsed/refractory; trAEs, treatment-related AEs; Tx, treatment.

*Ten patients are included in the study, but patient #9 does not appear to have received BV as upfront chemotherapy or during relapse

Grade 3 or 4 adverse events

Table 31 Grade 3 or 4 AEs reported in the included studies Study Indication Study design Setting

Study	Indication	Study design	Setting	BV Treatment	Total (N)	G3/4 AEs (n)	%
Franklin 2019 (NCT02979522)	HL	Prospective	Tx naïve	Combination	8	8	100
Harker-Murray 2019 (NCT02927769)	HL	Prospective	R/R	Combination	44	8	18
Hochberg 2017a (NCT02398240)	HL	Prospective	Tx naïve	Combination	23	3	13
Locatelli 2018 (NCT01492088)	HL	Prospective	R/R	Monotherapy	16	11	69
McMillan, 2020	HL	Observational	R/R	Combination	19	4	21
Titapiwatanakun, 2019	HL	Observational	Mixed	Combination /monotherapy	9*	3	33
Alternative data used for sensitivity analysis excluding treatment naïve patients							
Titapiwatanakun, 2019	HL	Observational	R/R	Combination	7	3	43

Abbreviations: BV, brentuximab vedotin; G3/4 AEs, grade 3 or 4 AEs; HL, Hodgkin Lymphoma; R/R, relapsed/refractory; tx, treatment.

*Ten patients are included in the study, but patient #9 does not appear to have received BV as upfront chemotherapy or during relapse

Summary, for the basecase:

- The odds of experiencing a grade 3 or 4 AE were 0.5 (95% CI 0.2, 1.5)
- The estimated proportion of patients experiencing a grade 3 or 4 AE was 35.1% (95% CI 16.1%, 60.4%)
- The heterogeneity between the studies was high (I2 = 77.3%, p=0.001

For the sensitivity analysis including only prospective studies (4 studies included):

- The odds of experiencing, and the proportion of patients experiencing, a grade 3 or 4 AE were 0.8 (95% CI 0.1, 3.9) and 43.1% (95% CI 13.0%, 79.4%), respectively
- There was a slight increase in the odds/proportion of patients experiencing a grade 3 or 4 AE, compared with the basecase

For the sensitivity analysis including only studies enrolling R/R patients (4 studies included):

- The odds of experiencing, and the proportion of patients experiencing, a grade 3 or 4 AE were 0.5 (95% CI 0.2, 1.7) and 35.0% (95% CI 14.9%, 62.3%), respectively, which was very similar to the basecase
- This analysis suggests that the treatment stage may not affect whether a patient will experience a grade 3 or 4 AE

For the sensitivity analysis including only studies reporting BV in combination treatment (5 studies included):

- The odds of experiencing, and the proportion of patients experiencing, a grade 3 or 4 AE were 0.3 (95% CI 0.1, 0.8) and 25.8% (95% CI 12.4%, 45.8%), respectively
- There was a decrease in the odds/proportion of patients experiencing a grade 3 or 4 AE, compared with the basecase, which may be somewhat unexpected from a clinical

perspective

For the sensitivity analysis including only studies reporting BV at a dose of 1.8 mg/kg/q3w (2 studies included):

- The odds of experiencing, and the proportion of patients experiencing, a grade 3 or 4 AE were 0.8 (95% CI 0.4, 1.7) and 44.5% (95% CI 27.2%, 63.2%), respectively
- There was a small increase in the odds/proportion of patients experiencing a grade 3 or 4 AE, compared with the basecase

For the sensitivity analysis including only studies enrolling paediatric patients (3 studies included):

- The odds of experiencing, and the proportion of patients experiencing a grade 3 or 4 AE were 1.9 (95% CI 0.4, 8.7) and 65.0% (95% CI 28.3%, 89.7%), respectively
- There was an increase in the odds/proportion of patients experiencing a grade 3 or 4 AE, compared with the basecase

