PASS Information

Title	Post-Authorisation Safety Study (PASS) MA25101: An Observational Cohort Study of the Safety of Brentuximab Vedotin in the Treatment of Relapsed or Refractory CD30+ Hodgkin Lymphoma and Relapsed or Refractory Systemic Anaplastic Large Cell Lymphoma (ARROVEN)
Version Identifier of the Final Study Report	V3.0
Date of Last Version of the Final Study Report	27 November 2019
EU PAS/ENCePP Register Number	ENCEPP/SDPP/3583
Active Substance	Active substance: brentuximab vedotin Pharmacotherapeutic group: Oncology ATC code: L01XC12
Medicinal Product	ADCETRIS® 50 mg powder for concentrate for solution for infusion
Product Reference	EU/1/12/794/001
Procedure Number	EMEA/H/C/002455
Marketing Authorisation Holder(s)	Takeda Pharma A/S Dybendal Alle 10 2630 Taastrup Denmark
Joint PASS	No
Research Question and Objectives	MA25101 was a post-authorisation safety study (PASS) mandated by the European Medicines Agency (EMA). This multi-centre, prospective, observational cohort study evaluated the safety profile of brentuximab vedotin in patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL) or systemic anaplastic large cell lymphoma (sALCL), treated with brentuximab vedotin as part of routine clinical care. A total of 311 patients were enrolled at 80 sites (of whom 310 were in the Safety Population) in Europe. The study lasted a total of 64 months (5 years 4 months), with the first patient in on 26 June 2013 and the last patient out on 4 October 2018. The median time since the first dose of brentuximab vedotin was 1.5 years (interquartile range

	[IQR]: 0.7, 2.5 years; range: 0.0-4.8 years). The median number of treatment cycles per patient was 6.0 cycles (IQR: 4.0, 9.0 cycles; range: 1.0-41.0 cycles). The objectives were to: • Evaluate the occurrence of serious adverse events (SAEs) and specified adverse events of special interest (AESIs), both serious and non-serious, in patients actively treated for relapsed or refractory CD30+ HL or relapsed or refractory sALCL in routine clinical practice with brentuximab vedotin; and • Identify and describe potential risk factors for peripheral neuropathy in relapsed or refractory CD30+ HL or relapsed or refractory sALCL patients treated with brentuximab vedotin.
Country(-ies) of Study	Austria, Denmark, France, Germany, Greece, Ireland, Italy, Netherlands, Slovakia, Spain, Sweden, Switzerland, and the United Kingdom (UK).
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SIGNATURE OF PRINCIPAL INVESTIGATOR

Study Title: Post-Authorisation Safety Study (PASS) MA25101: An Observational Cohort Study of the Safety of Brentuximab Vedotin in the Treatment of Relapsed or Refractory CD30+ Hodgkin Lymphoma and Relapsed or Refractory Systemic Anaplastic Large Cell Lymphoma (ARROVEN)

I have read this final analysis report and confirm to the best of my knowledge that it accurately describes the conduct and final results of this study.

Dr. Kim Linton, MBChB, MRCP, PhD Date
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1 ABSTRACT

Title

Post-Authorisation Safety Study (PASS) MA25101: An Observational Cohort Study of the Safety of Brentuximab Vedotin in the Treatment of Relapsed or Refractory CD30+ Hodgkin Lymphoma and Relapsed or Refractory Systemic Anaplastic Large Cell Lymphoma (ARROVEN)

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Date of Abstract: 27 November 2019

Keywords

brentuximab vedotin, Hodgkin lymphoma, systemic anaplastic large cell lymphoma, post-authorisation safety

Rationale and Background

Brentuximab vedotin is an antibody-drug conjugate for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL) or systemic anaplastic large cell lymphoma (sALCL). The European Medicine Agency (EMA) requested this study to better understand the safety profile of brentuximab vedotin in a real-world setting.

Research Question and Objectives

The objectives were to evaluate serious adverse events (SAEs) and adverse events of special interest (AESIs), in patients treated with brentuximab vedotin in routine practice, and to identify potential risk factors for peripheral neuropathy.

Study Design

This was a multi-centre, international, prospective, observational study of patients with relapsed or refractory CD30+ HL or sALCL, treated with brentuximab vedotin in routine clinical care.

Setting

Routine care by oncologists and haematologists.

Subjects and Study Size

Safety analyses included 310 patients (prospective: 156 and retrospective: 154) including 58 patients with sALCL. The median age at enrolment was 44.0 (range: 18 - 87) years, with 24.5% aged ≥65 years.

Variables and Data Sources

- Demographics, medical history, co-morbidities, disease and treatment history

- Brentuximab vedotin dosage regimen
- Other treatments and concomitant medications
- SAEs
- AESIs defined in the protocol per EMA's request: peripheral neuropathy, neutropenia (including febrile neutropenia), infections (including opportunistic infections), hyperglycaemia, and hypersensitivity reactions (including infusion-related reactions and allergic reactions)
- Survival status
- Potential risk factors for peripheral neuropathy
- Sub-population evaluations include: elderly (≥65 years), long-term treatment (>16 cycles), disease (CD 30+ HL or sALCL).

Results

Patients received a median of 6.0 treatment cycles (interquartile range [IQR]: 4.0, 9.0; range: 1.0-41.0 cycles); 9 patients received >16 cycles.

Of the 310 patients, 230 (74.2%) reported an SAE and/or AESI. This included 109 patients with an SAE (35.2%) and 213 patients with an AESI (68.7%), including: peripheral neuropathy (n=131, 42.3%), infections (n=97, 31.3%), neutropenia (n=54, 17.4%), hypersensitivity reactions (n=34, 11.0%), and hyperglycaemia (n=4, 1.3%).

Treatment-related SAEs and/or AESIs occurred in 186 (60.0%) patients, two thirds were Grade 1-2 (n=124, 40.0%); this included 68 SAEs (21.9% of patients), and 177 AESIs (57.1% of patients). There were 3 (1.0%) deaths due to treatment-related events.

SAEs and/or AESIs led to treatment discontinuations for 42 (13.5%) patients, of which 32 (10.3%) were serious; and led to study discontinuation for 16 patients, representing 5.2% of the study population. Dose modifications occurred for 15 (4.8%) patients due to SAEs.

Risk of peripheral neuropathy increased with body mass index (BMI) (OR=1.067 [95% CI 1.023, 1.113] per unit; p=0.003); compared to patients with a normal BMI, overweight patients had an OR of 1.520 (95% CI 0.897, 2.577) and obese patients had an OR of 1.849 (95% CI 0.971, 3.523).

Discussion

These results are consistent with the known safety profile of brentuximab vedotin, with the frequency of AESIs generally lower than in previous monotherapy clinical trials. No new important risks were identified. Increased BMI was identified as a potential risk factor for the development of peripheral neuropathy. This final analysis supports the favourable safety profile in line with the established benefit/risk profile of brentuximab vedotin in patients with relapsed or refractory CD30+ HL and sALCL.

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2 LIST OF ABBREVIATIONS

ABVD	Adriamycin® (doxorubicin), bleomycin, vinblastine, dacarbazine
AE	adverse event
AESI	adverse event of special interest
ALCL	anaplastic large cell lymphoma
ALK	anaplastic lymphoma kinase
ASCT	autologous hematopoietic stem cell transplantation
AVD	Adriamycin® (doxorubicin), vinblastine, and dacarbazine
BEACOPP	bleomycin, etoposide, Adriamycin® (doxorubicin), cyclophosphamide, Oncovin® (vincristine), procarbazine, prednisone
BMI	body mass index
CHMP	committee for human use of medicinal products
CHOP	cyclophosphamide, hydroxydaunomycin (doxorubicin), Oncovin® (vincristine), prednisone
CI	confidence interval
CIPN	chemotherapy-induced peripheral neuropathy
CRO	contract research organisation
CRF	case report forms
eCRF	electronic case report form
CTCL	CD30+ cutaneous T-cell lymphoma
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EU PAS	European Union post-authorisation study
FPI	first patient in
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HL	Hodgkin lymphoma
ICE	ifosfamide, carboplatin, etoposide
ICF	informed consent form

IEC	independent ethics committee
IQR	interquartile range
ISPE	International Society for Pharmacoepidemiology
LDH	lactate dehydrogenase
LPI	last patient in
MAA	marketing authorisation application
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	monomethyl auristatin E
MOPP	mechlorethamine, Oncovin® (vincristine), procarbazine, prednisone
N	number of patients
NA	not applicable
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin lymphoma
OR	objective response
PASS	post-authorisation safety study
PFS	progression-free survival
PRAC	Pharmacovigilance Risk Assessment Committee
PT	preferred term
PV	pharmacovigilance
RMP	risk management plan
SAE	serious adverse event
sALCL	systemic anaplastic large cell lymphoma
SAP	statistical analysis plan
SCT	stem cell transplant
SD	standard deviation
SmPC	summary of product characteristics
SMQ	standardised MedDRA query
SOC	system organ class
UK	United Kingdom

3 INVESTIGATORS

The full list of Investigators and their contact information is listed in Annex 1 (Number 1) and can be provided upon request.

4 OTHER RESPONSIBLE PARTIES

This study was performed by IQVIA, a contract research organisation (CRO), with guidance, input, review, and approval of Takeda, the Marketing Authorisation Holder (MAH).

5 MILESTONES

The planned and actual dates for the milestones of this study are listed as below in Table 5-1, dates by country can be found in Annex 1 (Number 2 - 3).

Table 5-1 Study milestones

Milestone	Planned Date	Actual Date	Comments
First IEC approval	January 2013	10 January 2013	
Last IEC approval		24 July 2018	
Registration in the EU PAS register	Prior to start of data collection	1 March 2013	
First Patient Enrolled[1]	March 2013	26 June 2013	
Last Patient Enrolled[1]	July 2017	28 December 2017	
Last Patient Out[2]	January 2020	07 September 2018	See Section 8 (protocol amendment 4)
Interim Data Lock 1		09 September 2015	
Interim Report 1	April 2016	4 March 2016	
Interim Data Lock 2		17 February 2017	
Interim Report 2	April 2017	10 March 2017	
End of Data Collection[3]	January 2020	04 October 2018	See Section 8 (protocol amendment 4)
Final Report v1.0	December 2020	13 June 2019	
Final Report v2.0[4]		11 October 2019	See Section 10.4.2.1
Final Report v3.0[5]		27 November 2019	

Abbreviations: EU PAS= European Union post-authorisation study; IEC= independent ethics committee; NA: not applicable
[1] Date informed consent was signed (EOT Listing 1.2)
[2] Last patient was dosed on 07Sep2018 (EOT Listing 8)
[3] Following a 30-day safety period, the end of study/data collection was 04Oct2018
[4] Updated following additional SAE reconciliation, no impact on results
[5] Administrative update, no impact on results

6 RATIONALE AND BACKGROUND

6.1 Background

Relapsed and refractory CD30+ lymphomas, including the most common forms Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (sALCL), are rare conditions. Although both are potentially curable types of lymphoma when conventional chemotherapy regimens and radiation therapy are used, some patients are not cured with currently available first line treatment regimens and go on to require additional therapies.

Hodgkin Lymphoma

There is wide international variation for both males and females in the incidence of HL, with the highest rates in Southern Europe and North America. The annual age-adjusted incidence of HL in Europe in males and females is estimated at 2.1/100,000 per year. (1) In many parts of Asia and Africa, incidence rates for HL are 1 per 100,000 population, with the world average being around 1.2 per 100,000 for males and 0.8 per 100,000 for females. (2) HL occurs in patients in all age groups and presents as a bimodal distribution with peaks at 15 to 35 years of age and over the age of 60. (3) Classical HL is defined histopathologically by the presence of malignant CD30 positive Hodgkin and Reed-Sternberg cells in a background of inflammatory cells. First line treatment for HL is typically ABVD (Adriamycin® [doxorubicin], bleomycin, vinblastine, dacarbazine) or BEACOPP (bleomycin, etoposide, Adriamycin® [doxorubicin], cyclophosphamide, Oncovin® [vincristine], procarbazine, prednisone), but other older options (eg, MOPP [mechlorethamine, Oncovin® [vincristine], procarbazine, prednisone]) and alternating regimens may be used. (4) Approximately 10 to 20% of patients presenting with HL will be refractory to initial therapy or relapse. Salvage therapy after relapse varies widely. Autologous hematopoietic stem cell transplantation (ASCT) is a viable option for only some patients with recurrent or progressive HL after failure of initial combination chemotherapy (ie, typically ≤65 years, have a performance status of 0-2, a life expectancy of more than 12 weeks, an absence of major organ dysfunction not attributable to HL). ASCT is only effective in half of such patients. (5) Predictive factors of poor progression-free survival (PFS) in those patients receiving ASCT included chemo-resistant disease, B symptoms at pre-transplantation relapse, the presence of residual disease at the time of transplantation, time from initial diagnosis to relapse, and presence of extranodal disease at relapse. (5,6) Patients who subsequently relapse after stem cell transplant (SCT) have an extremely poor prognosis. (7)

Systemic Anaplastic Large Cell Lymphoma

Primary sALCL represents only 2-8% of adult non-Hodgkin lymphoma (NHL) cases and as many as 30% of childhood NHL cases (8); NHL occurs in approximately 27.6 (males) and 19.9 (females) per 100,000. (9) sALCL can occur at any age and incidence increases steadily with age. sALCL cases are further classified according to the expression (or not) of anaplastic lymphoma kinase (ALK) fusion proteins, with ALK- ALCL tending to be more aggressive and more likely to relapse than ALK+ ALCL. ALK- ALCL also tends to occur in older patients (peak incidence in the late 50s), whereas ALK+ ALCL tends to occur in younger patients

(children and young adults). (10,11) The malignant cells in all types of ALCL strongly express the CD30 antigen on cell membranes, and histologic review reveals the characteristic tumour cells. Histologically, sALCL is characterised most commonly by sheets of large pleomorphic cells, with abundant cytoplasm, horseshoe- or wreath-shaped nuclei, and multiple prominent nucleoli. These hallmark tumour cells may be multinucleated and can be similar to Reed-Sternberg cells in appearance. sALCL is aggressive but potentially curable with systemic combination chemotherapy. Many combination therapies exist and are tailored to the individual patient based on multiple factors including disease stage, age, co-morbidities, and prognostic factors. The standard first line treatment for sALCL is CHOP (cyclophosphamide, hydroxydaunomycin (doxorubicin), Oncovin® (vincristine), prednisone), or a similar combination regimen. Approximately 40% to 65% of patients with sALCL experience recurrent disease after frontline treatment. (12) For CD30+ HL and sALCL patients who subsequently relapse or have refractory disease and fail to respond to first- or second-line therapies, treatment options have typically included additional combination therapy, investigational agents, or SCT, although this is less common in sALCL.

Brentuximab Vedotin

Antibody-drug conjugates are designed to selectively deliver potent drugs to a specific target antigen, thereby limiting systemic exposure to the drug by altering biodistribution, resulting in an altered safety profile of the drug. (13) CD30, a member of the tumour necrosis factor superfamily discovered in the early 1980s, is now known to be expressed on the malignant cells in classical HL (Hodgkin and Reed-Sternberg cells) and sALCL, but in a limited fashion in normal tissue, making it an ideal immunotherapeutic target. (14) Brentuximab vedotin (ADCETRIS®, Takeda Pharmaceuticals International Co. and Seattle Genetics), is a novel antibody-drug conjugate composed of a CD30-directed monoclonal antibody (brentuximab, a recombinant chimeric immunoglobulin G1 [IgG1] that is an anti-CD30 antibody) that is covalently linked to vedotin (monomethyl auristatin E [MMAE]), a cytotoxic and potent antimicrotubule agent. MMAE is an antimitotic agent that is too potent to be used as a drug alone but has an acceptable safety profile when used as an antibody-drug conjugate.

Safety Profile of Brentuximab Vedotin

Brentuximab vedotin was originally approved by the European Medicines Agency (EMA) on 25 October 2012 and has received additional favourable opinions expanding the approved indications. The full indication includes the treatment of adult patients with relapsed or refractory CD30+ HL who have had ASCT or at least 2 previous therapies when ASCT or multi-agent chemotherapy is not a treatment option; adult patients with CD30+ HL at increased risk of relapse or progression following ASCT; adult patients with previously untreated CD30+ Stage IV HL in combination with doxorubicin, vinblastine, and dacarbazine (AVD); adult patients with relapsed or refractory sALCL; and adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy.

During the clinical development program, the safety (and efficacy) of brentuximab vedotin was evaluated in 2,632 patients (15,080 person-months) with relapsed or refractory CD30+ HL, sALCL, and other CD30+ haematologic malignancies (eg, CTCL). An estimated >20,000 additional patients have been treated with brentuximab vedotin post-marketing.

Clinical data were collected from phase 1 dosing studies (SG035-0001 and SG035-0002), a pivotal phase 2 study in relapsed or refractory HL after ASCT (SG035-0003), a pivotal phase 2 study in relapsed or refractory sALCL (SG035-0004), and phase 3 clinical trials (ECHELON-1; ECHELON-2; AETHERA; ALCANZA). Analyses of safety data indicate that brentuximab vedotin has a manageable and tolerable safety profile in the studied populations resulting in a conditional approval by the EMA. The currently known safety profile is described in the summary of product characteristics (SmPC) in Annex 1 (Number 4).

- SG035-0001 (NCT00430846) was a phase 1 dose finding study of 45 patients with CD30+ haematologic malignancies (42 with HL, 2 with sALCL, 1 with angioimmunoblastic T-cell lymphoma) treated with brentuximab vedotin at dose levels of 0.1 to 3.6 mg/kg administered intravenously every 3 weeks. (15)
- SG035-0002 (NCT00649584) was a phase 1 dose escalation study of 44 patients with CD30+ haematologic malignancies (38 with HL, 5 with sALCL, and 1 with peripheral T-cell lymphoma) treated with brentuximab vedotin at dose levels of 0.4 to 1.4 mg/kg administered intravenously weekly for 3 of 4 weeks. Although this weekly regimen was designed to enable combination use with gemcitabine, efficacy with brentuximab vedotin monotherapy was deemed sufficient and the planned brentuximab vedotin/gemcitabine combination was not pursued. (16)
- SG035-0003 (NCT00848926) was a phase 2, single-arm, open-label study in 102 patients with relapsed or refractory HL post-ASCT treated for a median duration of approximately 27 weeks and 9 cycles (range: 1-16 cycles), and SG035-0004 (NCT00866047) was a phase 2 trial in 58 patients with relapsed or refractory sALCL treated for a median duration of approximately 20 weeks and 7 cycles (range: 1-16 cycles). (17,18)
- ECHELON-1 was a randomised, open-label, phase 3 trial (NCT01712490), in which 1,334 patients with previously untreated stage III or IV classic HL were treated with either A+AVD (brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine) (N=664), or ABVD (Adriamycin® (doxorubicin), bleomycin, vinblastine, and dacarbazine) (N=670). (19)
- ECHELON-2 was a randomised, double-blind, double-dummy, placebo-controlled, active-comparator phase 3 study (NCT01777152) in 452 patients with CD30+ peripheral T-cell lymphoma assigned 1:1 to brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone (A+CHP) or cyclophosphamide, hydroxydaunomycin (doxorubicin), Oncovin® (vincristine), and prednisone (CHOP). (20)

- AETHERA was a randomised, double-blind, placebo-controlled, phase 3 trial (NCT01100502), in which 329 patients (165 patients received brentuximab vedotin) with unfavourable-risk relapsed or primary refractory classic HL who had undergone ASCT were randomly assigned to brentuximab vedotin 1.8 mg/kg every 3 weeks (N=165), or placebo. (5) For patients in the brentuximab vedotin arm, the median duration of treatment was 48 weeks and number of cycles was 15 (range: 1-16 cycles).
- ALCANZA was a randomised, open-label, phase 3 trial (NCT01578499), in which 131 adult patients with CD30-positive mycosis fungoides or primary cutaneous ALCL, who had been previously treated, were randomly assigned to brentuximab vedotin monotherapy or physician's choice (oral methotrexate or oral bexarotene). (21)

Peripheral Neuropathy

Lymphomas can affect the peripheral nervous system and result in peripheral neuropathies in 5-8% of patients with lymphoma, (22) and peripheral nerve complications are most often reported in patients with NHL but are not commonly reported in patients with HL. (23) The causes of peripheral neuropathy in lymphoma patients may include lymphoma directly infiltrating nerves, metabolic and infectious processes, and as a side effect of treatments (eg, chemotherapy-induced, radiation therapy, stem cell transplantation). (24)

Chemotherapy-induced peripheral neuropathy (CIPN) is a common adverse effect associated with several chemotherapeutic agents and is often dose-dependent and progressive. Syndromes of CIPN include numbness of distal extremities, long-term touch, heat and cold dysesthesia, and in more severe cases, motor impairment that affect daily functioning. (25) The causes of CIPN are poorly understood and appear to be medication specific, it can have long-term effects, and may not be completely reversible. (26,27) Even following removal of the active substance, peripheral neuropathy can continue to develop. (25) There are six main chemotherapy groups that are known to be associated with CIPN: platinum-based antineoplastic (particularly oxaliplatin and cisplatin), the vinca alkaloids (particularly vincristine and vinblastine), the epothilones (ixabepilone), the taxanes (paclitaxel, docetaxel), the proteasome inhibitors (bortezomib) and immunomodulatory drugs (thalidomide, lenalidomide). (28)

A recent systematic review and meta-analysis aimed to determine the prevalence of CIPN. In 4,179 cancer patients from 31 studies, the prevalence of CIPN following the end of chemotherapy treatment was 68.1% within the first month, 60.0% at 3 months, and 30.0% at 6 months or later. When stratified by chemotherapy drug, the prevalence of CIPN was 96.2% in bortezomib and thalidomide therapy, 73.0% in cisplatin or carboplatin and paclitaxel therapy, 72.3% in oxaliplatin therapy, 70.8% in paclitaxel therapy, 63.5% in thalidomide therapy, 46.7% in bortezomib therapy, 42.2% in cisplatin therapy, 20.1% in cisplatin and vincristine therapy, and 19.6% in vincristine therapy. (29) A subset of studies (4 studies, 701 patients) also reported clinical risk factors for CIPN, these included baseline neuropathy, history of smoking, decreased creatinine clearance, and specific sensory changes (cold allodynia and cold hyperalgesia) during chemotherapy treatment. (28)

The epidemiology of CIPN is poorly understood, and incidence and prevalence rates thought to be under-reported. The development of CIPN may lead to chemotherapy dose reductions or changes in chemotherapy protocols, and negatively impact patient outcomes through dose reductions and discontinuations or quality of life. (26)

6.2 **Rationale**

This study was required by the EMA in order to better understand the safety profile of brentuximab vedotin in a real-world population (EMA Category 2). In addition to serious adverse events (SAEs), the following protocol-specified serious and non-serious adverse events of special interest (AESI) were specifically evaluated as part of the post-authorisation safety study (PASS): peripheral neuropathy, neutropenia (including febrile neutropenia), infections (including opportunistic infections), hyperglycaemia, and hypersensitivity reactions (including infusion-related reactions and allergic reactions). These events were selected by the EMA on the basis of safety findings in the pivotal phase 2 studies, and the available safety profile from 357 patients exposed to brentuximab vedotin at the time of the initial marketing authorisation application (MAA).