Serious adverse events

Table 32 SAEs reported in the included studies

Study	Indication	Study design	Setting	BV Treatment	Total (N)	SAE (n)	%
Cole 2018 (NCT01780662)	HL	Prospective	R/R	Combination	45	40	89
Franklin 2019 (NCT02979522)	HL	Prospective	Tx naïve	Combination	8	1	13
Koga 2020b	HL	Prospective	R/R	Mono	4	0	0
Locatelli 2018 (NCT01492088)	HL	Prospective	R/R	Mono	16	7	44

Abbreviations: BV, brentuximab vedotin; HL, Hodgkin Lymphoma; IRC, independent review committee assessment; R/R, relapsed/refractory; SAE, serious adverse event; tx, treatment.

In summary, for the basecase:

- The odds of experiencing a serious adverse event were 0.7 (95% CI 0.1, 5.1)
- The estimated proportion of patients experiencing an SAE was 42.2% (95% CI 9.4%, 83.6%)
- The heterogeneity between the studies was high (I2 = 86.2%, p=0.000), mostly due to especially high odds of experiencing an event from one study (Cole 2018)
- The 95% CIs reported for the pooled treatment effect were wide, due to the heterogeneity between studies.

For the sensitivity analysis including only studies enrolling R/R patients (3 studies included):

- The odds of experiencing an SAE and the proportion of patients experiencing an SAE were 1.2 (95% CI 0.1, 10.2) and 54.8% (95% CI 12.6%, 91.1%), respectively
- There was an increase in the odds/proportion of patients experiencing an SAE, compared with the basecase.

For the sensitivity analysis including only studies reporting BV in combination treatment (2 studies included):

- The odds of experiencing an SAE and the proportion of patients experiencing an SAE were 4.1 (95% CI 1.8, 9.7) and 80.5% (95% CI 63.8%, 90.6%), respectively
- There was an increase in the odds/proportion of patients experiencing an SAE, compared with the basecase, which may be expected since studies remaining were for combination treatments

For the sensitivity analysis including only studies enrolling paediatric patients (3 studies included):

- The odds of experiencing an SAE and the proportion of patients experiencing an SAE were 0.4 (95% CI 0.1, 1.3) and 26.4% (95% CI 8.8%, 57.3%), respectively
- The heterogeneity between the studies was medium (I2 = 36.7%, p=0.206), compared to high for the basecase
- There was a decrease in the odds/proportion of patients experiencing an SAE, compared with the basecase

Neutropenia grade 3 or 4

Table 33 Neutropenia grade 3 or 4 AEs reported in the included studies

Study	Indication	Study design	Setting	BV Treatment	Total (N)	Neut G3/4 (n)	%
Cole 2018 (NCT01780662)	HL	Prospective	R/R	Combination	42	15	36
Franklin 2019 (NCT02979522)	HL	Prospective	Tx naïve	Combination	8	6	75
Harker-Murray 2019 (NCT02927769)	HL	Prospective	R/R	Combination	44	1	2
Locatelli 2018 (NCT01492088)	HL	Prospective	R/R	Monotherapy	16	4	25
Titapiwatanakun, 2019	HL	Observational	Mixed	Combination /monotherapy	9*	1	11
Alternative data used for sensitivity analysis excluding treatment naïve patients							
Titapiwatanakun, 2019	HL	Observational	R/R	Combination	7	1	14

Abbreviations: AE, adverse event; BV, brentuximab vedotin; G3/4, grade 3 or 4; HL, Hodgkin Lymphoma; Neut, neutropenia; R/R, relapsed/refractory; tx, treatment.
*Ten patients are included in the study, but patient #9 does not appear to have received BV as upfront chemotherapy or during relapse

In summary, for the basecase:

- The odds of experiencing grade 3 or 4 neutropenia were 0.3 (95% CI 0.1, 1.1)
- The estimated proportion of patients experiencing grade 3 or 4 neutropenia was 24.5% (95% CI 8.9%, 51.8%)
- The heterogeneity between the studies was high (I2 = 75.2%, p=0.003), due to there being one study (Franklin 2019), reporting higher odds of experiencing neutropenia compared with the other studies

For the sensitivity analysis including only prospective (nRCT) studies (4 studies included):

- The odds of experiencing, and the proportion of patients experiencing, grade 3 or 4 neutropenia were 0.4 (95% CI 0.1, 1.5) and 27.7% (95% CI 9.1%, 59.6%), respectively
- There was an increase in the odds/proportion of patients experiencing grade 3 or 4 neutropenia, compared with the basecase

For the sensitivity analysis including only studies enrolling R/R patients (4 studies included):

- The odds of experiencing, and the proportion of patients experiencing, grade 3 or 4 neutropenia were 0.2 (95% CI 0.1, 0.7) and 16.9% (95% CI 5.7%, 40.2%), respectively

- There was a decrease in the odds/proportion of patients experiencing grade 3 or 4 neutropenia, compared to the basecase, due to Franklin 2019 being excluded from the analysis – the only study where the patients were more likely to experience neutropenia than not

For the sensitivity analysis including only studies reporting BV in combination treatment (4 studies included):

- The odds of experiencing, and the proportion of patients experiencing, grade 3 or 4 neutropenia were 0.3 (95% CI 0.1, 1.7) and 24.4% (95% CI 5.7%, 63.0%), respectively
- The results of this analysis were very similar to those of the basecase, suggesting that the type of therapy (monotherapy or combination) received may not affect whether a patient will experience grade 3 or 4 neutropenia

For the sensitivity analysis including only studies reporting BV at a dose of 1.8 mg/kg/q3w (2 studies included):

- The odds of experiencing, and the proportion of patients experiencing, grade 3 or 4 neutropenia were 0.5 (95% CI 0.3, 0.9) and 33.0% (95% CI 22.1%, 46.1%), respectively
- There was an increase in the odds/proportion of patients experiencing grade 3 or 4 neutropenia, compared with the basecase.

For the sensitivity analysis including only studies enrolling paediatric patients (3 studies included):

- The odds of experiencing, and the proportion of patients experiencing, grade 3 or 4 neutropenia were 0.5 (95% CI 0.1, 2.9) and 34.6% (95% CI 8.8%, 74.2%), respectively
- There was an increase in the odds/proportion of patients experiencing grade 3 or 4 neutropenia, and a widening of the confidence interval, compared with the basecase

8.2. Discussion safety data

Paediatric study C25004

The safety population consisted of 59 patients who received at least 1 dose of any drug in the A+AVD regimen. All treated patients completed the maximum 6 cycles of protocol therapy (A+AVD).

At least 1 TEAE of any grade was reported for all 59 patients (100%) and at least 1 drug-related TEAE of any grade for 57 patients (97%) in the safety population. At least 1 Grade 3 or higher TEAE was reported for 54 patients (92%) and was considered drug-related for 51 patients (86%). At least 1 SAE was reported for 24 patients (41%) and was considered drug-related for 19 patients (32%). No AEs were reported that resulted in the premature and permanent discontinuation of study treatment, and no on-study deaths were reported in the study.

The TEAE PTs of any grade reported for at least 20% of patients in the safety population were vomiting (85% of patients); nausea (75%); neutropenia (58%); pyrexia and WBC count decreased (42% each); abdominal pain (39%); constipation, neutrophil count decreased, and stomatitis (37% each); headache (32%); anaemia, decreased appetite, diarrhoea, and back pain (24% each); oropharyngeal pain and weight decreased (22% each); and fatigue (20%).

At least 1 Grade 3 or higher TEAE was reported for 54 patients (92%) in the safety population. The Grade 3 or higher TEAE PTs reported for at least 10% of patients were neutropenia (56% of patients), WBC count decreased (41%), neutrophil count decreased (37%), febrile neutropenia (17%), and anaemia and lymphocyte count decreased (10% each).