This PASS was a prospective, observational cohort study including patients prescribed brentuximab vedotin as part of routine clinical care and followed for up to 5 years for the occurrence of selected safety events. The safety profile of brentuximab vedotin was evaluated in the overall patient population, and to the extent possible in sub-populations under-represented in clinical trials, such as elderly patients (ie, ≥ 65 years) and patients with long-term exposure (ie, > 16 cycles).

This is the final study report for the PASS MA25101 (inclusive of full enrolment and all the lost to follow-up): An Observational Cohort Study of the Safety of Brentuximab Vedotin in the Treatment of Relapsed or Refractory CD30+ Hodgkin Lymphoma and Relapsed or Refractory Systemic Anaplastic Large Cell Lymphoma (ARROVEN), as specified in Art 36 to 38 and Art 40 of the Commission Implementing Regulation (EU) No 520/2012.

7 RESEARCH QUESTION AND OBJECTIVES

The objectives of the study were to:

- Evaluate the occurrence of SAEs and specified AESI, both serious and non-serious, in patients actively treated for relapsed or refractory CD30+ HL or relapsed or refractory sALCL in routine practice with brentuximab vedotin; and
- Identify and describe potential risk factors for peripheral neuropathy in relapsed or refractory CD30+ HL or relapsed or refractory sALCL patients treated with brentuximab vedotin.

8 AMENDMENTS AND UPDATES

The study protocol was amended 4 times (see Annex 1 Number 5 - 9). This report describes the study conduct as amended.

The original protocol (version 1.1, dated 14 June 2012) was submitted to the EMA (15 June 2012), and received agreement from the Committee for Human Use of Medicinal Products (CHMP) Pharmacovigilance Risk Assessment Committee (PRAC) during the initial assessment before MAA opinion.

Protocol amendment 1 (protocol version 2.0, dated 05 December 2013) was submitted to the PRAC for review. It was intended for review due to changes in the study design (addition of the retrospective cohort) and was never distributed to sites and no patients were enrolled under Amendment 1.

Protocol amendment 2 (protocol version 3.0, dated 11 March 2014) was prepared based on PRAC feedback provided for Amendment 1 (protocol version 2.0). This version was distributed to sites and used for patient enrolment.

Protocol amendment 3 (protocol version 4.0, dated 7 June 2016) was developed for sample size adjustment. It was intended for review due to changes in the study design (change in sample size) and never distributed to sites and no patients were enrolled under Amendment 3.

Protocol amendment 4 (protocol version 5.0, dated 27 January 2017) was developed to address PRAC comments on Amendment 3 (protocol version 4.0), which included a second interim analysis to be performed after enrolment of at least 200 patients.

Substantial changes of each amendment are described below in Table 8-1.

Table 8-1 Summary of Protocol Amendments

Number	Date	Section of Study Protocol	Amendment or Update	Reason
Amendment 1 (version 2.0)	05 December 2013	Synopsis, 2 (Rationale), 4.1 (Study Description), 4.2 (Study Population), 4.2.3 (Study Enrolment), 4.3 (Exposure Definition and Measures), Table 1	Inclusion of patients already treated with brentuximab vedotin at time of enrolment	Increase enrolment
		Section 4.5.3 (Follow-up)	Instructions provided for recording and reporting changes in intensity for peripheral neuropathy	Improve ability to characterise the resolution of peripheral neuropathy
		Synopsis, 5.2.1 (General Considerations), 5.2.2 (Planned analyses)	Differentiation between retrospective and prospective patient data in analyses	Ensure appropriate evaluation of safety data collected
		Synopsis, Section 7.2 (Procedures for Recording and Reporting), Table 1, Table 2	Adjustment of non-serious events to be recorded and reported	Consistent with GVP requirements
		Section 7.2.2 (Events to be reported to Takeda PV & RM)	Notification to sites that Takeda PV & RM will follow-up on SAEs until resolution, according to standard procedures	Clarify expectations for sites in terms of follow-up of reported SAEs
		All sections	Minor wording and administrative changes	Improve clarity
Amendment 2 (version 3.0)	11 March 2014	Section 4.5.1, Table 1 and text	Add expected frequency of visits. Minor wording and clarifications, including additional footnotes	Address PRAC's concerns Clarify data collection for sites
		Synopsis, Section 5.1	Add percentage of retrospective patients and other clarifications	Address PRAC's request
		Section 4.1	Added sentence on the retrospective patients	Improve clarity
		Section 4.2.3	Added recording of reason for not enrolling for retrospective patients	Address PRAC's concern with the retrospective patients

		Section 5.2.1	Add analyses to address differences between prospective and retrospective patients	Address PRAC's concern about evaluating the difference between the 2 cohorts
		All sections	Change the CRO name, Quintiles Outcome to Quintiles	Company name changed
		All sections	Clarify that the AESI include both serious and non-serious	PRAC request
Amendment 3 (version 4.0)	07 June 2016	Section 5.1	Decrease the sample size and increase the proportion of patients enrolled retrospectively	Sample size adjustment based on clinical relevance estimated from clinical study data and the results of the interim analysis
Amendment 4 (version 5.0)	27 January 2017	Study Synopsis	Added second interim analysis	As requested by EMA, amendment 4 adds a second interim analysis that will be performed after enrolment of at least 200 patients
		Study Milestones	Added a row for the second interim analysis	
		Section 5.3.2	Added second interim analysis	

CRO= contract research organisation; EMA= European Medicines Agency; GVP= good pharmacovigilance practices; PRAC= pharmacovigilance risk assessment committee; PV= pharmacovigilance; RM= risk management; SAE= serious adverse event

9 RESEARCH METHODS

9.1 Study Design

This was a multi-centre, international, prospective, observational cohort study of patients who had been diagnosed with relapsed or refractory CD30+ HL, or relapsed or refractory sALCL, and were treated with brentuximab vedotin monotherapy as part of routine clinical care. Patients were enrolled in the prospective cohort if they initiated the current regimen of monotherapy treatment with brentuximab vedotin following enrolment, or in the retrospective cohort if they had initiated the current regimen prior to enrolment and were currently on monotherapy with brentuximab vedotin at enrolment. All patients were then followed up prospectively until study discontinuation or end of study.

The study targeted to enrol approximately 300 patients (at least 50 of whom had a diagnosis of sALCL). It was assumed that up to 50% of the study population would be retrospectively enrolled (following changes applied in protocol amendment 3). No study specific visits or procedures were required as part of patient participation in the study. Patients were evaluated according to the physician's standard practice and discretion. No study medication was provided as part of this study. There were also no restrictions on concomitant treatments. However, all previous treatments, concomitant treatments and medications, and subsequent treatments for lymphoma during follow-up, were carefully recorded in order to evaluate their potential influence on the outcomes of interest.

Based on the results of the interim report (dated 4 March 2016) including data from 108 patients (78 with CD 30+ HL and 30 with CD30+ sALCL), amendment 3 was prepared to reduce the sample size from 500 to 300 patients and to increase the proportion of retrospective patients from 15-20% to 50%. Calculations showed that a population of 300 patients was large enough to detect the protocol-specified AESI at least as frequently as the observed incidence in the pivotal phase 2 trials. The study also had an unanticipated low recruitment rate and slower-than-expected opening of clinical sites. The proportion of retrospective patients enrolled was increased to improve study enrolment and promote unbiased enrolment at new sites. Interim results showed that the reported incidence of AEs and protocol-specified AESIs was similar between the prospective and retrospective cohorts.

The primary outcomes were safety events. The frequency, severity, and relationship to treatment were evaluated for all reported SAEs and protocol-specified AESIs. All dose modifications and discontinuations and reported reason for change(s) were also summarised. These outcomes were further evaluated within the elderly sub-population (age at enrolment ≥65 years), and patients treated with brentuximab vedotin for >16 cycles. However, there were only 76 patients ≥65 years and only 9 patients who received >16 cycles of brentuximab vedotin, limiting interpretation in these populations. Additional sub-populations also included evaluations by sex, lymphoma type (CD30+ HL or sALCL), ALK positivity, and post-ASCT status. The sample size for this study was based on the request for more information regarding the occurrence of protocol-specified

AESIs. With 300 patients, AEs occurring in 3% of the population (9 patients) would have a 95% CI of (1.4%, 5.6%).

9.2 Setting

Oncologists and haematologists routinely involved in the care and treatment of patients with relapsed or refractory CD30+ HL and sALCL were targeted for recruitment. Selection criteria and basic site information (eg, practice size, Investigator specialty, site type) were collected via a site qualification survey. The study planned an enrolment period of approximately 52 months (4 years, 4 months), which was estimated from the original recruitment target of 500 patients (subsequently reduced to 300 patients in protocol amendment 3), with an overall duration of approximately 76 months (6 years, 4 months) from the date of first patient enrolled. Patients had on-treatment follow-up (from enrolment through 30 days after the last dose of brentuximab vedotin), and post-treatment follow-up (31 days after the last dose of brentuximab vedotin and/or end of study).

The study enrolled 311 patients (of whom 310 received brentuximab vedotin and were included in the safety analyses) from 80 sites (of 100 sites opened for enrolment) in 13 countries that treated patients with relapsed or refractory CD30+ HL or sALCL, including Austria (N=11), Denmark (N=13), France (N=12), Germany (N=20), Greece (N=17), Ireland (N=15), Italy (N=46), Netherlands (N=19), Slovakia (N=8), Spain (N=41), Sweden (N=15), Switzerland (N=4), and the United Kingdom (UK) (N=90). Country and site selection were dependent on the timing of commercial availability of brentuximab vedotin, reimbursement status, and physician product adoption rates in the selected countries to ensure that an adequate number of patients treated with brentuximab vedotin were available for enrolment into the study. Enrolment was completed within 54 months, with the first patient in (FPI) on 26 June 2013 and the last patient in (LPI) on 28 December 2017 (date informed consent was signed).

9.3 Subjects

All patients presenting at a routine clinical visit during the enrolment period were assessed for eligibility; those that were considered eligible were invited to provide informed consent to participate in the study. The eligibility criteria were:

9.3.1 Inclusion Criteria

To be eligible for enrolment, patients must have met ALL of the following criteria:

- Age at enrolment ≥ 18 years
- Clinical diagnosis (with histologic confirmation) of relapsed or refractory CD30+ HL or relapsed or refractory sALCL

- Patient planned to start or was already receiving single-agent therapy with brentuximab vedotin as part of routine clinical care
- Willing and able to provide informed consent

9.3.2 Exclusion Criteria

Patients met ANY of the following criteria were not eligible for participation:

- Concurrent participation in an interventional clinical study
- Patients with primary cutaneous ALCL, unless the disease has transformed to systemic ALCL

9.3.3 Study Enrolment

The study enrolled 311 patients with relapsed or refractory CD30+ HL or sALCL (of whom 58 had a diagnosis of sALCL), from a total of 80 active sites specialising in oncology or haemato-oncology in 13 countries, during the 54-month (4 years, 6 months) enrolment period of the study.

Screening logs were maintained by each site to record the disposition of patients potentially eligible for study participation. In order to better assess the representativeness of the sampled population, minimal and non-identifiable information were recorded for all patients who were screened for study enrolment. To formally address the potential for selection bias for the retrospective patients, the reasons were collected, if possible, for each patient who received brentuximab vedotin but was not enrolled.

Patients may have withdrawn consent and discontinued participation in the study at any time, with no effect on their medical care or access to treatment. If a patient withdrew consent prior to completing the study, any known reason for withdrawal was documented in the database. All information already collected as part of the study was retained for analysis; however, no further efforts were made to obtain or record additional information regarding the patient. If the last assessment was more than 3 months prior to withdrawal from study and patient status had not been documented, a final assessment of treatment status and any AEs were recorded at the time of withdrawal from the study.

9.4 Variables

9.4.1 Exposure Definition and Measures

This observational study was intended to evaluate the use of brentuximab vedotin monotherapy and excluded patients on concomitant chemotherapeutic agents at enrolment. However, patients were treated in a real-world setting and concomitant use of other chemotherapeutic agents occurred during follow-up and was recorded. The following variables related to on-study

brentuximab vedotin exposure were collected (including use prior to enrolment for the retrospective cohort):

- Duration and number cycles of brentuximab vedotin treatment
- Brentuximab vedotin dose modification(s)
- Reasons for brentuximab vedotin treatment changes

9.4.2 Outcome Definition and Measures

9.4.2.1 Effectiveness Measures

The objective of this PASS was to evaluate safety; therefore, no measures or analyses regarding treatment effectiveness were included in the study.

9.4.2.2 Safety Measures: Serious Adverse Events and Adverse Events of Special Interest

The frequency, intensity, and relationship to treatment were collected for all reported SAEs, and for the following treatment-emergent, protocol-specified AESI, both serious and non-serious:

- Peripheral neuropathy (sensory, motor, or other)
- Neutropenia (including febrile neutropenia)
- Infections (including opportunistic infections)
- Hyperglycaemia
- Hypersensitivity reactions (including infusion-related reactions and allergic reactions)

During on-treatment follow-up, all SAEs and AESIs were recorded, during post-treatment follow-up only SAEs and AESI considered related to brentuximab vedotin were recorded. For retrospectively enrolled patients, all SAEs and AESI identified in the medical record which occurred prior to study enrolment but after initiating the current regimen of brentuximab vedotin were collected. Documentation regarding an SAE or AESI, observed by the Investigator or reported by the patient upon indirect questioning, were made as to the nature, date of onset, end date, severity, relationship to brentuximab vedotin, action(s) taken, and outcome. If any of the same SAE or AESI, occur on several occasions in the same patient, then the event in question was documented and assessed each time.

See Protocol (Amendment 4, dated 27 January 2017) Section 7 for procedures for reporting SAEs and AESI.

Definition of SAEs and AESIs

Adverse events (AEs)

An AE is any untoward medical occurrence in a patient or subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory

finding, for example), symptom, or disease temporally associated with the use of a product, whether or not considered related to the product. Pre-existing conditions that worsen during a study are considered AEs.

If, according to the Investigator, there is a worsening of a medical condition that was present prior to the administration of brentuximab vedotin, this should also be considered a new AE and collected in the eCRF if it meets the definitions of an SAE or AESI described below. Any medical condition present prior to the administration of brentuximab vedotin that remains unchanged or improved is not an AE.

An abnormal laboratory value should not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the Investigator to be a clinically significant change from baseline. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

Serious adverse events (SAEs)

Serious AE (SAE) means any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalisation or prolongation of an existing hospitalisation (planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the study are not to be considered AEs unless the condition deteriorated in an unexpected manner during the study).
- Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is a medically important event. This refers to an AE that may not result in death, be immediately life-threatening, or require hospitalisation, but may be considered serious when, based on appropriate medical judgment, may jeopardise the patient, require medical or surgical intervention to prevent one of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalisation, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

Adverse events of special interest (AESI)

For the purpose of this study, the following treatment-emergent AEs* were defined as AESI, regardless of their seriousness, intensity, or relationship to treatment:

- Peripheral neuropathy (sensory, motor and other)
- Neutropenia (including febrile neutropenia)
- Infections (including opportunistic infections)
- Hyperglycaemia
- Hypersensitivity reactions (including infusion-related reactions and allergic reactions)

* Treatment-emergent AEs are defined as those AEs that start or worsen on or after the first dose of brentuximab vedotin and within 30 days after the last dose of brentuximab vedotin.

Event intensity

Intensity for each AE, including any laboratory abnormality, were determined using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) (Version 4.03 effective date 14 June 2010, or higher). Clarification was made between an SAE and an AE that was considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term severe was often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This was NOT the same as serious, which was based on patient/event outcome or action criteria described above and were usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) did not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

Relationship to treatment

Relationship to treatment was determined by the Investigator responding yes or no to this question: Is there a reasonable possibility that the event is associated with brentuximab vedotin?

9.4.2.3 Risk Factors for Peripheral Neuropathy

A second objective of the study was to identify and describe potential risk factors for the occurrence of new onset or worsening of peripheral neuropathy during treatment with brentuximab vedotin. The following potential risk factors were chosen based on clinical relevance:

- Age (< 65 years and ≥ 65 years)
- Sex (male and female)
- Body mass index (BMI)
- Disease type (CD30+HL and sALCL)
- Disease stage at baseline (stage I, II, III, IV, and not defined [unknown])
- Extranodal involvement at baseline (yes, no, and unknown)

- Neuropathy at baseline (yes, no, and other)
- Previous history of peripheral neuropathy (yes and no)
- Most recent chemotherapy exposure
- Number of cycles from prior lines of therapy at baseline
- Diabetes mellitus at baseline (yes and no)
- Impaired renal function at baseline (yes and no)
- Thyroid dysfunction at baseline (yes and no)

Note: baseline refers to data collected in the baseline/enrolment form; refer to Section 9.5.1 for further details.

9.5 **Data Sources and Measurement**

Essential data for the study are presented in the schedule of recommended recording of essential data provided in Table 9-1. For eligible patients who provided informed consent, data elements were abstracted from information routinely recorded in the medical record and entered directly into the electronic data capture (EDC) system by the Investigators. Follow-up data were collected in conjunction with all routine care visits, typically occurring approximately every 3 months. No study visits or examinations, laboratory tests or procedures were mandated as part of this study.

Table 9-1 Schedule of recommended recording of essential data

	Enrolment[1]	**On-Treatment Follow-up**[2]	**Post-Treatment Follow-up**[3] (or study discontinuation)
Informed consent	X		
Demography	X		
Patient height & weight	X	X (weight only)	
ECOG Performance Status	X	X	
Relevant medical history & co-morbidities	X	X	
Laboratory test results (if performed as part of routine care)	X	X	
Relapsed or refractory CD30+ HL or sALCL disease and treatment history	X	X	
Brentuximab vedotin treatment details	X	X	
Concomitant medications	X	X	
Changes in treatment, including dose modifications		X	
Survival status			X
All SAEs and AESIs	X	X	
Only SAEs and AESIs considered related to brentuximab vedotin			X
Date and reason for discontinuation (if applicable)		X	X

Abbreviations: AESI= adverse event of special interest; sALCL= anaplastic large cell lymphoma (systemic); ECOG= Eastern Cooperative Oncology Group; eCRF= electronic case report form; HL= Hodgkin lymphoma; SAE= serious adverse event

[1] Exposure to brentuximab vedotin might have started prior to enrolment. All brentuximab vedotin treatment and concomitant medication exposures, SAEs/AESIs and relevant medical history since starting the current brentuximab vedotin regimen were recorded at the time of enrolment.

[2] The on-treatment follow-up period was defined as beginning at the time of enrolment and continuing through 30 days after the last dose of brentuximab vedotin.

[3] The post-treatment follow-up period was defined as beginning 31 days after the last dose of brentuximab vedotin and continuing until study discontinuation or end of study.

9.5.1 Enrolment/Baseline

The baseline/enrolment visit occurred on or after the date of informed consent. For the prospective cohort, this visit referred to the visit at which the patient received their first dose of brentuximab vedotin. For the retrospective cohort, this visit referred to the first routine visit following (or at the time of) informed consent.

The following data were recorded, where available, at baseline/enrolment for all enrolled patients.