Grade 4 neutropenia was the most commonly reported Grade 4 TEAE PT. Grade 4 neutropenia was

reported for 30 patients (51%), Grade 4 neutrophil count decreased for 16 patients (27%), and Grade 4 WBC count decreased for 12 patients (20%). Grade 4 lymphocyte count decreased was reported for 2 patients (3%). Grade 4 febrile neutropenia, leukopenia, mucosal inflammation, sepsis, and decubitus ulcer were reported for 1 patient each (2%).

At least 1 SAE was reported for 24 patients (41%) in the safety population. Febrile neutropenia was the most commonly reported SAE. Febrile neutropenia was reported for 17% of patients, and neutropenia and vomiting were reported for 5% of patients each.

PN is a well characterized adverse drug reaction for brentuximab vedotin. At least 1 PN (SMQ) event of any grade was reported for 14 patients (24%) in the safety population. A Grade 2 PN (SMQ) event (the highest severity reported in the study) was reported for 3 patients (5%), and a PN (SMQ) event led to dose reduction for 2 patients (3%). The PT, PMN was reported as an SAE for 1 patient (2%).

Resolution of all PN events was reported for most patients for whom at least 1 PN (SMQ) event was reported during treatment. At the time of the last follow-up, resolution of all PN events was reported for 11 patients (79%) among the 14 patients for whom at least 1 PN event was reported. Resolution of at least 1 PN event was reported at a median of 1.57 weeks (range, 0.3-50.3 weeks).

At least 1 TEAE that was considered infusion related was reported for 5 patients (8%) in the safety population. All 5 patients were ADA negative at all post baseline time points. No IRRs were reported for 4 patients who were reported to be transiently ADA positive with low ADA titers.

No additional safety signals were identified from the results of clinical laboratory data, vital signs assessments, or ECG results.

The applicant concluded that A+AVD had an acceptable safety profile and was well tolerated in this pediatric population of treatment-naïve patients with advanced (Stage III or Stage IV) CD30+ cHL. No new adverse drug reactions were observed in the pediatric population receiving the A+AVD combination.

Safety data for subgroups including patients 5-11 years of age and patients 12-17 years of age was provided. The toxicity profile of brentuximab-vedotin seemed to be similar across these age groups. It was stated that safety data in children was comparable to the known safety profile in adults, however potentially important similarities and differences were not thoroughly discussed. When the applicant will apply for a paediatric indication this comparison of adult and paediatric safety data should be further discussed.

In the PIP summary reports, it was suggested that the main benefit of brentuximab vedotin+ AVD for the paediatric population might be decrease of toxicity including pulmonary toxicity, in comparison to other used chemotherapy regimens. Due to the nature of the indirect comparison, it will be difficult to draw robust conclusion on the comparison of safety profiles for different first line treatment options for paediatric HL patients. Moreover, without all safety data of different treatment regimens and different populations the suggestions of a safety benefit for brentuximab vedotin+ AVD cannot be supported.

Furthermore, long term safety data for brentuximab vedotin+AVD is not yet available, therefore no conclusion can be drawn with regard to its long-term toxicity in paediatric population. Potentially the optional LTFU in Study C25004 will provide in due time additional long-term safety endpoints.

Meta-analysis

The safety analysis for the meta-analysis are only considered exploratory. In general, the heterogeneity between the studies was high. The exploratory analysis, conducted for safety outcomes, estimated that 73% of patients experienced a treatment-related AE of any grade. Around 35% of patients experienced a grade 3-4 AE and 42% an SAE. An estimated 25% of patients experienced

grade 3-4 neutropenia.

The sensitivity analyses for safety outcomes showed some variation in the exact proportions of patients estimated to experience an AE, however on the whole, findings were consistent with the basecase. The sensitivity analysis focusing on studies evaluating brentuximab- vedotin as a combination therapy was not intuitive and suggested that patients receiving combination therapy may experience slightly lower odds of experiencing a treatment-related AE, or a grade 3-4 AE, and similar odds of experiencing grade 3-4 neutropenia. This is clearly a reflection of the differences between study characteristics amongst the studies that impacted the outcome when monotherapy studies were removed and was (could not be) adjusted for.

Except for neutropenia the incidence of specific AEs were not analysed. The meta-analysis includes studies in which brentuximab is used in different combinational treatment regimens at different doses and in different patient populations (most patients with r/r disease). The sensitivity analysis that include studies sharing specific characteristic with regard to treatment or patients population, generally include only few studies. Considering all above the value of this meta-analysis in support of the safety profile of brentuximab vedotin-AVD combination therapy in newly diagnosed paediatric HL patients, is limited.

The following measures are considered necessary to address issues related to safety:

- When available the long term safety data need to be submitted (**OC**).

9. Risk management plan

The MAH submitted an updated RMP version 16, dated 3 June 2021 with this application. The main proposed RMP changes were the following:

Summary of significant changes in this RMP:

• **Module SI Epidemiology of the indication(s) and target population(s)**	Updated the epidemiology of HL and frontline treatment
• **Module SII Nonclinical part of the safety specification**	Added data for bone marrow hypocellularity (monkeys)
• **Module SIII Clinical trial exposure**	Updated Clinical trial exposure with a DLP 18-February-2021
• **Module SIV Populations not studied in clinical trials**	Removed paediatric patients from the list of "populations not studied"
• **Module SV Post-authorisation experience**	Updated Post Authorisation experience with a new methodology (US and Canada) and with a DLP 18-February-2021
• **Module SVII Identified and potential risks**	Removed the important potential risk of "thymus depletion (paediatric)"
• **Module SVIII Summary of the safety concerns**	Removed the important potential risk of "thymus depletion (paediatric)"
Part III Pharmacovigilance plan	Removed study C25004 from "Additional pharmacovigilance activities"

Part V Risk minimisation measures	Updated to reflect the removal of safety concern "thymus depletion (paediatric)"
Part VI Summary of the risk management plan	Updated to reflect the removal of safety concern "thymus depletion (paediatric)"
Part VII Annexes	Annexes 2: Updated to reflect the completion of study C25004 Annex 3: Removed C25004 study Annex 8: Updated to reflect the impacted section changes.

PRAC Rapporteur's assessment:

The proposed updates in the RMP covers the removal of C25004 study as a category 3 study in the RMP. This study is a phase I/II, open-label study of brentuximab vedotin + Adriamycin®, vinblastine, and dacarbazine in pediatric patients with advanced stage newly diagnosed Hodgkin lymphoma. This study was added to the RMP in order to address the safety concerns related to "safety in pediatrics" and "thymus depletion (pediatric)". As a result of completion of the study, the risk of "thymus depletion (paediatric)" has been removed as an important potential risk from the safety specifications and the risk minimization measures of the RMP. The MAH stated that important potential risk of "thymus depletion (paediatric)" is being removed after the completion of 2 paediatric studies, C25002 (completed in 2017) and C25004. No evidence of such risk was identified from the analysing the immune reconstitution data, or the safety data in clinical trials and post-marketing reports. Note that the recent review of the important potential risk of "thymus depletion (pediatric)" in the latest PSUR covering the period of 18/02/2020 to 18/02/2021 concluded that no new safety concern was identified. There have been no reports of pediatric thymus depletion in any patient treated with brentuximab vedotin. The updates are therefore accepted, provided that the MAH routinely review the risk of "thymus depletion (paediatric)" as safety concerns of the PSUR.

Other updates include updates related to the epidemiology of HL and frontline treatment, clinical trial exposure with a DLP 18-February-2021, post authorisation experience with a DLP 18-February-2021 and removal of paediatric patients from the list of "populations not studied", which are accepted.