- Demographics (date of birth, sex, race/ethnicity [where allowed by local regulations])
- Weight, height (calculated BMI)
- Eastern Cooperative Oncology Group (ECOG) performance status (if done)
- Relevant medical history and co-morbidities (diagnosed prior to initiating treatment with brentuximab vedotin): including cardiovascular (eg, congestive heart failure, rhythm abnormalities), diabetes, pulmonary (eg, chronic obstructive pulmonary disease), hepatic, renal, other malignancies, neurologic (eg, neuropathies), autoimmune disease, infectious disease (eg, Human Immunodeficiency virus, Epstein Barr virus), abnormal blood counts (cytopenias and growth factor exposure), thyroid dysfunction
- Relevant laboratory testing (eg, haematology, lactate dehydrogenase [LDH], CD30 expression %), if performed as part of routine care
- CD30+ HL or sALCL disease and treatment history
    - Disease type (CD30+ HL or sALCL)
    - HL subtype: nodular sclerosing, mixed cellularity, lymphocyte-rich, lymphocyte depleted, unspecified/unknown
    - ALK status (positive, negative, unknown) (sALCL patients only)
    - ALCL variant: common, small cell, lymphohistiocytic, sarcomatoid, other, unknown (sALCL patients only)
    - Date of initial diagnosis
    - Disease stage (at initiation of treatment with brentuximab vedotin)
    - Presence of lymphoma-related symptoms (B symptoms) (at initiation of treatment with brentuximab vedotin)
    - Evidence of bone marrow involvement (at initiation of treatment with brentuximab vedotin)
    - Evidence of extranodal involvement (at initiation of treatment with brentuximab vedotin)
    - History of bone marrow involvement
- Previous treatment (that ended prior to initiation of treatment with brentuximab vedotin)
    - Previous lines of therapy, number of cycles, start/end dates
    - Autologous SCT or allogenic SCT
    - Radiation therapy (prior and ongoing)
- Concomitant medications
- Brentuximab vedotin treatment prior to baseline/enrolment, including dose and treatment date for current regimen and any changes in treatment dose prior to enrolment
- Occurrence of SAEs and both serious and non-serious protocol-specified AESIs (per Section 9.4.2.1) prior to baseline/enrolment and since the start of the current treatment regimen of brentuximab vedotin

9.5.2 On-Treatment Follow-up

The following data were recorded, where available, at each on-treatment follow-up visit (enrolment through 30 days after the last dose of brentuximab vedotin).

- Visit date
- Current weight (calculated BMI)
- ECOG (if done)
- Additional treatments
    - Any newly initiated lines of therapy
    - Autologous SCT or allogenic SCT (enrolling sites will be expected to continue to provide follow-up data in the event the patient temporarily transfers to another healthcare provider for the purpose of autologous or allogeneic SCT)
    - Radiation therapy
- New onset co-morbidities and updated medical history, including development of secondary malignancies, risk factors for neuropathy and status of neuropathy if ongoing at end of treatment with brentuximab vedotin
- Updated brentuximab vedotin treatment status, including dose changes/discontinuations, change type, date (or duration) of change and reason for change
- Concomitant medications
- Relevant laboratory testing
- Occurrence of SAEs and both serious and non-serious protocol-specified AESIs (per Section 9.4.2.1), since last follow-up

9.5.3 Post-Treatment Follow-up

The following data were recorded, where available, during the post-treatment follow-up period (31 days after the last dose of brentuximab vedotin until study discontinuation).

- SAEs considered related to brentuximab vedotin
- AESIs, both serious and non-serious, considered related to brentuximab vedotin

9.5.4 Study Discontinuation

Patients were expected to remain on follow-up until the end of the study, continuing after completion of treatment with brentuximab vedotin. Reasons for early discontinuation are detailed in Section 10.1.3.

The following data were recorded, where available, at the time of discontinuing the study.

- Date of discontinuation
- Reason for discontinuation
- Updated assessments as outlined in Table 9-1, which depend on whether the patient is in the On-Treatment Follow-up or Post-Treatment Follow-up period
- Survival status, including date and cause of death (if applicable)

9.6 Bias

While clinical trials provide crucial information regarding the efficacy and safety of a drug, observational data can extend and augment what is known, including identifying potential safety issues for special populations of patients (eg, the elderly, high risk patients) who are unlikely to be adequately represented in clinical trials. However, it should be noted that there are some well-known limitations associated with observational study designs, such as this study.

Selection bias may arise if the study sample differs substantively from the underlying target population of patients with relapsed or refractory CD30+ HL or sALCL receiving brentuximab vedotin monotherapy. To minimise this source of bias, eligibility criteria were designed not to be restrictive, and it was expected that most patients indicated for treatment according to the product labelling were eligible for enrolment in the study. Eligible patients who planned to start treatment (prospectively) or had already started treatment (retrospectively) with brentuximab vedotin monotherapy as part of routine clinical care were enrolled. Sites were requested to maintain a screening log for non-enrolled patients newly prescribed brentuximab vedotin, which collected a limited amount of data (eg, age, lymphoma type, disease stage). This was used to provide a basic comparison of the enrolled and non-enrolled patients to have an idea about the generalisability of the results, this is described in Section 10.1.2. The screening log also collected the reasons for non-enrolment, which are summarised in Section 10.1.3. The only difference observed between the enrolled and non-enrolled populations based on the screening logs is that there were fewer elderly (≥65 years) patients enrolled.

Another potential source of selection bias was the exclusion of patients receiving a concomitant chemotherapeutic treatment at enrolment. Inclusion criterion 3 was differentially applied to the prospective and retrospective cohorts: 'Patient planned to start or was already receiving single-agent therapy with brentuximab vedotin as part of routine clinical care'. For the prospective cohort, this applied to the treatment received during cycle 1, whereas for the retrospective cohort this applied to the patients' current treatment cycle at the time of enrolment. This could introduce a bias as retrospective patients may have been more likely to be excluded due to combination therapy, and coincidentally prospective patients may have been more likely to be treated with another chemotherapeutic agent. The choice of additional chemotherapeutic treatments was decided following standard of care and may have been influenced by disease prognosis, response to previous treatments (including AEs), and response to current treatment. The use of concomitant chemotherapeutic treatment during follow-up was similar between the cohorts (prospective: 32.1% vs. retrospective: 27.9%), as described in Section 10.2.4.1.

The inclusion of a retrospective cohort presents potential for survival bias in this cohort. Patients who had already begun treatment with brentuximab vedotin and had early events leading to treatment discontinuation were less likely to be represented in this cohort. This could lead to reduced reporting of acute events that happened early in treatment, and inclusion of patients who had already undergone dose modifications. This is more likely to affect reporting of SAEs, but possibly less so for reporting of peripheral neuropathy since CIPN is often dose-dependent and shows a cumulative effect. This can be evaluated by comparing the occurrence of events, and

comparing the doses, between the prospective and retrospective cohorts. This was observed: the retrospective cohort received a higher median number of treatment cycles than the prospective cohort (7.5 cycles vs. 5.0 cycles, respectively).

Notably, patients in the retrospective cohort also contributed real-time safety data upon enrolment, and due to the nature of the collected safety data (SAEs and specified AESIs) the recall and reporting of pre-enrolment events are likely reliable. At the time of the interim report (dated 04Mar2016), retrospectively enrolled patients had a relatively low number of cycles with brentuximab vedotin, and similar reporting of AEs between the prospective and retrospective cohorts. The EMA approved increasing the number of patients in the retrospective cohort to up to 50% of the total number of patients enrolled in this study in view of the consistent safety profile observed at the interim analysis (Procedure no.: EMEA/H/C/PSA/0009.1). Likewise, in the final analysis, on average the period between initiation of treatment and enrolment in the study was approximately 2.4 months in the retrospective cohort.

Information bias (ie, bias related to how the data of interest are collected) is a common concern in observational studies because no data collection is mandated and is based on local standard of care. To minimise information bias, clear definitions of variables of interest were provided to ensure accurate assessment of the desired data elements and detailed eCRF completion guidelines were provided to the site staff to ensure accurate entry of data into the EDC (see Section 9.10). The eCRFs included programmable edits to identify missing, out of range, illogical, or potentially erroneous data. All eCRFs were completed by trained site personnel. In addition, routine monitoring was conducted to ensure the quality of the data collected.

Another form of information bias is missing data bias, in particular when data are missing not at random. In this study, it is possible that certain data elements were more likely to be collected in patients with certain profiles or responses to treatment. Due to the nature of observational studies, this can only be reported and taken into consideration in the interpretation of results.

The risk of developing some of the AESIs for this study, such as peripheral neuropathy, may be substantially affected by previous treatment regimens. The ability to assess the potential for confounding by previous exposures was inherently limited by the completeness of the retrospective data available regarding lines of therapy. Similarly, the ability to evaluate potential risk factors for peripheral neuropathy was limited by the availability of relevant medical history and exposure data across all patients. In general, information bias might be introduced since the quality of data from the retrospective cohort could be missing or not as robust compared to the prospective cohort.

The ability to meaningfully assess the safety of brentuximab vedotin in subgroups of interest, including the elderly and patients treated with more than 16 cycles of brentuximab vedotin, could be limited by the actual patterns of use of brentuximab vedotin in routine clinical care. Importantly, there were few patients in either of these categories which limits interpretation for these patients. Additionally, the patterns of disease (eg, more aggressive ALK- sALCL is more common in older patients), and differences in treatments (eg, ASCT less likely in patients >65yr)

could lead to confounding of the reporting of results by age group. Though the primary endpoints in this study are descriptive, differences in sub-populations were also described.

Finally, follow-up bias may occur when differences exist between study participants and patients lost to follow-up or discontinued. This study was managed to minimise patient loss to follow-up (eg, through careful procedures for following patients) and only 12 patients were reported as lost to follow-up. There were a number of discontinuations, which were well documented and were not unexpected given the nature of this patient population.

9.7 Study Size

The sample size for this study was chosen to allow for better evaluation of both serious and non-serious protocol-defined AESIs. Evaluation of the sample size was performed based on the expected rate of AESIs in patients with relapsed or refractory CD30+ HL or relapsed or refractory sALCL treated with brentuximab vedotin to ensure sufficient enrolment in the study.

Table 9-2 shows the estimated 95% CIs for given frequencies of AESIs from a study population of 300 patients which was calculated using the exact method to the binomial distribution. The targeted sample size of 300 (at least 50 of whom had a diagnosis of sALCL), provided an adequate level of precision to achieve the objectives of this study related to AESIs, through estimation of the proportion of patients with each individual AESIs. The actual enrolment of 311 patients (58 with a diagnosis of sALCL) meets this aim, of whom 49.7% were retrospectively enrolled (37.9% of sALCL patients were retrospectively enrolled).

Table 9-2. Incidence proportion and 95% confidence intervals for AESIs with a population size of 300

Proportion	Number of Events	95% Confidence Interval
0.00	0	(0.0%, 1.2%)
0.01	3	(0.2%, 2.9%)
0.02	6	(0.7%, 4.3%)
0.03	9	(1.4%, 5.6%)
0.04	12	(2.1%, 6.9%)
0.05	15	(2.8%, 8.1%)

9.8 Data Transformation

All SAEs and AESIs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 18.0 (for interim analysis) and version 20.0 (for final analysis) system organ class (SOC) and preferred term (PT), unless stated otherwise. The severity of AEs was graded according to NCI CTCAE v4.03. AESIs were summarised by AESIs type. All SAEs and AESIs were described in all enrolled patients who have taken at least one dose of brentuximab vedotin.

The frequency of SAEs and AESIs were also presented for the following subgroups:

- Age group (< 65 years and ≥ 65 years)
- Sex (male and female)
- CD30+ lymphoma type (HL and sALCL)
- ALK positivity (sALCL patients only)
- Long-term treatment (> 16 cycles and ≤ 16 cycles)
- Post-ASCT status (yes and no)

Incidence rates for SAEs and AESIs were reported for all the enrolled patients, which were calculated as follows:

- Incidence density rate = Number of patients who experienced a given SAE or AESI during at-risk period/ Person-years of follow-up during at-risk period
- Time at risk (in years)
    1. Patients with SAEs/AESIs: (min [(date of last dose+ 30), or onset date of first SAEs/AESIs, or date of death, or study discontinuation date, or data cut-off date for final analysis]) – date of first dose of brentuximab vedotin + 1, divided by 365.25
    2. Patients without SAEs/AESIs: (min [(date of last dose+ 30), or date of death, or study discontinuation date, or data cut-off date for final analysis]) – date of first dose of brentuximab vedotin + 1, divided by 365.25

Data transformations, calculations, and operations on the data are fully described in the statistical analysis plan (SAP) (see Annex 1 Number 10 - 11).

Peripheral neuropathy used a standardised MedDRA query (SMQ) to include PT terms: neuropathy peripheral, peripheral sensory neuropathy, peripheral motor neuropathy, peripheral sensorimotor neuropathy, polyneuropathy, myopathy, dysaesthesia, hypoaesthesia, paraesthesia, limb discomfort, pain in extremity, pruritus.

9.9 Statistical Methods

9.9.1 Main Summary Measures

All computations and generation of tables, listings and figures were performed using SAS® version 9.2 or higher (SAS Institute, Cary, NC, USA). No formal hypothesis or statistical significance testing was planned. This approach follows the Guidelines for Good Pharmacoepidemiology Practices, Section D, point 10.

Descriptive analyses were performed to gain an understanding of the qualitative and quantitative nature of the data collected and the characteristics of the sample studied. Descriptive statistics were reported for all measured variables captured in this study, either through the reporting of descriptive statistics or listing of outputs or a combination of both. Summary statistics for continuous variables included mean, median, standard deviation, 95% CI when appropriate, and range. Categorical variables were presented as counts, proportions, percentages, and 95% CI when appropriate. Time-to-event analyses included incidence density rates and the probability of event free survival, and their associated 95% CIs.

Analyses were presented separately for patients prospectively and retrospectively enrolled to account for potential differences in the data reported, in particular the number and nature of AEs. Analyses by cohort included disease history, ECOG performance status, and other background information to determine whether there was baseline difference between groups which could influence the safety results.

Risk factors (see Section 9.4.2.3 for details) for peripheral neuropathy were identified and described using covariate adjusted logistic regression. Multivariate analysis was performed for all safety patients and also summarised by disease type (CD30+HL and sALCL) separately.

9.9.2 Main Statistical Methods

9.9.2.1 Analysis Population

Analyses were presented separately for patients prospectively and retrospectively enrolled to account for potential differences in the data reported, in particular the number and nature of AEs. Analyses by cohort included disease history, ECOG performance status, and other background information to determine whether there was a difference between the cohorts which could influence the safety results.

- All Enrolled Patients Population: all patients enrolled in the study regardless of their treatment status.
- Safety Population: all enrolled patients who took at least one dose of brentuximab vedotin.
    - Prospective cohort: all patients enrolled in this study who took the first dose of brentuximab vedotin on or after the date informed consent was collected.

- Retrospective cohort: all patients enrolled in this study who took the first dose of brentuximab vedotin before the date informed consent was collected.

- Per-protocol Population: all enrolled patients who took at least one dose of brentuximab vedotin and did not have a major protocol deviation as the reason for discontinuation. The Per-protocol Population was used as a supplement to the Safety Population for selected safety analyses.
- Subgroup Analysis Set: the frequency of SAEs and AESIs were presented for each of the following subgroups. Any subgroup analysis, from the listing below, was presented in tabular form:
  - Age group (< 65 years and ≥ 65 years)
  - Sex (male and female)
  - CD30+ lymphoma type (HL and sALCL)
  - ALK positivity (sALCL patients only)
  - Long-term treatment (> 16 cycles and ≤ 16 cycles)
  - Post-ASCT status (yes and no)

9.9.2.2 Safety Analysis

The SAEs and protocol-specified AESIs were described in the Safety Population. All analyses of AEs were based on the number of patients with SAEs/AESIs and not the overall number of SAEs/AESIs. All SAEs and AESIs were coded using MedDRA version 18.0 (for previous interim analysis) and version 20.0 (for this final analysis) SOC and PT. The severity of AEs was graded according to the NCI CTCAE v4.03. AESIs were summarised by AESI type.

An overall summary AE table (includes only SAE and AESI) presenting the number and percentage of patients for the following conditions were tabulated in the Safety Population, as well as by cohort (prospective and retrospective cohorts): (a) patients with any AEs, (b) any treatment-related AEs. Relationship was assessed by the Investigator and collected in the CRF, (c) maximum severity of any AE (< Grade 3 or ≥ Grade 3), (d) any SAE, (e) any treatment-related SAE, (f) any AESI (includes both serious and non-serious AESI), (g) discontinued treatment due to AE (includes both action taken=discontinued from study, and/or action taken=dose (or drug) permanently discontinued).

The number and proportion of patients who experience SAEs and AESIs, time at risk in years, incidence rates and the associated 95% CIs were summarised in tables. The SAEs and AESIs were summarised separately by severity (CTCAE < Grade 3 or ≥ Grade 3) and by relatedness to brentuximab vedotin (relatedness = “yes” only) for all enrolled patients and by patient cohort (prospective and retrospective cohorts).

The following information were summarised in a table for treatment-emergent/related peripheral neuropathy by patient cohort:

- Patients with treatment-emergent peripheral neuropathy
- Patients with treatment-emergent peripheral neuropathy with severity ≤ Grade 2
- Patients with treatment-emergent peripheral neuropathy with severity ≥ Grade 3
- Patients with any treatment-related peripheral neuropathy
- Patients with treatment-related peripheral neuropathy with severity ≤ Grade 2
- Patients with treatment-related peripheral neuropathy with severity ≥ Grade 3
- Patients with any treatment-emergent treatment-related peripheral neuropathy
- Patients who discontinued treatment due to peripheral neuropathy

Incidence Rate of SAEs and AESI

The incidence rate and the associated 95% CI were reported for SAEs and protocol-specified AESIs in all safety patients. Calculation of incidence rates of SAEs and AESIs is described in Section 9.8.

Kaplan-Meier Analysis for Time to First Adverse Event

Time to first AE (defined as new onset or worsening of pre-existing condition, where applicable) was evaluated for protocol-specified AESIs, regardless of event grade.

Time-to-event analysis for peripheral neuropathy used Kaplan-Meier analysis for the occurrence of the first reported peripheral neuropathy event during the study follow-up. Patients were censored at the time of death, premature discontinuation from the study for any reason, or study closure, whichever occurred first. Kaplan-Meier estimates of the probability of event free survival and associated 95% CI were reported for each follow-up visit. The start time was the date of first dose of brentuximab vedotin.

9.9.2.3 Risk Factors for Peripheral Neuropathy

The analysis for identifying potential risk factors for new onset or worsening of peripheral neuropathy included all patients in the Safety Population. Stratification by cohort was not performed as part of the analysis, however analyses were also performed by lymphoma type (CD30+ HL and sALCL).

Logistic regression was performed to identify and describe potential risk factors. The following factors were chosen based on clinical relevance:

- Age (< 65 years and ≥ 65 years)
- Sex (male and female)
- BMI
- Disease type (CD30+HL and sALCL)
- Disease stage at baseline (stage I, II, III, IV, and not defined [unknown])

- Extranodal involvement at baseline (yes, no and unknown)
- Neuropathy at baseline (yes, no, and other)
- Previous history of peripheral neuropathy (yes and no)
- Most recent chemotherapy exposure
- Number of cycles from prior lines of therapy at baseline
- Diabetes mellitus at baseline (yes and no)
- Impaired renal function at baseline (yes and no)
- Thyroid dysfunction at baseline (yes and no)

Note: baseline refers to data collected in the baseline/enrolment form, refer to Section 9.5.1 for further details.

9.9.2.4 Treatment Patterns

Treatment patterns, including initial and subsequent treatment strategies and dose modifications, were summarised using descriptive analyses.

The potential influence of brentuximab vedotin on treatment interruptions or dose modifications in all safety patients was explored as part of the safety analysis. The following summary statistics were presented overall and by patient cohort:

- Number of patients with SAEs and AESIs leading to dose increased by SOC and PT
- Number of patients with SAEs and AESIs leading to dose reduced by SOC and PT
- Number of patients with SAEs and AESIs leading to dose held, delayed and interrupted by SOC and PT
- Number of patients with SAEs and AESIs leading to dose permanently discontinued by SOC and PT
- Number of patients with SAEs and AESIs leading to discontinuation from the study by SOC and PT

9.9.3 Missing Values

Complete details on handling of all missing data, which are common in observational studies, were described separately in the Section 5.4 of the SAP. The number of missing data were reported for each measured variable in the study. Missing data were not imputed, and the data were analysed as they were recorded in the study CRFs. There were no missing or partially missing dates for AEs in this study.

9.9.4 Sensitivity Analyses

No sensitivity analyses were performed.

9.9.5 Amendments to the Statistical Analysis Plan

The SAP for the final analysis is version 3.0 dated 31 May 2018. There were no deviations from the final SAP.

9.10 Quality Control

To ensure the quality and integrity of research, this study was conducted under the Guideline on Good Pharmacovigilance Practices (GVP Module VIII – Post-authorisation Safety Studies) issued by the EMA (30), Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE) (31), the principles outlined in the Declaration of Helsinki (32), the European Network of Centres for pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (33), and any applicable national guidelines. The protocol has been included in the EU PAS register (EUPAS3583).

All data were collected and entered directly into the EDC system. All sites were fully trained on using the on-line data capture system, including electronic case report form (eCRF) completion guidelines and help files. Investigators and site personnel were able to access their account with a username and password. All eCRFs were completed by designated, trained personnel or the study coordinator, as appropriate. In most cases, the eCRF were reviewed, electronically signed, and dated by the Investigator. All changes or corrections to eCRFs were documented in an audit trail and an adequate explanation is required. All participating sites had access to the data entered by the individual site on their own enrolled patients through the EDC system.

A data management plan was created before data collection began and described all functions, processes, and specifications for data collection, cleaning and validation. The eCRFs included programmable edits to obtain immediate feedback if data were missing, out of range, illogical or potentially erroneous. Concurrent manual data review was performed based on parameters dictated by the plan. Ad hoc queries were generated within the EDC system and followed up for resolution. High data quality standards were maintained, and processes and procedures utilised to repeatedly ensure that the data were as clean and accurate as possible when presented for analysis. Data quality was enhanced through a series of programmed data quality checks that automatically detect out of range or anomalous data.

The source documents were contained in the patient's medical record and data collected on the eCRFs matched the data in the medical records. All original source documentation was expected to be stored at the site for the longest possible time required by local applicable regulations. The site was instructed to notify the Sponsor before any destruction of medical records of study participants.

A study monitoring plan, including for-cause monitoring, that was appropriate for the study design was developed and implemented. During the site initiation visit, the monitor provided training on the conduct of the study to the Investigator and all site staff involved in the study. In

order to ensure the integrity of the data, sites were monitored. Site monitoring was performed by clinical research associates to examine compliance with the protocol and adherence to the data collection procedures, to assess the accuracy and completeness of submitted clinical data, and to verify that records and documents are being properly maintained for the duration of the study. The monitor performed source data verification by review of original patient records. The monitor closed out each site after the last patient's final follow-up assessment was completed, all data had been entered and all outstanding monitoring issues and data queries had been resolved or addressed. All monitoring procedures and frequency of monitoring visits were described in a monitoring plan. Monitor contact details for each participating site were maintained in the Investigator Site File.

10 RESULTS

10.1 Participants

10.1.1 Site Recruitment

A total of 319 sites were contacted by February 2016 in 17 countries, of which 219 (69%) declined to participate, had no response, or were not qualified based on responses to the site selection questionnaire. Reasons for declining participation included prioritisation of early stage studies, insufficient compensation, lack of resources and lack of interest in participating in an observational study. Of the 319 sites contacted, 100 sites (n=100/319, 31%) in 13 countries were qualified to participate (Table 10-1).

Table 10-1. Overall Summary of Site Recruitment by Country

Country	Target number of Sites	Number of Sites contacted	Number of Sites "Declined, No response, or Not qualified"	Number of Qualified sites	Number of Enrolling Sites
Austria	8	23	16	7	7
Denmark	2	10	8	2	2
France	11	41	29	12	11
Germany	14	65	52	13	13
Greece	3	6	2	4	4
Ireland	2	6	3	3	3
Italy	11	20	7	13	13
Netherlands	4	12	9	3	3
Slovakia	2	4	1	3	3
Spain	11	32	12	20	20
Sweden	6	12	7	5	5
Switzerland	1	8	7	1	1
UK	18	61	46	15	15
Total	100	319	218	101	100

Abbreviations: UK= United Kingdom

Of the 100 sites in 13 countries that were qualified, 80 enrolled patients into the study. A total of 311 patients were enrolled from sites in Austria (n=11), Denmark (n=13), France (n=12), Germany (n=20), Greece (n=17), Ireland (n=15), Italy (n=46), Netherlands (n=19), Slovakia

(n=8), Spain (n=41), Sweden (n=15), Switzerland (n=4), UK (n=90). The timing of the first enrolled patient in each country is shown in Table 10-2.

Table 10-2. Site and Patient Enrolment by Country

Country	Number of enrolling sites	Number of enrolled patients	Date of first patient enrolled[1]
Austria	8	11[§]	11-Oct-2013
Denmark	2	13	26-Jun-2013
France	11	12	16-Oct-2015
Germany	12	20	17-Oct-2014
Greece	4	17	13-May-2015
Ireland	3	15	02-Sep-2015
Italy	13	46	10-Apr-2015
Netherlands	3	19	02-Jul-2014
Slovakia	3	8	25-Sep-2015
Spain	20	41	25-Feb-2015
Sweden	5	15	10-Oct-2013
Switzerland	1	4	19-Aug-2013
UK	15	90	27-Sep-2013
TOTAL	100	311	---

Abbreviations: UK= United Kingdom
[1] Date informed consent form (ICF) signed
[§] One patient was enrolled but was never dosed with brentuximab vedotin, and was therefore excluded from the Safety Population
Source: EOT Listing 1.2

10.1.2 Patient Enrolment

Patients who were enrolled and took at least one dose of brentuximab vedotin (Safety Population) were compared with patients that were not enrolled to evaluate the comparability, which could indicate the generalisability. The data were taken from enrolment logs completed by the sites and was not subject to the same quality control and cleaning processes as data entered into the eCRF. There were data missing in the screening logs that were available in the eCRF, the following description therefore provides only an indication of differences between the enrolled and non-enrolled populations.

There were 310 patients included in the Safety Population, one patient enrolled but did not receive brentuximab vedotin and thus was not included in the safety analyses, and 106 patients

were screened but not enrolled in the study (EOT Listing 1.2). The median age was similar between the Safety Population (45.5 years [range: 18-86 years]) and the non-enrolled population (45.0 years [range: 16-89 years]), however the enrolled population had proportionally fewer patients ≥65 years (n=74/310, 23.9%) than the non-enrolled population (n=37/106, 34.9%). The distributions by sex were similar. The non-enrolled population had more patients with advanced (stage IV) disease (n=44/106, 41.5%) than the enrolled population (n=116/310, 37.3%), but also had patients with different types of lymphoma that made them ineligible for the study.

10.1.3 Study Participants

The study sample size per the protocol (following amendment 3, version 4.0, dated 07 June 2016) was 300 patients and 311 patients were enrolled. The enrolment period lasted 54 months (4 years 6 months), from the first patient enrolled on 26 June 2013 (informed consent form [ICF] signed) to last the patient enrolled on 28 December 2017 (ICF signed). The study duration was a total of 64 months (5 years 4 months), the last patient received their last dose on 7 September 2018, and following an additional 30 days of safety follow-up data collection was completed on 4 October 2018. Final database lock for the final analyses occurred on 15 November 2018.

This final report presents the results for the 310 patients who received at least 1 dose of brentuximab vedotin (Safety Population). Figure 1 shows a flowchart of patient enrolment and disposition. Data from patients who discontinued or died during follow-up are included in the analysis up to the date of their study withdrawal or death.

The safety analyses (Section 10.4) were based primarily on the 310 patients in the Safety Population, with additional analyses on the 284 patients in the Per-protocol Population which excluded patients with major protocol violations related to eligibility criteria. The 156 patients in the prospective cohort took the first dose of brentuximab vedotin on or after the date of informed consent. The 154 patients in the retrospective cohort had taken the first dose of brentuximab vedotin before the date of informed consent.

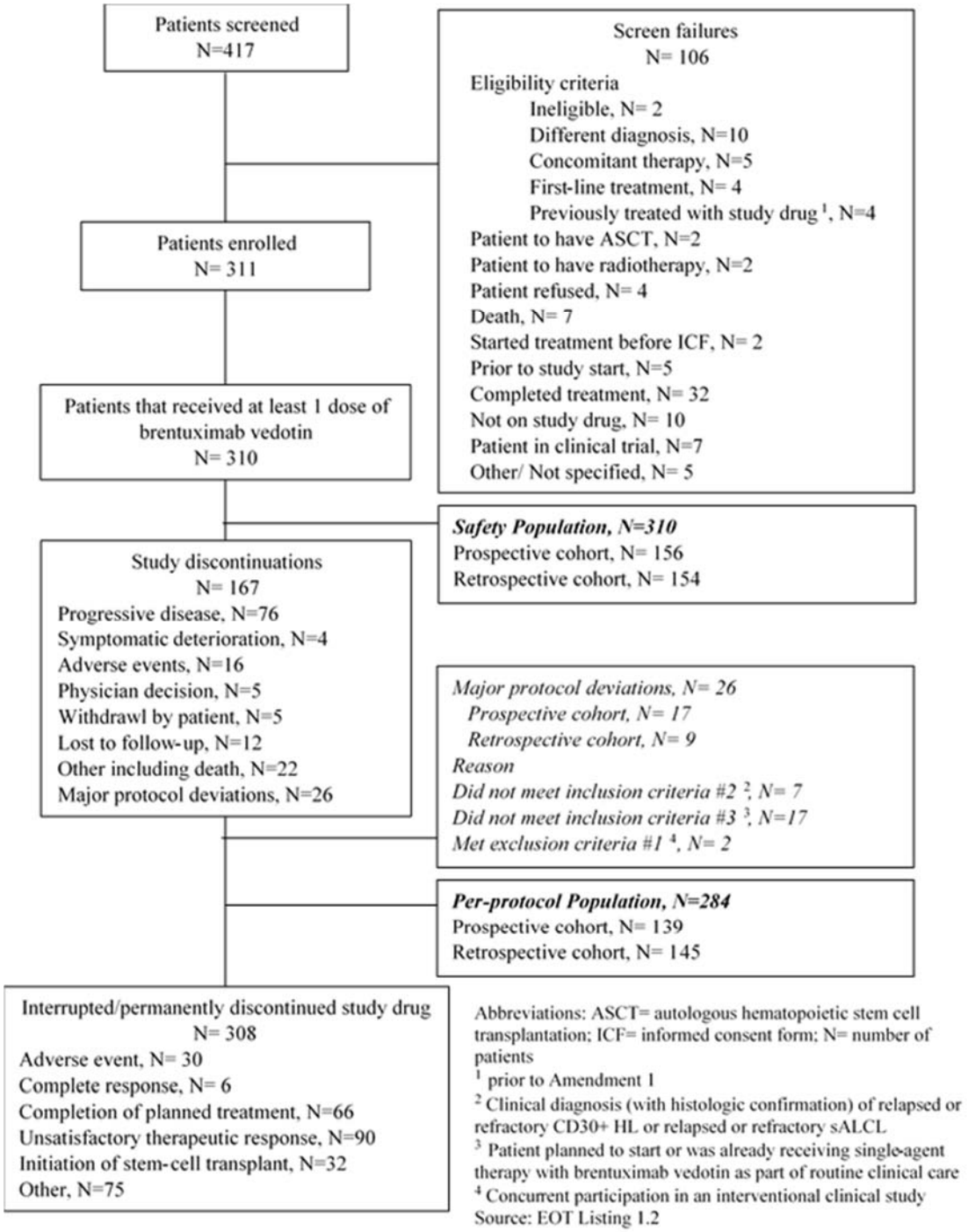

Figure 1. Study Enrolment Flowchart

The patient disposition overall, as well as by prospective and retrospective cohort, are presented for the Safety Population and Per-protocol Population in Table 10-3. The definitions of the analysis populations were detailed in Section 9.9.2.1.

Overall, 167 of the 310 patients in the Safety Population discontinued from the study (n=167/310, 53.9%). There were 101 discontinuations in the prospective cohort (n=101/156, 64.7%) compared with 66 discontinuations in the retrospective cohort (n=66/154, 42.9%). The reasons for discontinuation were: progressive disease (n=76/167, 45.5%), major protocol violations related to eligibility criteria (n=26/167, 15.6%), other (n=22/167, 13.2%), adverse event (n=16/167, 9.6%),, lost to follow-up (n=12/167, 7.2%), physician decision (n=6/167, 3.6%), withdrawal by patient (n=5/167, 3.0%), and symptomatic deterioration (n=4/167, 2.4%). Within the category "other", the main reason for discontinuation was death (n=6/167, 3.6%), 7 patients listed various complications/AEs (n=7/167, 4.2%), 4 patients left the Investigator site (n=4/167, 2.4%), 2 patients did not re-consent to follow-up past 4 years (n=2/167, 1.2%), 1 patient entered a clinical trial (n=1/167, 0.6%), 1 patient had an ASCT (n=1/167, 0.6%), and 1 patient was mis-classified as having a concomitant treatment at enrolment (EOT Listing 1, note that death was not available as a reason for discontinuation). The majority of patients that discontinued from the study due to protocol violations were being treated with other chemotherapeutics at enrolment and did not meet inclusion criterion 3: Patient planned to start or was already receiving single-agent therapy with brentuximab vedotin as part of routine clinical (n=17/26, 65.4%) (Figure 1). The reasons for discontinuation were similar between the cohorts. A greater proportion of the retrospective cohort discontinued due to progressive disease than in the prospective cohort (54.5% vs. 39.6%, respectively), whereas a greater proportion of the prospective cohort was lost to follow-up than in the retrospective cohort (8.9% vs. 4.5%, respectively) and were discontinued due to physician decision (5.0% vs. 1.5%, respectively). There were 17 patients with major protocol violations related to eligibility criteria in the prospective cohort (n=17/156, 10.9%) compared with 9 patients in the retrospective cohort (n=9/154, 5.8%).

A total of 88 patients died (n=88/310, 28.4%), of whom 13 patients (n=13/310, 4.2%) died while on-study (ie, within 30 days of the last dose of brentuximab vedotin), and 75 patients (n=75/310, 24.2%) died during post-treatment follow-up (ie, 31 days or more following the last dose of brentuximab vedotin). There were more deaths overall in the prospective cohort than in the retrospective cohort (35.3% vs. 21.4%, respectively). The median time to death was also shorter in the prospective cohort compared to the retrospective cohort (8.1months [range: 0.4-26.9 months] vs. 12.0 months [range: 2.9-35.9 months], respectively). The primary cause of death was more commonly "related to disease under study or complications" in the retrospective cohort than in the prospective cohort (69.7% vs. 54.5%, respectively).

The disposition of the Per-protocol Population was nearly identical to the Safety Population, both overall and within each of the cohorts. There were minor differences that would be expected from the early discontinuations, ie, decreases in the proportions of patients discontinuing, the

proportion of patients who did not complete the study, and a negligible increase on the years since enrolment.

Table 10-3. Patient Disposition

		Safety Population			Per-protocol Population		
		Prospective Cohort	**Retrospective Cohort**	**Total**	**Prospective Cohort**	**Retrospective Cohort**	**Total**
N		156	154	310	139	145	284
Patients completed[1]	n (%)	55 (35.3%)	88 (57.1%)	143 (46.1%)	55 (39.6%)	88 (60.7%)	143 (50.4%)
Patients discontinued	n (%)	101 (64.7%)	66 (42.9%)	167 (53.9%)	84 (60.4%)	57 (39.3%)	141 (49.6%)
Years since enrolment[2]	Mean (SD)	1.4 (1.16)	1.8 (1.05)	1.6 (1.12)	1.5 (1.18)	1.8 (1.02)	1.7 (1.11)
	Median (IQR)	1.1 (0.5, 2.0)	1.8 (0.7, 2.7)	1.4 (0.6, 2.4)	1.3 (0.6, 2.1)	1.9 (0.8, 2.7)	1.6 (0.7, 2.5)
	Range	0.0-4.8	0.0-4.0	0.0-4.8	0.0-4.8	0.1-4.0	0.0-4.8
Years since first dose	Mean (SD)	1.4 (1.17)	2.0 (1.10)	1.7 (1.17)	1.5 (1.18)	2.0 (1.08)	1.8 (1.16)
	Median (IQR)	1.1 (0.5, 2.0)	2.0 (1.0, 2.9)	1.5 (0.7, 2.5)	1.3 (0.6, 2.1)	2.0 (1.1, 3.0)	1.6 (0.8, 2.6)
	Range	0.0-4.8	0.1-4.6	0.0-4.8	0.0-4.8	0.1-4.6	0.0-4.8
Reason for study discontinuation[3]							
Progressive disease	n (%)	40 (39.6%)	36 (54.5%)	76 (45.5%)	40 (47.6%)	36 (63.2%)	76 (53.9%)
Adverse event	n (%)	10 (9.9%)	6 (9.1%)	16 (9.6%)	10 (11.9%)	6 (10.5%)	16 (11.3%)
Symptomatic deterioration	n (%)	4 (4.0%)	0	4 (2.4%)	4 (4.8%)	0	4 (2.8%)
Lost to follow-up	n (%)	9 (8.9%)	3 (4.5%)	12 (7.2%)	9 (10.7%)	3 (5.3%)	12 (8.5%)
Physician decision	n (%)	5 (5.0%)	1 (1.5%)	6 (3.6%)	5 (6.0%)	1 (1.8%)	6 (4.3%)
Withdrawal by patient	n (%)	3 (3.0%)	2 (3.0%)	5 (3.0%)	3 (3.6%)	2 (3.5%)	5 (3.5%)
Protocol violation[4]	n (%)	17 (16.8%)	9 (13.6%)	26 (15.6%)	NA	NA	NA
Other[5]	n (%)	13 (12.9%)	9 (13.6%)	22 (13.2%)	13 (15.5%)	9 (15.8%)	22 (15.6%)

		Safety Population			Per-protocol Population		
		Prospective Cohort	**Retrospective Cohort**	**Total**	**Prospective Cohort**	**Retrospective Cohort**	**Total**
N		156	154	310	139	145	284
Survival status at end of study							
Alive	n (%)	91 (58.3%)	115 (74.7%)	206 (66.5%)	77 (55.4%)	106 (73.1%)	183 (64.4%)
Deceased	n (%)	55 (35.3%)	33 (21.4%)	88 (28.4%)	53 (38.1%)	33 (22.8%)	86 (30.3%)
On-study deaths	n (%)	11 (20.0%)	2 (6.1%)	13 (14.8%)	10 (18.9%)	2 (6.1%)	12 (14.0%)
Unknown	n (%)	10 (6.4%)	6 (3.9%)	16 (5.2%)	9 (6.5%)	6 (4.1%)	15 (5.3%)
Months to death[6]	Mean (SD)	9.9 (7.94)	13.4 (8.28)	11.2 (8.21)	10.1 (8.03)	13.4 (8.28)	11.4 (8.25)
	Median (IQR)	8.1 (3.0, 15.2)	12.0 (7.0, 16.8)	9.4 (4.8, 15.6)	8.1 (3.2, 15.2)	12.0 (7.0, 16.8)	9.5 (5.0, 16.0)
	Range	0.4-26.9	2.9-35.9	0.4-35.9	0.4-26.9	2.9-35.9	0.4-35.9
Primary cause of death							
Related to disease under study or complications	n (%)	30 (54.5%)	23 (69.7%)	53 (60.2%)	28 (52.8%)	23 (69.7%)	51 (59.3%)
Other	n (%)	25 (45.5%)	10 (30.3%)	35 (39.8%)	25 (47.2%)	10 (30.3%)	35 (40.7%)

Abbreviations: IQR= interquartile range; n/N= number of patients; NA= not applicable; SD= standard deviation
[1] As collected on end of study form: responded "Yes" to "Did the patient complete the study?"
[2] Years since patient enrolment = (the last known date - date of informed consent + 1)/365.25
[3] Percentages are based on patients who had early study discontinuation, otherwise patients were expected to remain on follow-up until the end of the study
[4] Patients with protocol violations remained on follow-up
[5] Other reasons for discontinuation include death
[6] Months to death = (date of death - date of first dose of brentuximab vedotin + 1)/ 30.44
Source: EOT Table 1, EOT Table 1_pp

10.1.4 Protocol Deviations

There were 27 patients with major protocol deviation relating to eligibility criteria, summarised in Table 10-4. One patient was enrolled but never received brentuximab vedotin and was discontinued from the study.

The remaining 26 patients did not meet the eligibility criteria (prospective cohort: 17 patients; retrospective cohort: 9 patients) but were included in the safety analyses as they had taken at least one dose of brentuximab vedotin. The most common deviation was related to inclusion criterion 3: 17 patients were not on single-agent therapy at enrolment (n=17/26, 65.4%) (Section 9.3.1).

Table 10-4. Summary of Major Protocol Deviations

Reason	n	Patient ID	Action
Patient was enrolled but never received brentuximab vedotin	1	03001-004	Discontinued from study
Eligibility criteria			
Patient did not meet inclusion criteria #3: "Patient is planned to start or is already receiving single-agent therapy with brentuximab vedotin as part of routine clinical care"	17 (11 prospective; 6 retrospective)	13001-001, 19010-001, 28010-001, 18001-001, 28004-003, 28010-002, 28010-003, 28010-004, 28010-005, 28010-006, 28010-007, 28004-001, 53001-004, 03001-006, 18009-001, 18009-002, 57013-004	Retained in Safety Population, excluded from Per-protocol Population
Patient did not meet inclusion criteria #2: "Clinical diagnosis (with histologic confirmation) of relapsed or refractory CD30+ HL or relapsed or refractory sALCL"	7 (5 prospective; 2 retrospective)	03001-001, 13001-004, 03004-002, 13002-003, 51006-003, 51007-001, 19004-004	Retained in Safety Population, excluded from Per-protocol Population
Patient met exclusion criteria #1: "Concurrent participation in an interventional clinical study"	2 (1 prospective; 1 retrospective)	19008-001, 19008-002	Retained in Safety Population, excluded from Per-protocol Population

Abbreviation: HL= Hodgkin's lymphoma, sALCL= systemic anaplastic large cell lymphoma
Source: EOT Listing 1.3

10.2 Descriptive Data

The population characteristics are presented overall, as well as for the prospective and retrospective cohorts, to highlight any potential differences between the cohorts that may affect interpretation of the results.

10.2.1 Patient Demographics and Vital Signs

Patient demographics at enrolment are presented for the Safety Population and Per-protocol Population in Table 10-5.

Overall, the median age at study enrolment was 44.0 years (range: 18-87 years); including 76 patients ≥65 years (n=76/310, 24.5%). The prospective cohort had a slightly higher median age than the retrospective cohort (46.0 years vs. 42.5 years, respectively). Most of the patients in both the prospective and retrospective cohorts were in the age category of 25 to <40 years (32.7% and 40.3%, respectively), slightly more elderly patients were enrolled in the prospective cohort than the retrospective cohort (26.9% vs. 22.1%, respectively). Overall, 61% of the population was male (n=190/310, 61.3%), with similar proportions in the prospective and retrospective cohorts (59.6% vs. 63.0%, respectively).

The median BMI was 24.6 kg/m^2 (range: 16-46 kg/m^2), with most of the patients in the BMI category of ≥18.5 to <25 kg/m^2 (n=137/310, 44.3%). The majority of patients were White overall (n=246/310, 79.4%) and in both cohorts. Most of the patients were not Hispanic or Latino (n=223/310, 71.9%), with more in the prospective cohort than the retrospective cohort (81.4% vs. 62.3%).

The Per-protocol Population had very similar distributions to the Safety Population, both overall and by cohort.

Table 10-5. Patient Demographics at Enrolment

		Safety Population			Per-protocol Population		
		Prospective Cohort	**Retrospective Cohort**	**Total**	**Prospective Cohort**	**Retrospective Cohort**	**Total**
N		156	154	310	139	145	284
Age (years)	Mean (SD)	48.3 (18.65)	47.0 (18.06)	47.6 (18.34)	48.1 (19.06)	47.0 (18.25)	47.6 (18.62)
	Median (IQR)	46.0 (32, 66)	42.5 (33, 62)	44.0 (33, 64)	44.0 (32, 67)	43.0 (33, 62)	43.0 (32, 65)
	Range	18 - 87	19 - 86	18 - 87	18 - 87	19 - 86	18 - 87
Sex							
Female	n (%)	63 (40.4%)	57 (37.0%)	120 (38.7%)	59 (42.4%)	53 (36.6%)	112 (39.4%)
Male	n (%)	93 (59.6%)	97 (63.0%)	190 (61.3%)	80 (57.6%)	92 (63.4%)	172 (60.6%)
BMI (kg/m^2)	Mean (SD)	25.2 (5.23)	25.8 (5.75)	25.5 (5.50)	25.5 (5.30)	25.8 (5.72)	25.7 (5.52)
	Median (IQR)	23.9 (21, 29)	25.2 (22, 29)	24.6 (22, 29)	23.9 (22, 30)	25.4 (22, 29)	24.6 (22, 29)
	Range	17 - 39	16 - 46	16 - 46	17 - 39	16 - 46	16 - 46

Abbreviations: BMI= body mass index; IQR= interquartile range; n/N= number of patients; SD= standard deviation
Note(s): There were no missing data.
Source: EOT Table 3, EOT Table 3_pp

10.2.2 Medical History

Medical history is presented in Table 10-6, and additional details are provided in EOT Table 4. This includes medical history diagnosed prior to initiating treatment with brentuximab vedotin and collected at the baseline/enrolment visit.

Abnormal blood counts

Abnormal blood counts were the most common medical history reported, present in 138 patients (n=138/310, 44.5%), including 84 patients in the prospective cohort (n=84/156, 53.8%) and 54

patients in the retrospective cohort (n=54/154, 35.1%). The most common forms were anaemia (n=115/310, 37.1%), thrombocytopenia (n=41/310, 13.2%), neutropenia (n=34/310, 11.0%), leukopenia (n=26/138, 8.4%), and growth factor exposure (n=16/310, 5.2%). All were more common in the prospective cohort than the retrospective cohort: anaemia (n=69/156, 44.2% vs. n=46/154, 29.9%, respectively), thrombocytopenia (n=26/156, 16.7% vs. n=15/154, 9.7%), neutropenia (n=22/156, 14.1% vs. n=12/154, 7.8%), leukopenia (n=15/156, 9.6% vs. n=11/154, 7.1%), growth factor exposure (n=11/156, 7.1% vs. n=5/154, 3.2%).

Ongoing abnormal blood counts at enrolment were common for anaemia (n=89/310, 28.7%), thrombocytopenia (n=23/310, 7.4%), neutropenia (n=10/310, 3.2%), leukopenia (n=5/310, 1.6%), and growth factor exposure (n=4/310, 1.3%).

Amongst patients with abnormal blood counts, the distributions were anaemia (n=115/138, 83.3%), thrombocytopenia (n=41/138, 29.7%), neutropenia (n=34/138, 24.6%), leukopenia (n=26/138, 18.8%), and growth factor exposure (n=16/138, 11.6%). The distributions were similar between the cohorts, with slightly higher rates in the retrospective cohort than the prospective cohort for anaemia (85.2% vs. 82.1%, respectively), leukopenia (20.4% vs. 17.9%, respectively), and growth factor exposure (13.1% vs. 9.3%, respectively). There were slightly higher rates in the prospective cohort than the retrospective cohort for thrombocytopenia (31.0% vs. 27.8%, respectively) and neutropenia (26.2% vs. 22.2%, respectively).

Ongoing abnormal blood counts at enrolment were common for anaemia (n=89/115, 77.4%), thrombocytopenia (n=23/41, 56.1%), neutropenia (n=10/34, 29.4%), leukopenia (n=5/26, 19.2%), and growth factor exposure (n=4/16, 25.0%). Ongoing anaemia was more common in the prospective cohort than the retrospective cohort (82.6% vs. 69.6%, respectively), and thrombocytopenia was more common in the retrospective cohort than the prospective cohort (60.0% vs. 53.8%, respectively).

Cardiovascular medical history

History of cardiovascular disease was reported for 83 patients (n=83/310, 26.8%), with similar distributions between the prospective and retrospective cohorts (26.3% vs. 27.3%, respectively). Rhythm abnormalities were reported for 16 patients (n=16/310, 5.2%), and congestive heart failure for 4 patients (n=4/310, 1.3%), all others were reported as ‘other’. Most rhythm abnormalities (n=14/310, 4.5%) and congestive heart failure (n=3/310, 1.0%) were ongoing at enrolment.

Of the 41 patients with cardiovascular medical history in the prospective cohort (n=41/156, 26.3%), 12 patients had rhythm abnormalities (n=12/41, 29.3%) with a median of 4.8 months (range: 0.9-51.2 months) since onset, 3 patients had congestive heart failure (n=3/41, 7.3%) with a median of 10.6 months (range: 4.6-19.3 months) since onset. Two patients had ongoing congestive heart failure (n=2/3, 66.7%) and 10 patients had ongoing rhythm abnormality (n=10/12, 83.3%). Of the 42 patients with cardiovascular medical history in the retrospective cohort (n=42/154, 27.3%), 4 patients had rhythm abnormalities (n=4/42, 9.5%) with a median of 38.5 months (range: 38.5-38.5 months) since onset, 1 patient had congestive heart failure

(n=1/42, 2.4%), and 41 patients had other types of cardiovascular medical history (n=41/42, 97.6%). All cardiovascular disease in patients with rhythm abnormalities and congestive heart failure were ongoing at enrolment.

Neurologic medical history and peripheral neuropathy

Neurologic medical history was reported for 48 patients (n=48/310, 15.5%), of whom 35 patients had a history of peripheral neuropathy (n=35/310, 11.3%), and 25 patients had ongoing peripheral neuropathy at enrolment (n=25/310, 8.1%). Neurologic medical history was more common in the prospective cohort than the retrospective cohort (17.3% vs. 13.6%, respectively); a similar pattern was reported for history of peripheral neuropathy in the prospective cohort compared with the retrospective cohort (12.8% vs. 9.7%, respectively). The median time since the onset of peripheral neuropathy was 14.8 months (interquartile range [IQR]: 3.8, 25.6 months; range: 0.6-108.8 months), which was much longer in the retrospective cohort, 25.6 months (IQR: 5.5, 49.8 months; range: 0.6-108.8 months) than the prospective cohort, 13.5 months (IQR: 3.8, 22.3 months; range: 2.0-57.7 months).

Of the 20 patients with history of peripheral neuropathy in the prospective cohort (n=20/156, 12.8%), 13 patients had ongoing peripheral neuropathy at enrolment (n=13/20, 65.0%). Of the 15 patients with history of peripheral neuropathy in the retrospective cohort (n=15/154, 9.7%), 12 patients had ongoing peripheral neuropathy at enrolment (n=12/15, 80.0%). Motor peripheral neuropathy and autonomic peripheral neuropathy were all <Grade 3. Sensory peripheral neuropathy was <Grade 3 for most patients (n=15/17, 88.2%).

Pulmonary disease

History of pulmonary disease was reported in 47 patients (n=47/310, 15.2%), which was more common in the prospective cohort than the retrospective cohort (17.9% vs. 12.3%, respectively). Chronic obstructive pulmonary disease was reported for 12 patients (n=12/310, 3.9%), and almost all (n=11/310, 3.5%) were ongoing at enrolment.

Of the 28 patients with pulmonary disease in the prospective cohort, 7 patients had chronic obstructive pulmonary disease (n=7/28, 25.0%) with a median of 42.4 months (range: 10.1-135.9 months) since onset. Six patients had ongoing chronic obstructive pulmonary disease at enrolment (n=6/7, 85.7%). Of the 19 patients with pulmonary disease in the retrospective cohort, 5 patients had chronic obstructive pulmonary disease (n=5/19, 26.3%) with a median of 142.0 months (range: 142.0-142.0 months) since onset. All patients with chronic obstructive pulmonary disease had ongoing disease at enrolment.

Diabetes mellitus

History of diabetes mellitus was reported in 29 patients (n=29/310, 9.4%), which was slightly more common in the retrospective cohort than the prospective cohort (11.0% vs. 7.7%, respectively); 28 patients had ongoing disease at enrolment (n=28/310, 9.0%). Of the 12 patients with diabetes mellitus in the prospective cohort (n=12/156, 7.7%), the median time since onset was 3.3 months (range: 1.3-420.4 months). Of the 17 patients with diabetes mellitus in the

retrospective cohort (n=17/154, 11.0%), the median time since onset was 31.2 months (range: 2.0-180.2 months).

Renal medical history

Renal medical history was reported in 18 patients (n=18/310, 5.8%), with similar distributions between the prospective and retrospective cohorts (5.1% vs. 6.5%, respectively); 11 patients had ongoing disease at enrolment (n=11/310, 3.5%). Of the 8 patients with renal medical history in the prospective cohort (n=8/156, 5.1%), the median time since onset was 5.0 months (range: 0.5-183.0 months), and 4 patients (n=4/8, 50.0%) had ongoing renal impairment at enrolment. Of the 10 patients with renal medical history in the retrospective cohort (n=10/154, 6.5%), the median time since onset was 12.8 months (range: 0.3-268.4 months), and 7 patients (n=7/10, 70.0%) had ongoing renal impairment at enrolment.

Hepatic impairment

History of hepatic impairment was reported in 10 patients (n=10/310, 3.2%), which was more common in the prospective cohort than the retrospective cohort (5.1% vs. 1.3%, respectively); 6 patients had ongoing disease at enrolment (n=6/310, 1.9%). Of the 8 patients with hepatic impairment in the prospective cohort (n=8/156, 5.1%), the median time since onset was 27.0 months (range: 1.7-61.9 months), and 5 patients (n=5/8, 62.5%) had ongoing hepatic impairment at enrolment. Of the 2 patients with hepatic impairment in the retrospective cohort (n=2/154, 1.3%), 1 patient had ongoing hepatic impairment at enrolment.

Table 10-6. Patient Medical History

		Safety Population		
		Prospective Cohort	Retrospective Cohort	Total
N		156	154	310
Diabetes mellitus	n (%)	12 (7.7%)	17 (11.0%)	29 (9.4%)
Hepatic impairment	n (%)	8 (5.1%)	2 (1.3%)	10 (3.2%)
Renal medical history	n (%)	8 (5.1%)	10 (6.5%)	18 (5.8%)
Other malignancies	n (%)	15 (9.6%)	12 (7.8%)	27 (8.7%)
Autoimmune disease	n (%)	7 (4.5%)	7 (4.5%)	14 (4.5%)
Thyroid dysfunction	n (%)	16 (10.3%)	14 (9.1%)	30 (9.7%)
Cardiovascular medical history	n (%)	41 (26.3%)	42 (27.3%)	83 (26.8%)
Pulmonary disease	n (%)	28 (17.9%)	19 (12.3%)	47 (15.2%)
Neurologic medical history	n (%)	27 (17.3%)	21 (13.6%)	48 (15.5%)
Peripheral neuropathy	n (%)	20 (12.8%)	15 (9.7%)	35 (11.3%)
Months since peripheral neuropathy onset	Mean (SD)	15.7 (14.54)	32.4 (36.11)	21.4 (24.87)
	Median (IQR)	13.5 (3.8, 22.3)	25.6 (5.5, 49.8)	14.8 (3.8, 25.6)
	Range	2.0 - 57.7	0.6 - 108.8	0.6 - 108.8
Infectious disease	n (%)	18 (11.5%)	17 (11.0%)	35 (11.3%)
Abnormal blood counts	n (%)	84 (53.8%)	54 (35.1%)	138 (44.5%)
Anaemia	n (%)	69 (82.1%)	46 (85.2%)	115 (83.3%)
Thrombocytopenia	n (%)	26 (31.0%)	15 (27.8%)	41 (29.7%)
Neutropenia	n (%)	22 (26.2%)	12 (22.2%)	34 (24.6%)
Leukopenia	n (%)	15 (17.9%)	11 (20.4%)	26 (18.8%)
Growth factor exposure	n (%)	11 (13.1%)	5 (9.3%)	16 (11.6%)
Granulocytopenia	n (%)	4 (4.8%)	4 (7.4%)	8 (5.8%)
Pancytopenia	n (%)	3 (3.6%)	4 (7.4%)	7 (5.1%)
Other	n (%)	15 (17.9%)	5 (9.3%)	20 (14.5%)

Abbreviations: IQR= interquartile range; n/N= number of patients; SD= standard deviation
Note(s): There were no missing data. Medical history was diagnosed prior to initiating treatment with brentuximab vedotin.
Source: EOT Table 4

10.2.3 CD30+ HL and sALCL Disease History

Disease history of CD30+ HL and sALCL is presented in Table 10-7. This includes patient diagnoses, as well as disease history at the time of initiation of treatment with brentuximab vedotin, collected at the baseline/enrolment visit.

Safety Population

Diagnosis

Amongst the 310 patients in the Safety Population, 252 were CD30+ HL patients (n=252/310, 81.3%) (prospective cohort: n=120/156, 76.9%; retrospective cohort: n=132/154, 85.7%) and 58 were sALCL patients (n=58/310, 18.7%) (prospective cohort: n=36/156, 23.1%; retrospective cohort: n=22/154, 14.3%).

Of the 252 CD30+ HL patients, nodular sclerosis HL was the most common subtype of HL (n=164/252, 65.1%), followed by mixed cellularity (n=48/252, 19.0%), unspecified/unknown (n=33/252, 13.1%), lymphocyte-rich (n=5/252, 2.0%), and lymphocyte depleted (n=2/252, 0.8%). Similar distributions of CD30+ HL subtypes were reported in both cohorts.

Of the 58 sALCL patients, most of the patients were ALK negative (n=41/58, 70.7%) and in both cohorts (prospective cohort: n=25/36, 69.4%; retrospective cohort: n=16/22, 72.7%). The most frequently reported ALCL variant was unknown (n=31/58, 53.4%), followed by common type (n=16/58, 27.6%), other type (n=6/58, 10.3%), lymphohistiocytic (n=4/58, 6.9%), and small cell (n=1/58, 1.7%). A similar distribution of sALCL variant was reported in both cohorts.

The median time since initial diagnosis was 21.4 months (IQR: 10.6, 46.2 months; range: 0.1-377.4 months). Reporting of patients with 0.1 months since onset (also included in the Per-protocol Population) indicated that some reports may be for the current relapse, while other reports could be from the initial diagnosis. The median time since diagnosis was 20.8 months (IQR: 10.1, 41.9 months) in the prospective cohort and 22.2 months (IQR: 11.5, 50.5 months) in the retrospective cohort. The time since initial diagnosis was almost identical in the Per-protocol Population.

Disease history

At initiation of treatment, 118 patients were Stage IV (n=118/310, 38.1%), 63 patients were Stage III (n=63/310, 20.3%), 96 patients were Stage II (n=96/310, 31.0%), and 11 patients were Stage I (n=11/310, 3.5%). A similar distribution of disease stage was reported in both cohorts.

Presence of lymphoma-related symptoms (B symptoms) at initiation of treatment was reported for 156 patients (n=156/310, 50.3%), and was slightly higher in the prospective cohort than the retrospective cohort (53.2% vs. 47.4%, respectively). Overall, the most common B symptoms was drenching night sweats (n=118/156, 75.6%), followed by unexplained weight loss (n=79/156, 50.6%), and unexplained fever/chills (n=62/156, 39.7%). A similar distribution of B symptoms was reported in both cohorts.

Evidence of extranodal involvement at initiation of treatment was reported for 116 patients (n=116/310, 37.4%), with similar distributions between the prospective and retrospective cohorts (39.7% vs. 35.1%, respectively). The median number of extranodal involved sites was 1.0 (range: 0.0-6.0). Evidence of bone marrow involvement at initiation of treatment was reported in 37 patients (n=37/310, 11.9%), and history of bone marrow involvement was reported for 40 patients (n=40/310, 12.9%), both had similar distributions between the prospective and retrospective cohorts.

The Per-protocol Population had very similar distributions, both overall and by cohort.

Table 10-7. Patient CD30+ Lymphoma Disease Diagnosis and History

		Safety Population			Per-protocol Population		
		Prospective Cohort	**Retrospective Cohort**	**Total**	**Prospective Cohort**	**Retrospective Cohort**	**Total**
N		156	154	310	139	145	284
Disease type							
CD30+ HL		120 (76.9%)	132 (85.7%)	252 (81.3%)	110 (79.1%)	124 (85.5%)	234 (82.4%)
sALCL		36 (23.1%)	22 (14.3%)	58 (18.7%)	29 (20.9%)	21 (14.5%)	50 (17.6%)
Months since initial diagnosis[1]	Mean (SD)	39.2 (49.08)	44.2 (58.06)	41.7 (53.70)	39.6 (49.05)	43.4 (57.33)	41.6 (53.38)
	Median (IQR)	20.8 (10.1, 41.9)	22.2 (11.5, 50.5)	21.4 (10.6, 46.2)	21.3 (9.9, 42.3)	21.7 (11.5, 49.5)	21.5 (10.6, 48.2)
	Range	0.1 - 279.7	0.1 - 377.4	0.1 - 377.4	0.1 - 279.7	0.1 - 377.4	0.1 - 377.4
Disease Stage[2]							
I	n (%)	8 (5.1%)	3 (1.9%)	11 (3.5%)	8 (5.8%)	3 (2.1%)	11 (3.9%)
II	n (%)	48 (30.8%)	48 (31.2%)	96 (31.0%)	44 (31.7%)	44 (30.3%)	88 (31.0%)
III	n (%)	21 (13.5%)	42 (27.3%)	63 (20.3%)	20 (14.4%)	39 (26.9%)	59 (20.8%)
IV	n (%)	66 (42.3%)	52 (33.8%)	118 (38.1%)	57 (41.0%)	51 (35.2%)	108 (38.0%)
Unknown	n (%)	10 (6.4%)	6 (3.9%)	16 (5.2%)	7 (5.0%)	6 (4.1%)	13 (4.6%)
Other	n (%)	3 (1.9%)	3 (1.9%)	6 (1.9%)	3 (2.2%)	2 (1.4%)	5 (1.8%)
Presence of B symptoms[2]	n (%)	83 (53.2%)	73 (47.4%)	156 (50.3%)	70 (50.4%)	68 (46.9%)	138 (48.6%)
Evidence of extranodal involvement[2]	n (%)	62 (39.7%)	54 (35.1%)	116 (37.4%)	54 (38.8%)	51 (35.2%)	105 (37.0%)
Evidence of bone marrow involvement[2]	n (%)	20 (12.8%)	17 (11.0%)	37 (11.9%)	17 (12.2%)	17 (11.7%)	34 (12.0%)
History of bone marrow involvement	n (%)	19 (12.2%)	21 (13.6%)	40 (12.9%)	17 (12.2%)	20 (13.8%)	37 (13.0%)

Abbreviations: HL= Hodgkin's lymphoma; IQR= interquartile range; n/N= number of patients; sALCL= systemic anaplastic large cell lymphoma; SD= standard deviation
[1] Months since initial diagnosis = (date of first dose of brentuximab vedotin – date of initial diagnosis + 1)/ 30.44
[2] At time of initiation of treatment with brentuximab vedotin
Note(s): There were no missing data
Source: EOT Table 5, EOT Table 5_pp

10.2.4 Cancer Treatment History

Treatment history is summarised in Table 10-8.

10.2.4.1 Chemotherapy

Treatment history

Treatment history includes any chemotherapy that ended prior to initiation of treatment with brentuximab vedotin and was recorded at the baseline/enrolment visit. Per eligibility criteria patients were required to be on brentuximab vedotin monotherapy at enrolment but were treated following standard of care and there were no restrictions on the use of additional lines of chemotherapeutic treatments during follow-up. Treatment history is presented in EOT Table 6.1.

Overall 308 patients received a prior line of chemotherapy that finished prior to initiation of treatment with brentuximab vedotin (n=308/310, 99.4%), this included 154 patients in the prospective cohort (n=154/156, 98.7%) and all 154 patients in the retrospective cohort. Note: the 2 patients with no prior lines of therapy recorded were both found to have major protocol deviations related to eligibility criteria (patients 13001-004 and 51006-003 [Section 10.1.4]). The most commonly prescribed regimen prior to initiation of treatment with brentuximab vedotin was ABVD in 209 patients (n=209/310, 67.9%), followed by "Other" regimen prescribed to more than one third of the patients (n=114/310, 37.0%). ABVD was slightly more commonly used in the retrospective cohort (n=111/154, 72.1%), than in the prospective cohort (n=98/154, 63.6%).

Additional regimens that were prescribed prior to initiation of treatment with brentuximab vedotin for 10% to 20% of the study population were, in order of decreasing frequency, ESHAP (etoposide, methylprednisolone, Ara C [cytarabine], cisplatin) (n=55/310, 17.9%), DHAP (dexamethasone, high dose Ara C [cytarabine], cisplatin) (n=51/310, 16.6%), Gemcitabine or combination (n=45/310, 14.6%), IGEV (ifosfamide, gemcitabine, and vinorelbine) (n=42/310, 13.6%), CHOP (cyclophosphamide, Adriamycin®, Oncovin®, prednisolone) (n=38/310, 12.3%), and ICE (ifosfamide, carboplatin, etoposide) (n=36/310, 11.7%). DHAP was more commonly prescribed in the retrospective cohort (n=30/154, 19.5%) than the prospective cohort (n=21/154, 13.6%); IGEV was more commonly prescribed in the retrospective cohort (n=28/154, 18.2%) than the prospective cohort (n=14/154, 9.1%); ICE was more commonly prescribed in the retrospective cohort (n=21/154, 13.6%) than the prospective cohort (n=15/154, 9.7%); and BEACOPP (bleomycin, etoposide, Adriamycin®, cyclophosphamide, Oncovin®, procarbazine, prednisolone) was more commonly prescribed in the prospective cohort (n=18/154, 11.7%) than the retrospective cohort (n=11/154, 7.1%). Otherwise there were similar distributions of prior regimens between the cohorts. The median number of treatment cycles per patient was 8.0 cycles (IQR: 6.0, 10.0 cycles; range: 1.0-44.0 cycles). The median number of treatment cycles in the prospective cohort was 8.0 cycles (IQR: 6.0, 10.0 cycles), and in the retrospective cohort was 9.0 cycles (IQR: 6.0, 10.0 cycles); indicating that number of prior treatment cycles was similar in the two cohorts.

Prior treatment with brentuximab vedotin was permitted following protocol amendment 1 (version 2.0, dated 05 December 2013). Review of EOT Listing 2.3 found 6 patients who were treated with brentuximab vedotin prior to the current round of treatment; 1 patient completed the previous treatment 4 months prior to enrolment, and the remaining completed treatment at least 2 years prior to enrolment.

Concomitant treatment

Concomitant treatment includes any chemotherapy that was taken at the same time as treatment with brentuximab vedotin and was collected at baseline/enrolment and during follow-up visits. Concomitant chemotherapeutic treatment during follow-up is presented in EOT Table 6.2.

Of the 310 patients in the Safety Population, 93 patients received at least one additional line of chemotherapy while on-treatment (between the first dose and 30 days after the last dose of brentuximab vedotin) (n=93/310, 30.0%), this was similar between the two cohorts: 50 patients in the prospective cohort (n=50/156, 32.1%) and 43 patients in the retrospective cohort (n=43/154, 27.9%). This includes patients with protocol violations for use of concomitant chemotherapy at enrolment (inclusion criterion #3) (Section 10.1.4).

The most commonly used regimen was "Other" (n=49/93, 52.7%), with similar distributions between the two cohorts. Review of EOT Listing 5, found that within the category "Other" a variety of treatments were reported, the most common were: 9 patients were treated with nivolumab (n=9/310, 2.9%), 6 patients were treated with mini-BEAM (n=6/310, 1.9%), and 5 patients were treated with fludarabine (alone or in combination therapy) (n=5/310, 1.6%).

This was followed by bendamustine (n=37/93, 39.8%), which was used more frequently in the prospective cohort (n=22/50, 44.0%) than the retrospective cohort (n=15/43, 34.9%). Gemcitabine (alone or in combination therapy) was less commonly used (n=11/93, 11.8%), but was used more frequently in the prospective cohort (n=7/50, 14.0%) than the retrospective cohort (n=4/43, 9.3%). Rituximab wasn't commonly used (n=6/93, 6.5%), but was used more frequently in the retrospective cohort (n=4/43, 9.3%) than the prospective cohort (n=2/50, 4.0%). All other treatments were used by less than 4% of patients. The median number of additional treatment cycles per patient was 3.0 cycles (IQR: 2.0, 4.0 cycles; range: 0.0-19.0 cycles).

Of the 284 patients in the Per-protocol Population, 76 patients received at least one line of chemotherapy during follow-up (n=76/284, 26.8%), this was also similar between the two cohorts. The only chemotherapy that had a different frequency was bendamustine, which was less commonly prescribed in the Per-protocol Population (n=23/76, 30.3%), and in both the prospective cohort (n=13/39, 33.3%) and retrospective cohort (n=10/37, 27.0%). This would be expected given the number of patients with protocol violations due to the use of concomitant therapy.

10.2.4.2 Stem Cell Transplant

Prior SCT that was performed before initiation of treatment with brentuximab vedotin is presented in EOT Table 8.1; SCT that was performed while on-treatment is presented in EOT Table 8.2.

At enrolment, 111 patients had received a SCT (n=111/310, 35.8%), which was more common in the retrospective than in the prospective cohort (46.8% vs. 25.0%, respectively). Overall 104 of the SCTs were autologous (n=104/111, 93.7%), all 39 patients in the prospective cohort and 65 patients in the retrospective cohort (n=65/72, 90.3%) had ASCT.

Following initiation of treatment with brentuximab vedotin, 106 patients received a SCT (n=106/310, 34.2%), of which 47 (n=47/106, 44.3%) were autologous. The frequency of transplants was similar between the two cohorts, and in both cohorts less than half of the transplants were autologous. Most transplants occurred within the first year of treatment. In the prospective cohort, the number of patients receiving SCT at Month 6, Month 12, Month 18, and Month 24 were 30 (n=30/156, 19.2%), 18 (n=18/156, 11.5%), 4 (n=4/156, 2.6%), 3 (n=3/156, 1.9%), respectively, and in the retrospective cohort were 25 (n=25/154, 16.2%), 19 (n=19/154, 12.3%), 5 (n=5/154, 3.2%), and 1 (n=1/154, 0.6%), respectively. One patient had an ASCT at Month 42, otherwise there were no SCTs following Month 24.

10.2.4.3 Radiation Therapy

Prior radiation therapy that finished prior to initiation of treatment with brentuximab vedotin is presented in EOT Table 7.1. Concomitant radiation therapy while on-treatment is presented in EOT Table 7.2.

Prior to initiation of treatment, 97 patients had radiation therapy (n=97/310, 31.3%), this was more frequent in the retrospective cohort than the prospective cohort (35.7% vs. 26.9%, respectively). The most common anatomical site was mediastinal in both prospective cohort (n=11/42, 26.8%) and retrospective cohort (n=20/55, 36.4%). ‘Other’ anatomical site was reported in more than one third of patients in both cohorts (prospective cohort: n=16/42, 39.0%; retrospective cohort: n=21/55, 38.2%).

While on-treatment, 23 patients had radiation therapy (n=23/310, 7.4%) (including therapies that were ongoing at initiation of treatment), this was more frequent in the prospective cohort than the retrospective cohort (9.6% vs. 5.2%, respectively). In the retrospective cohort, mediastinal was the most common anatomical site receiving radiation therapy (n=3/8, 37.5%). Most of the patients in the prospective cohort received radiation therapy at ‘other’ anatomical site (n=10/15, 66.7%).

Table 10-8. Other Treatments at Baseline and While On-Treatment

		Safety Population		
		Prospective Cohort	**Retrospective Cohort**	**Total**
N		156	154	310
Baseline[1]				
Patients with prior line(s) of therapy	n (%)	154 (98.7%)	154 (100%)	308 (99.4%)
Number of cycles	Mean (SD)	8.5 (5.40)	9.5 (4.86)	9.0 (5.15)
	Median (range)	8.0 (1.0 - 44.0)	9.0 (1.0 - 27.0)	8.0 (1.0 - 44.0)
Patients with prior stem cell transplant	n (%)	39 (25.0%)	72 (46.8%)	111 (35.8%)
Autologous	n (%)	39 (100%)	65 (90.3%)	104 (93.7%)
Allogenic	n (%)	0	7 (9.7%)	7 (6.3%)
Patients with prior radiation therapy	n (%)	42 (26.9%)	55 (35.7%)	97 (31.3%)
On-treatment				
Patients with at least one line of therapy during follow-up	n (%)	50 (32.1%)	43 (27.9%)	93 (30.0%)
Number of cycles	Mean (SD)	3.7 (3.27)	3.7 (2.83)	3.7 (3.07)
	Median (range)	3.0 (1.0 - 19.0)	3.0 (0.0 - 10.0)	3.0 (0.0 - 19.0)
Patients with stem cell transplant				
Month 6	n (%)	30 (19.2%)	25 (16.2%)	55 (17.7%)
Month 12	n (%)	18 (11.5%)	19 (12.3%)	37 (11.9%)
Month 18	n (%)	4 (2.6%)	5 (3.2%)	9 (2.9%)
Month 24	n (%)	3 (1.9%)	1 (0.6%)	4 (1.3%)
Month 42	n (%)	1 (0.6%)	0	1 (0.3%)
Total*	n (%)	56 (35.9%)	50 (32.5%)	106 (34.2%)
Autologous*	n (%)	24 (42.9%)	23 (46.0%)	47 (44.3%)
Allogenic*	n (%)	32 (57.1%)	27 (54.0%)	59 (55.7%)
Patients with radiation therapy	n (%)	15 (9.6%)	8 (5.2%)	23 (7.4%)
		Per-protocol Population		
N		139	145	284
Patients with at least one line of therapy during follow-up	n (%)	39 (28.1%)	37 (25.5%)	76 (26.8%)
Number of cycles	Mean (SD)	3.5 (3.42)	3.8 (2.97)	3.6 (3.19)
	Median (range)	2.0 (1.0 - 19.0)	3.0 (0.0 - 10.0)	3.0 (0.0 - 19.0)

Abbreviations: n/N= number of patients; SD= standard deviation
* Calculated manually from Monthly data
[1] Previous treatment that ended prior to initiation of treatment with brentuximab vedotin
Note(s): There were no missing data
Source: EOT Table 6.1, EOT Table 6.2, EOT Table 6.2_pp, EOT Table 7.1, EOT Table 7.2, EOT Table 8.1, EOT Table 8.2

10.2.5 ECOG Performance Status

ECOG performance status at enrolment is presented in EOT Table 9.1. ECOG performance status during on-treatment follow-up is presented in EOT Table 9.2.

ECOG performance status, a quantitative prognostic descriptor of the status of symptoms and functions with respect to ambulatory status and need for care, was available for the majority of patients at enrolment. Overall 260 patients had ECOG performance status (n=260/310, 83.9%), which had the same distribution in both cohorts. Most of the patients had a performance status of 0 (fully active) (n=155/260, 59.6%), with a slightly higher proportion in the retrospective than in the prospective cohort (62.0% vs. 57.3%, retrospective). Another 82 patients had a score of 1 (symptomatic but completely ambulatory) (n=82/310, 31.5%), 19 patients had a score of 2 (ambulatory but still needing some care) (n=19/310, 7.3%), and 4 patients had a score of 3 (limited capability for self-care, >50% of time in bed) (n=4/310, 1.5%).

During follow-up, ECOG performance was reported bi-annually, throughout the study most patients (≥82%) had ECOG scores 0 or 1. At Month 6, 87.2% of patients, at Month 12, 84.0% of patients, at Month 18, 82.2% of patients, and at Month 24, 89.7% of patients had an ECOG score of 0 or 1. Past Month 24, less than 15% of patients had ECOG scores reported.

10.2.6 Concomitant Medication

Concomitant medication (other than chemotherapy and radiotherapy) taken by patients from the first dose of brentuximab vedotin through 30 days after the last dose of brentuximab is presented in EOT Table 10.

Of the 310 patients in the Safety Population, 281 patients reported at least 1 concomitant medication (n=281/310, 90.6%), the distribution was similar in the prospective and retrospective cohorts (89.7% and 91.6%, respectively).

The most common concomitant medications received in the prospective cohort were paracetamol (n=52/140, 37.1%), allopurinol (n=50/140, 35.7%), aciclovir (n=46/140, 32.9%), fluconazole (n=35/140, 25.0%), Bactrim® (sulfamethoxazole) (n=34/140, 24.3%), ondansetron (n=27/140, 19.3%), co-trimoxazole (n=25/140, 17.9%), omeprazole (n=23/140, 16.4%), filgrastim (n=21/140, 15.0%), lansoprazole (n=21/140, 15.0%), furosemide (n=17/140, 12.1%), zopiclone (n=17/140, 12.1%), dexamethasone (n=16/140, 11.4%), hydrocortisone (n=16/140, 11.4%), prednisolone (n=16/140, 11.4%), pantoprazole (n=15/140, 10.7%), ciprofloxacin (n=14/140, 10.0%), and meropenem (n=14/140, 10.0%). Other medication was prescribed in less than 10% of patients in the prospective cohort.

The most common concomitant medications received in the retrospective cohort were aciclovir (n=47/141, 33.3%), Bactrim® (sulfamethoxazole) (n=44/141, 31.2%), allopurinol (n=38/141, 27.0%), paracetamol (n=34/141, 24.1%), omeprazole (n=31/141, 22.0%), ondansetron (n=23/141, 16.3%), fluconazole (n=20/141, 14.2%), lansoprazole (n=19/141, 13.5%), pregabalin (n=15/141, 10.6%), filgrastim (n=15/141, 10.6%), and pantoprazole (n=15/141, 10.6%). Other medication was prescribed in less than 10% of patients in the retrospective cohort.

10.3 Outcome Data

The primary outcome for this PASS was safety-related events, and all patients were followed from enrolment until discontinuation from the study or patient end of study. The end of study was defined as following the last dose of the last patient (plus an additional 30-day safety follow-up), giving all patients the opportunity to complete 16 treatment cycles. Once the last patient received their last dose (07 September 2018), sites completed the end of study form for all patients that had not already discontinued. Each patient's study completion date was reported as either date of final contact to determine patient's survival status, or date of the last visit if it had occurred within the last 3 months. At the end of study, two patients were continuing to receive brentuximab vedotin (both have received >16 cycles).

Within this study, only SAEs and protocol-specified AESIs were collected. The SAEs and protocol-specified AESIs were presented primarily for the Safety Population (all patients who received at least 1 dose of brentuximab vedotin); when relevant, comparisons were made with the Per-protocol Population (patients excluded due to major protocol violations relating to eligibility). Results were always presented overall and by cohort (prospective and retrospective cohort). When relevant, results were also presented as treatment-related or treatment-emergent. On-treatment follow-up was from enrolment until 30 days following the last dose of brentuximab vedotin, post-treatment follow-up was from 31 days following the last dose of brentuximab vedotin.

Reported SAEs and/or AESIs are presented in Section 10.4.2, SAEs are presented in Section 10.4.3, and AESIs are presented in Section 10.6. All AE verbatim terms were recorded and coded to MedDRA PT level.

Safety Population

A total of 310 patients were included in the Safety Population, of whom 58 (18.7%) patients had a diagnosis of sALCL. The Safety Population included 156 patients in the prospective cohort (of whom 36 [23.1%] patients had a diagnosis of sALCL) and 154 patients in the retrospective cohort (of whom 22 [14.3%] patients had a diagnosis of sALCL).

Per-protocol Population

A total of 284 patients were included in the Per-protocol Population (of whom 50 [17.6%] patients had a diagnosis of sALCL). The Per-protocol Population included 139 patients in the prospective cohort (of whom 29 [20.9%] patients had a diagnosis of sALCL) and 145 patients in the retrospective cohort (of whom 21 [14.5%] patients had a diagnosis of sALCL).

10.4 Main Results

The purpose of this EU post-autorisation safety study was to further evaluate the safety profile of brentuximab vedotin administered in routine clinical practice. The first objective was to evaluate the occurrence of SAEs and protocol-specified AESIs, both serious and non-serious, in patients actively treated for relapsed or refractory CD30+ HL or relapsed or refractory sALCL in routine

practice with brentuximab vedotin. The second objective was to identify and describe potential risk factors for peripheral neuropathy (using SMQ) in relapsed or refractory CD30+ HL or relapsed or refractory sALCL patients treated with brentuximab vedotin.

10.4.1 Brentuximab Vedotin Exposure

A summary of brentuximab vedotin dosing information is in Table 10-9. Per product labelling, brentuximab vedotin is administered as an intravenous infusion over 30 minutes every three weeks until disease progression or unacceptable toxicity. The recommended dose for patients with normal renal and hepatic function is 1.8 mg/kg, up to 180 mg (the dose is capped at 100 kg). All patients included in the analyses were treated with at least 1 cycle of brentuximab vedotin.

The median time since first dose of brentuximab vedotin was 1.5 years (IQR: 0.7, 2.5 years; range: 0.0-4.8 years). The median number of treatment cycles per patient was 6.0 cycles (IQR: 4.0, 9.0 cycles; range: 1.0-41.0 cycles). The retrospective cohort had a slightly higher number of treatment cycles per patient with a median 7.5 cycles (IQR: 5.0, 11.0 cycles; range: 1.0-23.0 cycles) than the prospective cohort with a median 5.0 cycles (IQR: 3.0, 8.0 cycles; range: 1.0-41.0). The Per-protocol Population had small increases in years since first dose and treatment cycles per patient; this is due to the early discontinuation of 26 patients with major protocol violations who contributed with shorter study durations.

In the Safety Population, 125 patients had at least one dose interruption or modification (n=125/310, 40.3%); treatment interruptions or modifications were about twice as frequent in the retrospective cohort (n=82/154, 53.2%) than in the prospective cohort (n=43/156, 27.6%).

Overall 75 patients initiated another chemotherapy after enrolment (n=75/310, 24.2%), the distributions of use of different chemotherapies were similar between the retrospective and prospective cohorts. This excludes the 17 patients that had recorded use of other chemotherapies at the time of initiation of treatment of brentuximab vedotin (Section 10.1.4), and 1 patient that was mis-classified as having a concomitant treatment at enrolment. Review of the database found that no retrospective patients had records of initiating another chemotherapy between initiation of treatment with brentuximab vedotin and enrolment. The Per-protocol Population had similar distributions.

Table 10-9. Summary of Brentuximab Vedotin Dosing

		Safety Population			Per-protocol Population		
		Prospective Cohort	**Retrospective Cohort**	**Total**	**Prospective Cohort**	**Retrospective Cohort**	**Total**
Number of patients treated with brentuximab vedotin at enrolment	N	156	154	310	139	145	284
Number of patients who initiated another chemotherapy after enrolment[1]	n (%)	39 (25.0%)	36 (23.4%)	75 (24.2%)	37 (26.6%)	34 (23.4%)	71 (25.0%)
Number of patients with at least one dose interruption or modification[2]	n (%)	43 (27.6%)	82 (53.2%)	125 (40.3%)	39 (28.1%)	78 (53.8%)	117 (41.2%)
Number of patients permanently discontinued treatment	n (%)	154 (98.7%)	154 (100%)	308 (99.4%)	137 (98.6%)	145 (100%)	282 (99.3%)
Years since first dose[3]	Mean (SD)	1.4 (1.17)	2.0 (1.10)	1.7 (1.17)	1.5 (1.18)	2.0 (1.08)	1.8 (1.16)
	Median (IQR)	1.1 (0.5, 2.0)	2.0 (1.0, 2.9)	1.5 (0.7, 2.5)	1.3 (0.6, 2.1)	2.0 (1.1, 3.0)	1.6 (0.8, 2.6)
	Range	0.0-4.8	0.1-4.6	0.0-4.8	0.0-4.8	0.1-4.6	0.0-4.8
Treatment cycles per patient	Mean (SD)	6.3 (4.97)	8.3 (4.61)	7.3 (4.89)	6.5 (5.11)	8.5 (4.66)	7.5 (4.97)
	Median (IQR)	5.0 (3.0, 8.0)	7.5 (5.0, 11.0)	6.0 (4.0, 9.0)	5.0 (4.0, 8.0)	8.0 (5.0, 11.0)	6.0 (4.0, 9.0)
	Range	1.0-41.0	1.0-23.0	1.0-41.0	1.0-41.0	1.0-23.0	1.0-41.0
Injected volume per patient (mL)	Mean (SD)	1191.1 (972.17)	1649.4 (1219.31)	1418.8 (1123.79)	1232.9 (991.97)	1680.4 (1227.71)	1461.4 (1138.86)
	Median (range)	900.0 (100.0 - 6150.0)	1279.0 (150.0 - 8000.0)	1109.5 (100.0 - 8000.0)	900.0 (100.0 - 6150.0)	1350.0 (150.0 - 8000.0)	1141.8 (100.0 - 8000.0)

Abbreviations: IQR= interquartile range; n/N= number of patients; SD= standard deviation
[1] If the start date of the concomitant therapy is later than the date of first dose of brentuximab vedotin, the patient is counted as having initiated another line of therapy after baseline.
[2] Interruption/modification includes increased, reduced, held, missed, delayed and interrupted action on drug
[3] Years since first dose = (the last known date - first dose of brentuximab vedotin + 1)/365.25
Source: EOT Table 1, EOT Table 1_pp, EOT Table 11, EOT Table 11_pp

Patients were to be followed for their entire treatment course and until the end of the study, or study discontinuation. By the end of the study 308 patients had permanently discontinued treatment with brentuximab vedotin (n=308/310, 99.4%), which includes completion of planned treatment course. Two patients remained on long-term treatment at the end of study. A total of 90 patients discontinued treatment due to "an unsatisfactory therapeutic response" (n=90/310, 29.0%), 70 patients discontinued for "other" reasons (n=70/310, 22.6%), 66 patients discontinued due to "completion of planned treatment course" (n=66/310, 21.3%), 32 patients discontinued to "initiate SCT" (n=32/310, 10.3%), 30 patients discontinued due to an AE (n=30/301, 9.7%) and 15 patients discontinued because they had a "complete response" (n=15/310, 4.8%). The distributions were similar between both cohorts, except for "Other" as a reason for discontinuation, which was higher in the prospective cohort (n=43/156, 27.9%) than the retrospective cohort (n=32/154, 21.8%), and could be attributed to the greater number of protocol violations relating to eligibility criteria in the prospective cohort. A summary of treatment discontinuations by number of treatment cycles is presented in Table 10-10.

The median number of treatment cycles per patient was 6.0 (IQR: 4.0, 9.0 cycles; range: 1.0-41.0 cycles). Most patients discontinued treatment within 16 cycles (inclusive), there were only 9 patients who received more than 16 cycles of brentuximab vedotin (n=9/310, 2.9%). Of the 9 patients who received >16 cycles, the reasons for discontinuation were "complete response" (n=3/9, 33.3%), "completion of planned treatment course" (n=3/9, 33.3%), and "other" (n=1/9, 11.1%); 2 patients remained under treatment, one had received 20 cycles and the other 41 cycles at the end of study, both patients from the prospective cohort. Discontinuations occurred in cycles 17 (n=3), 18 (n=1), 21 (n=1), 22 (n=1) and 23 (n=1). The reasons for discontinuation were "complete response" (n=1/3, 33.3%), "completion of planned treatment course" (n=1/3, 33.3%), and "other: PI decision," (n=1/3, 33.3%) in patients with 17 cycles; "completion of planned treatment course" (n=1/1, 100%) in patients with 18 cycles and 23 cycles; and "complete response" (n=1/1, 100%) in patients with 21 cycles and 22 cycles.

Table 10-10. Summary of Treatment Discontinuation by Number of Cycles

		≤ 16 cycles[1]			> 16 cycles[2]		
		Prospective Cohort	**Retrospective Cohort**	**Total**	**Prospective Cohort**	**Retrospective Cohort**	**Total**
	N	156	154	310	156	154	310
	n	154	147	301	2	7	9
Patients that permanently discontinued treatment	n (%)	154 (98.7%)	147 (95.5%)	301 (97.1%)	0	7 (4.5%)	7 (2.3%)
Primary reason							
Adverse event	n (%)	14 (9.1%)	16 (10.9%)	30 (10.0%)	0	0 (0%)	0 (0%)
Complete response	n (%)	6 (3.9%)	7 (4.8%)	13 (4.3%)	0	3 (1.9%)	3 (1%)
Unsatisfactory therapeutic response	n (%)	43 (27.9%)	47 (32.0%)	90 (29.9%)	0	0	0
Completion of planned treatment course	n (%)	31 (20.1%)	33 (22.4%)	64 (21.3%)	0	3 (1.9%)	3 (1%)
Initiation of stem cell transplant	n (%)	17 (11.0%)	15 (10.2%)	32 (10.6%)	0	0	0
Pregnancy	n (%)	0	0	0	0	0	0
Other	n (%)	43 (27.9%)	32 (21.8%)	75 (24.9%)	0	1 (0.6%)	1 (0.3%)

Abbreviations: n/N= number of patients
[1] Patients reported as 'permanently discontinued' up to and including cycle 16
[2] Patients with any record from and including cycle 17
Note: there were no missing data.
Source: EOT Table 12

10.4.2 All Adverse Events

10.4.2.1 Results of Additional SAE Reconciliation

Following completion of the ARROVEN study, an additional SAE reconciliation was performed between the clinical database used to prepare these results and the global safety database. These reconciliation findings are included for transparency and accuracy but had no impact the interpretation of results.

Overall 3 patients with SMQ peripheral neuropathy had events reported as serious in the clinical database (and reported as serious in this CSR), when they were reported as non-serious in the safety database and confirmed by the sites to be non-serious. Of these, 1 patient had a subsequent report of a serious event and therefore would still have been reported as having an SAE using patient-level consolidated results. This resulted in 2 events reported as serious in Section 10.4.3 and Section 10.6.3 when they were actually non-serious.

Another 2 events (for 1 patient) of SMQ peripheral neuropathy were reported as non-serious in the clinical database and serious in the safety database, and were confirmed to be non-serious. This had no impact on the CSR results, but has been included here for completeness. All 4 patients with SMQ peripheral neuropathy (including 5 events) were in the retrospective cohort, and 2 of the events occurred before patient enrolment.

Summary of SAE reconciliation

Patient ID	SAE [1]	Date	Clinical database	Safety database	Outcome
19008-001 [2,3]	Peripheral neuropathy	22Aug2016	Serious	Non-serious	It was confirmed that the event is non-serious
51001-004 [2]	Paresthesia in fingers	18Jan2016	Serious	Non-serious	It was confirmed that the event is non-serious.
51021-001 [2,3]	Peripheral neuropathy	6Aug2015	Non-serious	Serious	It was confirmed that the event is non-serious.
51021-001 [2,3]	Sensorial hand neurophathy	23Jun2016	Non-serious	Serious	It was confirmed that the event is non-serious.
52001-003 [4]	Peripheral neuropathy sensory and motor	18Jul2017	Serious	Non-serious	It was confirmed that events are non-serious.

Abbreviations: SAE= serious adverse event
[1] SAE term as reported by PI using text-entry
[2] Patient did not have any other SAE reported in EOT Listing 7.2
[3] Patient had other AESI reported in EOT Listing 7.1
[4] Patient 52001-003 had a subsequent peripheral neuropathy reported as serious (28Mar2018) in EOT Listing 7.2

10.4.2.2 Summary of Severity

A summary of the frequencies and maximum severity of combined SAEs and/or protocol-specified AESIs, including treatment-emergent and treatment-related events are summarised in Table 10-11 described as mild or moderate (<Grade 3) and severe or life-threatening (≥Grade 3).

Overall, 230 patients reported at least one SAE and/or AESI (n=230/310, 74.2%). This was similar between cohorts, 110 patients in the prospective cohort (n=110/156, 70.5%) and 120 patients in the retrospective cohort (n=120/154, 77.9%). Overall, 97 patients had an event with a maximum severity of ≥Grade 3 (97/310, 31.3%), and 133 patients had an event with a maximum severity of <Grade 3 (n=133/310, 42.9%). A greater proportion of events were mild or moderate (<Grade 3) in the retrospective cohort than the prospective cohort (62.5% vs. 52.7%, respectively).

Most of the reported SAEs and/or AESIs were treatment-emergent, occurring in 228 of the 230 patients with an event (n=228/310, 73.5%). Treatment-related SAEs and/or AESIs were reported in 186 of the 230 with an event (n=186/310, 60.0%). Treatment-related events were about twice as frequently <Grade 3 (n=124/310, 40.0%) than ≥Grade 3 (n=62/310, 20.0%), the distributions were similar between cohorts.

Of the 109 patients that reported at least one SAE (n=109/310, 35.2%), more reported a maximum severity of ≥Grade 3 (n=67/310, 21.6%) than <Grade 3 (n=42/310, 13.5%). The distributions were similar between the cohorts. Treatment-related SAEs were reported in 68 of the 109 with an event (n=68/310, 21.9%). Treatment-related events were equally distributed between <Grade 3 and ≥Grade 3 (n=34/310, 11.0%). The prospective cohort had more events <Grade 3 than ≥Grade 3 (13.5% vs. 10.3%, respectively), whereas the retrospective cohort had more events ≥Grade 3 than <Grade 3 (11.7% vs. 8.4%, respectively).

Overall SAE and/or AESI led to 42 patients discontinuing treatment (n=42/310, 13.5%), which was identical between cohorts; and SAEs led to 32 patients discontinuing treatment (n=32/310, 10.3%), and 15 patients having dose modifications (n=15/310, 4.8%). Almost twice as many patients in the prospective cohort discontinued treatment due to an SAE than in the retrospective cohort (13.5% vs. 7.1%, respectively), whereas and more patients in the retrospective cohort had at least one dose modification due to an SAE than the prospective cohort (5.8% vs. 3.8%, respectively).

There were 72 patient deaths amongst the 230 patients who had an SAE and/or AESI (n=72/310, 23.2%). The event outcome was listed as death for 12 patients (n=12/310, 3.9%), 11 of whom were in the prospective cohort and only 1 in the retrospective cohort. There were 3 deaths due to treatment-related events (n=3/310, 1.0%).

The Per-protocol Population had similar results for all reporting of AEs in Table 10-11.

Table 10-11. Overview of adverse events, serious adverse events, and deaths

		Safety Population			Per-protocol Population		
		Prospective Cohort	Retrospective Cohort	Total	Prospective Cohort	Retrospective Cohort	Total
N		156	154	310	139	145	284
SAE and/or protocol-specified AESI							
Patients with any SAE and/or AESI and maximum severity							
n	n (%)	110 (70.5%)	120 (77.9%)	230 (74.2%)	105 (75.5%)	117 (80.7%)	222 (78.2%)
<Grade 3	n (%)	58 (37.2%)	75 (48.7%)	133 (42.9%)	56 (40.3%)	73 (50.3%)	129 (45.4%)
≥Grade 3	n (%)	52 (33.3%)	45 (29.2%)	97 (31.3%)	49 (35.3%)	44 (30.3%)	93 (32.7%)
Patients with any treatment-emergent[1] SAE and/or AESI and maximum severity							
n	n (%)	109 (69.9%)	119 (77.3%)	228 (73.5%)	104 (74.8%)	116 (80.0%)	220 (77.5%)
<Grade 3	n (%)	59 (37.8%)	76 (49.4%)	135 (43.5%)	57 (41.0%)	74 (51.0%)	131 (46.1%)
≥Grade 3	n (%)	50 (32.1%)	43 (27.9%)	93 (30.0%)	47 (33.8%)	42 (29.0%)	89 (31.3%)
Patients with any post-treatment[2] SAE and/or AESI and maximum severity							
n	n (%)	10 (6.4%)	5 (3.2%)	15 (4.8%)	10 (7.2%)	5 (3.4%)	15 (5.3%)
<Grade 3	n (%)	5 (3.2%)	3 (1.9%)	8 (2.6%)	5 (3.6%)	3 (2.1%)	8 (2.8%)
≥Grade 3	n (%)	5 (3.2%)	2 (1.3%)	7 (2.3%)	5 (3.6%)	2 (1.4%)	7 (2.5%)
Patients with any treatment-related[3] SAE and/or AESI and maximum severity							
n	n (%)	89 (57.1%)	97 (63.0%)	186 (60.0%)	87 (62.6%)	95 (65.5%)	182 (64.1%)
<Grade 3	n (%)	57 (36.5%)	67 (43.5%)	124 (40.0%)	55 (39.6%)	66 (45.5%)	121 (42.6%)
≥Grade 3	n (%)	32 (20.5%)	30 (19.5%)	62 (20.0%)	32 (23.0%)	29 (20.0%)	61 (21.5%)
Serious Adverse Events							
Patients with any SAE and maximum severity							
n	n (%)	59 (37.8%)	50 (32.5%)	109 (35.2%)	57 (41.0%)	48 (33.1%)	105 (37.0%)
<Grade 3	n (%)	23 (14.7%)	19 (12.3%)	42 (13.5%)	23 (16.5%)	17 (11.7%)	40 (14.1%)
≥Grade 3	n (%)	36 (23.1%)	31 (20.1%)	67 (21.6%)	34 (24.5%)	31 (21.4%)	65 (22.9%)
Patients with any treatment-emergent[1] SAE and maximum severity							
n	n (%)	57 (36.5%)	49 (31.8%)	106 (34.2%)	55 (39.6%)	47 (32.4%)	102 (35.9%)
<Grade 3	n (%)	22 (14.1%)	19 (12.3%)	41 (13.2%)	22 (15.8%)	17 (11.7%)	39 (13.7%)
≥Grade 3	n (%)	35 (22.4%)	30 (19.5%)	65 (21.0%)	33 (23.7%)	30 (20.7%)	63 (22.2%)
Patients with any post-treatment[2] SAE and maximum severity							
n	n (%)	4 (2.6%)	1 (0.6%)	5 (1.6%)	4 (2.9%)	1 (0.7%)	5 (1.8%)
<Grade 3	n (%)	2 (1.3%)	0	2 (0.6%)	2 (1.4%)	0	2 (0.7%)

		Safety Population			Per-protocol Population		
		Prospective Cohort	**Retrospective Cohort**	**Total**	**Prospective Cohort**	**Retrospective Cohort**	**Total**
≥Grade 3	n (%)	2 (1.3%)	1 (0.6%)	3 (1.0%)	2 (1.4%)	1 (0.7%)	3 (1.1%)
Patients with any treatment-related[3] SAE and maximum severity							
n	n (%)	37 (23.7%)	31 (20.1%)	68 (21.9%)	37 (26.6%)	30 (20.7%)	67 (23.6%)
<Grade 3	n (%)	21 (13.5%)	13 (8.4%)	34 (11.0%)	21 (15.1%)	12 (8.3%)	33 (11.6%)
≥Grade 3	n (%)	16 (10.3%)	18 (11.7%)	34 (11.0%)	16 (11.5%)	18 (12.4%)	34 (12.0%)
Patients with any treatment-emergent[1] treatment-related[3] SAE							
n	n (%)	34 (21.8%)	30 (19.5%)	64 (20.6%)	34 (24.5%)	29 (20.0%)	63 (22.2%)
Dose Modifications and Discontinuation							
Patient discontinued treatment[4] due to SAE and/or AESI	n (%)	21 (13.5%)	21 (13.6%)	42 (13.5%)	21 (15.1%)	21 (14.5%)	42 (14.8%)
Patient discontinued treatment[4] due to SAE	n (%)	21 (13.5%)	11 (7.1%)	32 (10.3%)	20 (14.4%)	11 (7.6%)	31 (10.9%)
Patient with dose modification[5] due to SAE	n (%)	6 (3.8%)	9 (5.8%)	15 (4.8%)	6 (4.3%)	8 (5.5%)	14 (4.9%)
Patient Deaths							
All deaths in SAE and/or AESI patients[6]	n (%)	45 (28.8%)	27 (17.5%)	72 (23.2%)	43 (30.9%)	27 (18.6%)	70 (24.6%)
SAE and/or AESI outcome[7]	n (%)	11 (7.1%)	1 (0.6%)	12 (3.9%)	10 (7.2%)	1 (0.7%)	11 (3.9%)
Due to treatment-related[3] SAE and/or AESI	n (%)	2 (1.3%)	1 (0.6%)	3 (1.0%)	2 (1.4%)	1 (0.7%)	3 (1.1%)

Abbreviations: AESI= adverse event of special interest; n/N= number of patients; SAE= serious adverse event
[1] Treatment-emergent adverse events started or worsened on or after the first dose of brentuximab vedotin and within 30 days after the last dose of brentuximab vedotin
[2] Post-treatment adverse events started at least 31 days after the last dose of brentuximab vedotin
[3] Treatment-related adverse events were determined to be related to brentuximab vedotin by the treating physician
[4] Discontinued includes "action taken"= "discontinued from study" and "dose permanently discontinued"
[5] Dose modification includes "action taken"= "dose increased", "dose reduced", "dose held", "dose interrupted" and "dose delayed"
[6] Deaths recorded in patients that had any SAE or protocol-specified AESI during the study
[7] Deaths recorded as the outcome of an SAE or protocol-specified AESI
Note(s): Percentages are based on total number of patients N
Source: EOT Table 13, EOT Table 13_pp, EOT Table 15.2, EOT Table 15.2_pp

10.4.2.3 Summary by System Organ Class

10.4.2.3.1 **All Serious Adverse Events and/or Adverse Events of Special Interest**

Overall 230 patients reported any SAE and/or AESI (n=230/310, 74.2%), these are summarised by MedDRA SOC and PT in Table 10-12. The most commonly reported SAE and/or AESI (SOCs and PTs reported in 5 or more patients in the Safety Population) were, in order of decreasing frequency:

- Nervous System Disorders (n=133/310, 42.9%): peripheral sensory neuropathy (n=72/310, 23.3%), neuropathy peripheral (n=40/310, 12.9%), paraesthesia (n=13/310, 4.2%), peripheral sensorimotor neuropathy (n=5/310, 1.6%)
- Infections and Infestations (n=95/310, 30.6%): pneumonia (n=16/310, 5.2%), upper respiratory tract infection (n=11/310, 3.5%), herpes zoster (n=5/310, 1.6%), lower respiratory tract infection (n=5/310, 1.6%), lung infection (n=5/310, 1.6%), respiratory tract infection (n=5/310, 1.6%), sepsis (n=5/310, 1.6%)
- Blood and Lymphatic System Disorders (n=53/310, 17.1%): neutropenia (n=46/310, 14.8%) and febrile neutropenia (n=6/310, 1.9%)
- General Disorders and Administration Site Conditions (n=38/310, 12.3%): pyrexia (n=27/310, 8.7%)
- Skin and Subcutaneous Tissue Disorders (n=28/310, 9.0%): rash (n=10/310, 3.2%), erythema (n=5/310, 1.6%)
- Respiratory, Thoracic and Mediastinal Disorders (n=12/310, 3.9%)
- Gastrointestinal Disorders (n=9/310, 2.9%)
- Cardiac Disorders (n=7/310, 2.3%)
- Neoplasms Benign, Malignant and Unspecified (including cysts and polyps) (n=6/310, 1.9%)
- Immune System Disorders (n=5/310, 1.6%)
- Injury, Poisoning and Procedural Complications (n=5/310, 1.6%)
- Metabolism and Nutrition Disorders (n=5/310, 1.6%)
- Renal and Urinary Disorders (n=5/310, 1.6%)

Differences reported between the prospective and retrospective cohorts are the following:

Nervous system disorders were more frequent in the retrospective cohort (n=79/154, 51.3%) than the prospective cohort (n=54/156, 34.6%), specifically neuropathy peripheral was more frequent in the retrospective cohort (n=29/154, 18.8%) than the prospective cohort (n=11/156, 7.1%), and paraesthesia was more frequent in the retrospective cohort (n=11/154, 7.1%,) than the prospective cohort (n=2/156, 1.3%). There was no difference in distributions between cohorts for peripheral sensory neuropathy.

Respiratory, thoracic and mediastinal disorders were more frequent in the retrospective cohort (n=8/154, 5.2%) than the prospective cohort (n=4/156, 2.6%).

Gastrointestinal disorders were more frequent in the retrospective cohort (n=8/154, 5.2%) than the prospective cohort (n=1/156, 0.6%).

Infections and infestations were more frequent in the prospective cohort (n=52/156, 33.3%) than the retrospective cohort (n=43/154, 27.9%), specifically pneumonia (n=12/156, 7.7% vs. n=4/154, 2.6%, respectively) and upper respiratory tract infections (n=7/154, 4.5% vs. n=4/154, 2.6%, respectively); lower respiratory tract infections (n=5/156, 3.2%), and sepsis (n=5/156, 3.2%) occurred only in the prospective cohort.

Blood and lymphatic system disorders were slightly more frequent in the prospective cohort (n=31/156, 19.9%) than the retrospective cohort (n=22/154, 14.3%), specifically neutropenia (n=27/156, 17.3% vs. n=19/154, 12.3%, respectively).

General disorders and administration site conditions were slightly more frequent in the prospective cohort (n=22/156, 14.1%) than the retrospective cohort (n=16/154, 10.4%), specifically pyrexia (n=17/156, 10.9% vs. n=10/154, 6.5%, respectively).

Neoplasms benign, malignant and unspecified (including cysts and polyps) were more frequent in the prospective cohort (n=5/156, 3.2%) than the retrospective cohort (n=1/154, 0.6%).

Table 10-12. Summary of Adverse Events Frequently Observed[§]

		Safety Population			Per-protocol Population		
		Prospective Cohort	**Retrospective Cohort**	**Total**	**Prospective Cohort**	**Retrospective Cohort**	**Total**
N		156	154	310	139	145	284
Any SAE and/or AESI[1]	n (%)	110 (70.5%)	120 (77.9%)	230 (74.2%)	105 (75.5%)	117 (80.7%)	222 (78.2%)
Blood and lymphatic system disorders	n (%)	31 (19.9%)	22 (14.3%)	53 (17.1%)	31 (22.3%)	21 (14.5%)	52 (18.3%)
Neutropenia	n (%)	27 (17.3%)	19 (12.3%)	46 (14.8%)	27 (19.4%)	18 (12.4%)	45 (15.8%)
Febrile neutropenia	n (%)	4 (2.6%)	2 (1.3%)	6 (1.9%)	4 (2.9%)	2 (1.4%)	6 (2.1%)
Cardiac disorders	n (%)	5 (3.2%)	2 (1.3%)	7 (2.3%)	5 (3.6%)	2 (1.4%)	7 (2.5%)
Gastrointestinal disorders	n (%)	1 (0.6%)	8 (5.2%)	9 (2.9%)	1 (0.7%)	8 (5.5%)	9 (3.2%)
General disorders and administration site conditions	n (%)	22 (14.1%)	16 (10.4%)	38 (12.3%)	22 (15.8%)	15 (10.3%)	37 (13.0%)
Pyrexia	n (%)	17 (10.9%)	10 (6.5%)	27 (8.7%)	17 (12.2%)	10 (6.9%)	27 (9.5%)
Immune system disorders	n (%)	3 (1.9%)	2 (1.3%)	5 (1.6%)	3 (2.2%)	2 (1.4%)	5 (1.8%)
Infections and infestations	n (%)	52 (33.3%)	43 (27.9%)	95 (30.6%)	50 (36.0%)	43 (29.7%)	93 (32.7%)
Pneumonia	n (%)	12 (7.7%)	4 (2.6%)	16 (5.2%)	12 (8.6%)	4 (2.8%)	16 (5.6%)
Upper respiratory tract infection	n (%)	7 (4.5%)	4 (2.6%)	11 (3.5%)	6 (4.3%)	4 (2.8%)	10 (3.5%)
Herpes zoster	n (%)	2 (1.3%)	3 (1.9%)	5 (1.6%)	2 (1.4%)	3 (2.1%)	5 (1.8%)
Lower respiratory tract infection	n (%)	5 (3.2%)	0	5 (1.6%)	5 (3.6%)	0	5 (1.8%)
Lung infection	n (%)	3 (1.9%)	2 (1.3%)	5 (1.6%)	3 (2.2%)	2 (1.4%)	5 (1.8%)
Respiratory tract infection	n (%)	2 (1.3%)	3 (1.9%)	5 (1.6%)	2 (1.4%)	3 (2.1%)	5 (1.8%)
Sepsis	n (%)	5 (3.2%)	0	5 (1.6%)	5 (3.6%)	0	5 (1.8%)
Injury, poisoning and procedural complications	n (%)	3 (1.9%)	2 (1.3%)	5 (1.6%)	3 (2.2%)	2 (1.4%)	5 (1.8%)
Metabolism and nutrition disorders	n (%)	1 (0.6%)	4 (2.6%)	5 (1.6%)	1 (0.7%)	4 (2.8%)	5 (1.8%)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	n (%)	5 (3.2%)	1 (0.6%)	6 (1.9%)	4 (2.9%)	1 (0.7%)	5 (1.8%)

		Safety Population			Per-protocol Population		
		Prospective Cohort	**Retrospective Cohort**	**Total**	**Prospective Cohort**	**Retrospective Cohort**	**Total**
Nervous system disorders	n (%)	54 (34.6%)	79 (51.3%)	133 (42.9%)	53 (38.1%)	76 (52.4%)	129 (45.4%)
Peripheral sensory neuropathy	n (%)	37 (23.7%)	35 (22.7%)	72 (23.2%)	37 (26.6%)	35 (24.1%)	72 (25.4%)
Neuropathy peripheral	n (%)	11 (7.1%)	29 (18.8%)	40 (12.9%)	11 (7.9%)	28 (19.3%)	39 (13.7%)
Paraesthesia	n (%)	2 (1.3%)	11 (7.1%)	13 (4.2%)	2 (1.4%)	10 (6.9%)	12 (4.2%)
Peripheral sensorimotor neuropathy	n (%)	3 (1.9%)	2 (1.3%)	5 (1.6%)	2 (1.4%)	2 (1.4%)	4 (1.4%)
Renal and urinary disorders	n (%)	2 (1.3%)	3 (1.9%)	5 (1.6%)	2 (1.4%)	3 (2.1%)	5 (1.8%)
Respiratory, thoracic and mediastinal disorders	n (%)	4 (2.6%)	8 (5.2%)	12 (3.9%)	4 (2.9%)	7 (4.8%)	11 (3.9%)
Skin and subcutaneous tissue disorders	n (%)	13 (8.3%)	15 (9.7%)	28 (9.0%)	12 (8.6%)	14 (9.7%)	26 (9.2%)
Rash	n (%)	5 (3.2%)	5 (3.2%)	10 (3.2%)	4 (2.9%)	5 (3.4%)	9 (3.2%)
Erythema	n (%)	2 (1.3%)	3 (1.9%)	5 (1.6%)	2 (1.4%)	2 (1.4%)	4 (1.4%)

Abbreviations: AESI= adverse event of special interest; n/N= number of patients; SAE= serious adverse event; SOC= system organ class; PT= preferred term
[§] SOCs and PTs reported in 5 or more patients
[1] Includes only serious adverse events (SAEs) and adverse events of special interest (AESIs)
Note(s): Percentages are based on total number of patients N.
Source: EOT Table 14.1.1.1, EOT Table 14.1.1.1_pp

10.4.2.3.2 Treatment-Related Serious Adverse Events and/or Adverse Events of Special Interest

Overall, 186 patients reported treatment-related SAE and/or AESI (n=186/310, 60.0%), these are summarised by MedDRA SOC and PT in Table 10-13. The most commonly reported treatment-related SAE and/or AESI (SOCs and PTs reported in 5 or more patients in the Safety Population) were, in order of decreasing frequency:

- Nervous system disorders (n=129/310, 41.6%): peripheral sensory neuropathy (n=72/310, 23.3%), neuropathy peripheral (n=39/310, 12.6%), paraesthesia (n=12/310, 3.9%), peripheral sensorimotor neuropathy (n=5/310, 1.6%)
- Infections and infestations (n=47/310, 15.2%): upper respiratory tract infection (n=9/310, 2.9%), pneumonia (n=7/310, 2.3%)
- Blood and lymphatic system disorders (n=40/310, 12.9%): neutropenia (n=37/310, 11.9%)
- General disorders and administration site conditions (n=19/310, 6.1%): pyrexia (n=17/310, 5.5%)
- Skin and subcutaneous tissue disorders (n=17/310, 5.5%): rash (n=6/310, 1.9%)
- Respiratory, thoracic and mediastinal disorders (n=6/310, 1.9%)

Differences reported between the prospective and retrospective cohorts are the following:

Nervous system disorders were more frequent in the retrospective cohort (n=75/154, 48.7%) than in the prospective cohort (n=54/156, 34.6%), specifically neuropathy peripheral was more frequent in the retrospective cohort (n=28/154, 18.2%) than the prospective cohort (n=11/156, 7.1%), and paraesthesia was more frequent in the retrospective cohort (n=10/154, 6.5%) than the prospective cohort (n=2/156, 1.3%). There was no difference in distributions between cohorts for peripheral sensory neuropathy.

Infections and infestations were more frequent in the prospective cohort (n=27/156, 17.3%) than in the retrospective cohort (n=20/154, 13.0%), specifically upper respiratory tract infections (n=6/154, 3.8% vs. n=3/154, 1.9%, respectively) and pneumonia (n=5/156, 3.2% vs. n=2/154, 1.3%, respectively).

Blood and lymphatic system disorders were slightly more frequent overall in the prospective cohort (n=25/156, 16.0%) than in the retrospective cohort (n=15/154, 9.7%), specifically neutropenia (n=23/156, 14.7% vs. n=14/154, 9.1%, respectively).

General disorders and administration site conditions were twice as frequent in the prospective cohort (n=13/156, 8.3%) than in the retrospective cohort (n=6/154, 3.9%), specifically pyrexia (n=13/156, 8.3% vs. n=4/154, 2.6%, respectively).

Table 10-13. Summary of Treatment-related Adverse Events Frequently Observed[§]

		Safety Population		
		Prospective Cohort	**Retrospective Cohort**	**Total**
N		156	154	310
Treatment-related[1] SAE and/or AESI [2]	n (%)	89 (57.1%)	97 (63.0%)	186 (60.0%)
Blood and lymphatic system disorders	n (%)	25 (16.0%)	15 (9.7%)	40 (12.9%)
Neutropenia	n (%)	23 (14.7%)	14 (9.1%)	37 (11.9%)
Febrile neutropenia	n (%)	3 (1.9%)	1 (0.6%)	4 (1.3%)
General disorders and administration site conditions	n (%)	13 (8.3%)	6 (3.9%)	19 (6.1%)
Pyrexia	n (%)	13 (8.3%)	4 (2.6%)	17 (5.5%)
Immune system disorders	n (%)	3 (1.9%)	2 (1.3%)	5 (1.6%)
Infections and infestations	n (%)	27 (17.3%)	20 (13.0%)	47 (15.2%)
Upper respiratory tract infection	n (%)	6 (3.8%)	3 (1.9%)	9 (2.9%)
Pneumonia	n (%)	5 (3.2%)	2 (1.3%)	7 (2.3%)
Lower respiratory tract infection	n (%)	4 (2.6%)	0	4 (1.3%)
Lung infection	n (%)	1 (0.6%)	2 (1.3%)	3 (1.0%)
Sepsis	n (%)	3 (1.9%)	0	3 (1.0%)
Herpes Zoster	n (%)	2 (1.3%)	0	2 (0.6%)
Respiratory tract infection	n (%)	0	1 (0.6%)	1 (0.3%)
Nervous system disorders	n (%)	54 (34.6%)	75 (48.7%)	129 (41.6%)
Peripheral sensory neuropathy	n (%)	37 (23.7%)	35 (22.7%)	72 (23.2%)
Neuropathy peripheral	n (%)	11 (7.1%)	28 (18.2%)	39 (12.6%)
Paraesthesia	n (%)	2 (1.3%)	10 (6.5%)	12 (3.9%)
Peripheral sensorimotor neuropathy	n (%)	3 (1.9%)	2 (1.3%)	5 (1.6%)
Respiratory, thoracic and mediastinal disorders	n (%)	1 (0.6%)	5 (3.2%)	6 (1.9%)
Skin and subcutaneous tissue disorders	n (%)	9 (5.8%)	8 (5.2%)	17 (5.5%)
Rash	n (%)	3 (1.9%)	3 (1.9%)	6 (1.9%)
Erythema	n (%)	1 (0.6%)	1 (0.6%)	2 (0.6%)

Abbreviations: AESI= adverse event of special interest; n/N= number of patients; SAE= serious adverse event; SOC= system organ class; PT= preferred term
[§] SOCs reported in 5 or more patients. For all SOC that were reported as treatment-related in at least 5 patients, the PT that were included in Table 10-12 were retained for comparison.
[1] Treatment-related adverse events were determined to be related to brentuximab vedotin by the treating physician
[2] Includes only serious adverse events (SAEs) and adverse events of special interest (AESIs)
Note(s): Percentages are based on total number of patients N.
Source: EOT Table 14.1.3

10.4.2.3.3 **Severity of Serious Adverse Events and/or Adverse Events of Special Interest**

The severity of SAEs and/or AESIs described as mild or moderate (<Grade 3) and severe or life-threatening (≥Grade 3) are presented by MedDRA SOC and PT for the Safety Population in EOT Table 14.1.2. The highest severity of each event per patient was reported.

Overall more patients had an SAE and/or AESI of maximum severity <Grade 3 (n=133/310, 42.9%) than ≥Grade 3 (n=97/310, 31.1%). The distribution of SAE and/or AESI ≥Grade 3 was similar between the prospective cohort and retrospective cohorts (33.3% vs. 29.2%, respectively), and SAE and/or AESI mild or moderate (<Grade 3) were more frequent in retrospective cohort than the prospective cohort (48.7% vs. 37.2%).

SAE and/or AESI that presented most commonly with ≥Grade 3 were: blood and lymphatic disorders (n=35/310, 11.3%), infections and infestations (n=34/310, 11.0%), nervous system disorders (n=16/310, 5.2%), general disorders and administration site conditions (n=11/310, 3.5%), cardiac disorders (n=5/310, 1.6%), gastrointestinal disorders (n=5/310, 1.6%), neoplasms benign, malignant and unspecified (including cysts and polyps) (n=5/310, 1.6%).

Blood and lymphatic system disorders were almost twice as frequently ≥Grade 3 (n=35/310, 11.3%) than <Grade 3 (n=18/310, 5.8%), which was similar between cohort. These were primarily neutropenia which had the same distribution, febrile neutropenia was always ≥Grade 3 (n=6/310, 1.9%).

Infections and infestations were almost twice as frequently <Grade 3 (n=61/310, 19.7%) than ≥Grade 3 (n=34/310, 11.0%). These were primarily pneumonia which was more frequently ≥Grade 3 (n=10/310, 3.2%) than <Grade 3 (n=6/310, 1.9%), upper respiratory tract infections (n=11/310, 3.5%) and respiratory tract infections (n=5/310, 1.6%) were always <Grade 3, and sepsis that was mostly ≥Grade 3 (n=4/310, 1.3%), with only 1 event <Grade 3 (n=1/310, 0.3%).

Nervous system disorders were predominantly <Grade 3 (n=117/310, 57.1%) than ≥Grade 3 (n=16/310, 5.2%). These were primarily neuropathy peripheral which was more frequently <Grade 3 (n=34/310, 11.0%) than ≥Grade 3 (n=6/310, 1.9%), and peripheral sensory neuropathy which was more frequently <Grade 3 (n=67/310, 21.6%) than ≥Grade 3 (n=5/310, 1.6%), and paraesthesia was always <Grade 3 (n=13/310, 4.2%).

General disorders and administration site conditions were more frequently <Grade 3 (n=27/310, 8.7%) than ≥Grade 3 (n=11/310, 3.5%). These were primarily pyrexia which had the similar distribution.

10.4.2.4 Adverse Events by Subgroups

The frequency of AEs was also described by subgroups of interest, including age group (EOT Table 14.1.1.2), sex (EOT Table 14.1.1.3), CD30+ lymphoma type (EOT Table 14.1.1.4), ALK positivity (EOT Table 14.1.1.5), long-term treatment (EOT Table 14.1.1.6), and post-autologous SCT status (EOT Table 14.1.1.7)

10.4.2.4.1 **Adverse Events by Age group (<65 years vs. ≥65 years)**

In the Safety Population there were 234 patients <65 years (n=234/310, 75.5%), and 76 patients ≥65 years (n=76/310, 24.5%). In the prospective cohort, 114 patients were <65 years (n=114/156, 73.1%) and 42 patients were ≥65 years (n=42/156, 26.9%). In the retrospective cohort, patients were <65 years 120 (n=120/154, 77.9%) and 34 patients were ≥65 years (n=34/154, 22.1%).

More patients ≥65 years than <65 years reported SAEs and/or AESIs (85.5% vs. 70.5%, respectively). The majority of the patients ≥65 years reported at least one SAE and/or AESI (n=65/76, 85.5%), the rate of occurrence was slightly higher in the retrospective cohort (n=30/34, 88.2%) than the prospective cohort (n=35/42, 83.3%). Of the patients <65 years, 165 reported at least one SAE and/or AESI (n=165/234, 70.5%), the frequency was slightly higher in the retrospective cohort (n=90/120, 75.0%) than the prospective cohort (n=75/114, 65.8%).

Infections and infestations were more frequent in patients ≥65 years (n=28/76, 36.8%) than <65 years (n=67/234, 28.6%); pneumonia was reported more frequently in elderly patients (9.2% vs. 3.8%, respectively), whereas upper respiratory tract infections were reported more frequently in patients <65 years (4.7% vs. 2.6%, respectively), and sepsis was more frequent in elderly patients (2.6% vs.1.3%, respectively).

Blood and lymphatic system disorders were more frequent in patients aged ≥65 years (n=20/76, 26.3%) than <65 years (n=33/234, 14.1%); febrile neutropenia was more frequent in elderly patients (5.3% vs. 0.9%, respectively).

Nervous system disorders (primarily peripheral sensory neuropathy and neuropathy peripheral) were more frequent in patients aged ≥65 years (n=39/76, 51.3%) than <65 years (n=94/234, 40.2%).

10.4.2.4.2 **Adverse Events by Sex**

In the Safety Population there were 190 males (n=190/310, 61.3%) and 120 females (n=120/310, 38.7%). In the prospective cohort, 93 patients were male (n=93/156, 59.6%) and 63 patients were female (n=63/156, 40.4%). In the retrospective cohort, 97 patients were male (n=97/154, 63.0%) and 57 patients were female (n=57/154, 37.0%).

There was a similar frequency of SAEs and/or AESIs between males and females (73.7% vs. 75.0%, respectively): 140 males and 90 females had at least one event. Blood and lymphatic system disorders (specifically neutropenia) were more frequent in females (n=26/120, 21.7%) than males (n=27/190, 14.2%), however febrile neutropenia was more frequent in males than females (n=5/190, 2.6% vs. 1/120, 0.8%, respectively).

10.4.2.4.3 **Adverse Events by Lymphoma Type (CD30+ HL and sALCL)**

In the Safety Population there were 252 patients with CD30+ HL (n=252/310, 81.3%) and 58 patients with sALCL (n=58/310, 18.7%). In the prospective cohort, 120 patients had CD30+ HL

(n=120/156, 76.9%) and 36 patients had sALCL (n=36/156, 23.1%). In the retrospective cohort, 132 patients had CD30+ HL (n=132/154, 85.7%) and 22 patients had sALCL (n=22/154, 14.3%).

There was a similar frequency of SAEs and/or AESIs between CD30+ HL and sALCL patients (74.2% vs. 74.1%, respectively): 187 CD30+ HL patients and 43 of sALCL patients had at least one event. Blood and lymphatic system disorders (including neutropenia) were more frequent in CD30+ HL patients (n=46/252, 18.3%) than sALCL patients (n=7/58, 12.1%).

10.4.2.4.4 **Adverse Events by ALK Positivity (sALCL Only)**

In the Safety Population, only 17 patients were ALK+, out of 58 sALCL patients.

Amongst the ALK+ sALCL patients, 7 patients experienced at least 1 SAE and/or AESI (n=7/17, 41.2%), these were primarily nervous system disorders (n=5/7, 71.4%). This was different from the rates reported in sALCL patients overall, 74.1% for any SAE and/or AESI and 43.1% for nervous system disorders, however, the small sample size of ALK+ patients prevents meaningful interpretation.

10.4.2.4.5 **Adverse Events by Long-Term Treatment (>16 Cycles vs. ≤16 Cycles)**

In the Safety Population there were 9 patients with >16 cycles (n=9/310, 2.9%) and 301 patients with ≤16 cycles (n=301/310, 97.1%) of treatment with brentuximab vedotin. In the prospective cohort, 2 patients had >16 cycles (n=2/156, 1.3%) and 154 patients had ≤16 cycles (n=154/156, 98.7%). In the retrospective cohort, 7 patients had >16 cycles (n=7/154, 4.5%) and 147 patients had ≤16 cycles (n=147/154, 95.5%).

All 9 patients with >16 cycles and 221 of 301 patients with ≤16 cycles (n=221/310, 71.2%) had at least one SAE and/or AESI. The small sample size of patients with >16 cycles prevents meaningful interpretation.

10.4.2.4.6 **Adverse Events by Post-Autologous Stem Cell Transplant status**

In the Safety Population there were 150 patients post-ASCT (n=150/310, 48.4%). In the prospective cohort, 63 patients were post-ASCT (n=63/156, 40.4%) and in the retrospective cohort, 87 patients were post-ASCT (n=87/154, 56.5%).

Overall, 93 patients post-ASCT had at least one SAE and/or AESI (n=93/150, 62.0%). Blood and lymphatic system disorders (including neutropenia) were less frequent in post-ASCT patients (n=19/150, 12.6%) than the overall population (n=53/310, 17.1%). Infections and infestations were less frequent in post-ASCT patients (n=35/150, 23.2%) than the overall population (n=95/310, 30.6%). Nervous system disorders were slightly less frequent in post-ASCT patients (n=56/150, 37.1%) than the overall population (n=133/310, 42.9%).

10.4.3 Serious Adverse Events

10.4.3.1 Summary by System Organ Class

A summary of the frequencies and incidence of SAEs, including treatment-related SAEs, by SOC and PT are presented in Table 10-14. Reporting as incidence in person-years removes potential differences due to differential length of observation between the cohorts.

Overall, 109 patients reported at least one SAE (n=109/310, 35.2%), this includes 59 patients in the prospective cohort (n=59/156, 37.8%) and 50 patients in the retrospective cohort (n=50/154, 32.5%). Following additional SAE reconciliation, it was found that 2 patients were reported as experiencing an SAE in the clinical database, when they should have been reported as non-serious, both were in the retrospective cohort. Therefore, 107 patients actually experienced at least one SAE (n=107/310, 34.5%). The following reporting of results remains consistent with the original results, and has not been altered to reflect the findings of the SAE reconciliation since they do not affect interpretation of the results. The SAE incidence was similar (differences partly owing to shorter periods of time at risk) between the Safety Population and Per-protocol Populations.

Almost all SAEs were on-treatment (ie, after the first dose of brentuximab vedotin and until 30 days following the last dose of brentuximab vedotin) (n=106/310, 34.2%). Three patients (n=3/310, 1.0%) had post-treatment SAEs (ie, began at least 31 days after the last dose of brentuximab vedotin).

Treatment-related SAEs occurred in 68 patients (n=68/310, 21.9%), with similar distributions between cohorts.

Table 10-14. Summary of Serious Adverse Events

		Safety Population			Per-protocol Population		
		Prospective Cohort	Retrospective Cohort	Total	Prospective Cohort	Retrospective Cohort	Total
N		156	154	310	139	145	284
Any SAE	n (%)	59 (37.8%)	50 (32.5%)	109 (35.2%)	57 (41.0%)	48 (33.1%)	105 (37.0%)
On-treatment[1] SAE	n (%)	57 (36.5%)	49 (31.8%)	106 (34.2%)	---	---	---
Post-treatment[2] SAE	n (%)	4 (2.6%)	1 (0.6%)	5 (1.6%)	---	---	---
Treatment-related[3] SAE	n (%)	37 (23.7%)	31 (20.1%)	68 (21.9%)	---	---	---

Abbreviations: CI= confidence interval; n/N= number of patients; SAE= serious adverse event; ---= not available in EOT Tables
[1] On-treatment events began after the first dose of brentuximab vedotin and until 30 days following the last dose of brentuximab vedotin
[2] Post-treatment events began at least 31 days after the last dose of brentuximab
[3] Treatment-related adverse events were determined to be related to brentuximab vedotin by the treating physician
Note(s): Percentages are based on total number of patients N.
Source: EOT Table 14.2.1.1, EOT Table 14.2.1.1_pp, EOT Table 14.2.1.1a, EOT Table 14.2.1.1b, EOT Table 14.2.2

10.4.3.1.1 **All Serious Adverse Events**

The most commonly reported SAEs (SOCs and PTs reported in 5 or more patients in the Safety Population) are presented in Table 10-15. In order of decreasing incidence these were:

- Infections and infestations (29.6 [95% CI 20.5, 38.7] per 100 person-years; n=45/310, 14.5%): pneumonia (8.5 [95% CI 4.0, 13.1] per 100 person-years; n=14/310, 4.5%), sepsis (3.0 [95% CI 0.3, 5.7] per 100 person-years; n=5/310, 1.6%)
- General disorders and administration site conditions (19.2 [95% CI 12.2, 26.1] per 100 person-years; n=30/310, 9.7%): pyrexia (13.3 [95% CI 7.6, 19.0] per 100 person-years; n=21/310, 6.8%)
- Nervous system disorders (16.1 [95% CI 9.6, 22.5] per 100 person-years; n=25/310, 8.1%): peripheral sensory neuropathy (