Overall conclusion on the RMP

The changes to the RMP are acceptable, provided that the MAH maintains "thymus depletion (paediatric)" as an important potential risk in the summary of safety concerns of the PSUR and provides reviews accordingly.

10. Changes to the Product Information

As a result of this variation, section(s) 4.2, 4.8, 5.1, and 5.2 of the SmPC are being updated as proposed below. The Package Leaflet (PL) is updated accordingly.

Proposed SmPC Changes

- Section 4.2, *Posology and method of administration, Dose Adjustments, Paediatric population subsection,* was modified to refer to observations from Study C25004, including deletion of text from this subsection relating to thymus depletion in nonclinical studies as thymus depletion was not observed in paediatric studies C25002 and C25004. Throughout section 4.2, the recommendation for use of G-CSF was clarified to apply to adult patients.

- Section 4.8*, Undesirable effects, Immunogenicity* was modified to add a subsection describing observations in paediatric patients in Study C25004.
- Section 4.8*, Undesirable effects, Paediatric Population* was enlarged to report safety observations from study C25004.
- Section 5.1, *Pharmacodynamic properties, Clinical efficacy, Paediatric Population* was enlarged to include a subsection describing efficacy data for study C25004. Also in the section, a statement describing the deferral of paediatric studies as these have now completed.
- Section 5.2, *Pharmacokinetic properties, Paediatric Population*, was modified to describe ADC and MMAE exposures observed in paediatric patients with BSA-based dosing.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

11. Request for supplementary information

11.1. Other concerns

Clinical aspects

1) The MAH is requested to correct Table 3f of the clinical summary 2.7.2. It is preferred to express Cmax and Cmin of MMAE in ng/ml unit and not in µM unit.
2) The text in section 5.2 of the SmPC should be amended to report the pharmacokinetics of ADC and MMAE as determined by non-compartmental analysis (see separate SmPC document).
3) Long term safety data for brentuximab vedotin+AVD is not yet available. The MAH should commit to submit the long term safety data when available.

12. Assessment of the responses to the request for supplementary information

12.1. Other concerns

Clinical aspects

Question 1

The MAH is requested to correct Table 3f of the clinical summary 2.7.2. It is preferred to express Cmax and Cmin of MMAE in ng/ml unit and not in µM unit.

Summary of the MAH's response

Please refer below to an updated version of Table 3.f from the Summary of Clinical Pharmacology (module 2.7.2), in which Cmax values for both Study C25002 and C25004 have been corrected, with corrections displayed in red bold for convenience.

Table 3.f Model Simulated MMAE PK Parameters

Parameter (Unit)	Study	Cycle	Median	Mean	Geometric Mean	Lowest 5th Percentile	Highest 95th percentile	SD	CV%
$AUC_{(0\text{-}21days)}$ (ng*day/mL)	C25002	1	36.3	45.1	34.1	11.9	89.5	34.7	76.9
		5	11.3	14.5	11.0	4.2	28.4	11.7	80.7
$AUC_{(0\text{-}14days)}$ (ng*day/mL)	C25004	1	26.7	35.5	26.3	9.4	72.1	30.0	84.5
		5	12.0	14.3	11.8	5.2	26.0	9.4	65.7
C_{max} (ng/mL)	C25002	1	**2.626**	**6.646**	**2.706**	**0.294**	**26.160**	**12.141**	**183**
		5	**0.702**	**1.367**	**0.758**	**0.166**	**4.904**	**2.263**	**166**
C_{max} (ng/mL)	C25004	1	**2.170**	**4.988**	**2.305**	**0.353**	**19.420**	**8.890**	**178**
		5	**1.012**	**1.318**	**0.993**	**0.272**	**3.366**	**1.111**	**84**
C_{min} (ng/mL)	C25002	1	0.102	0.198	0.077	0.004	0.688	0.316	159.6
		5	0.040	0.085	0.027	0.001	0.307	0.149	175.3
C_{min} (ng/mL)	C25004	1	0.173	0.352	0.168	0.021	1.294	0.565	160.5
		5	0.108	0.198	0.093	0.008	0.678	0.294	148.5

Source: Adcetris pop PK Report C25002 C25004 Tables 22, 23, 24, 25, 26, and 27.

AUC_{14D}: area under the concentration-time curve from time 0 to 14 days postdose; AUC_{21D}: area under the concentration-time curve from time 0 to 21 days postdose; C_{max}: maximum observed concentration; C_{min}: minimum observed concentration; CV: coefficient of variation; MMAE: monomethyl auristatin E; PK: pharmacokinetic.

Assessment of the MAH's response

The popPK simulated Cmax values of MMAE have been corrected and the Table in the report has been replaced by this corrected Table.

Conclusion

Issue resolved.

Question 2

The text in section 5.2 of the SmPC should be amended to report the pharmacokinetics of ADC and MMAE as determined by non-compartmental analysis.

"Please, report ADC and MMAE exposure parameter values as determined in the noncompartmental analysis. The variability in the popPK was considerably higher than the observed non-compartmental data. Currently the model is considered suitable for descriptive purposes only, and not for simulation purposes (see report). Reference to simulated dosing of 72 mg/m^2 Q3W and comparison with adults data should be deleted."

Summary of the MAH's response

The marketing authorization holder (MAH) has amended Section 5.2 as agreed. The MAH accepts and has removed the strikethrough of the C25002 pharmacokinetics (PK) data.

The MAH further accepts and proposes to add the ADC and MMAE exposure parameter values as determined in the non-compartmental analysis from the clinical study report for Study C25004 as follows:

The pharmacokinetics of brentuximab vedotin ADC and MMAE following a 30-minute intravenous infusion of BV administered at 48 mg/m^2 every 2 weeks in combination with doxorubicin, vinblastine, and dacarbazine (AVD) were evaluated in a phase 1/2 clinical trial of 59 paediatric patients (6-17 years

of age) with advanced-stage newly diagnosed CD30+ classical Hodgkin lymphoma (children aged 6-11 years, n = 11 and adolescents aged 12 to 17 years, n = 48). The Cmax of ADC occurred in serum approximately at the end of infusion and declined in a multiexponential manner with a terminal half-life of approximately 4 days. The Cmax of MMAE occurred in plasma approximately 2 days following BV administration with a half-life of approximately 2 days. Geometric mean Cmax and AUC of ADC following a single 48 mg/m^2 dose were 22.5 µg/mL and 46.7 µg*day/mL, respectively. Geometric mean Cmax and AUC of MMAE following a single 48 mg/m^2 dose were 4.9 ng/mL and 27.2 ng*day/mL, respectively. Similar ADC exposures were achieved following body surface area-based dosing of BV at 48 mg/m^2 in combination with AVD among pediatric age groups (<12 years, 12 – 16 years and >16 years).

Last, the MAH also accepts deletion of the text that references the simulated dosing of 72 mg/m^2 every 3 weeks in pediatric patients and its comparison with the adult data.

Assessment of the MAH's response

The applicant has amended the SmPC as requested, however the information with the popPK analysis has not been deleted. The applicant is kindly requested to delete the last paragraph of section 5.2 "*Population pharmacokinetics…..* in combination with AVD..

Updated assessment

The last paragraph of section 5.2 has been deleted as requested.

Conclusion

Issue resolved

Question 3

Long term safety data for brentuximab vedotin+AVD is not yet available. The MAH should commit to submit the long term safety data when available.

Company Response

The MAH agrees to provide long-term follow up data on Study C25004 when available. Reporting of study data after a minimum of 10 years' follow-up for all consenting patients is projected to occur by 31 March 2030.

Assessment of the MAH's response

The applicant has agreed to submit in due time the 10 year follow up data.

Conclusion

Issue is resolved.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly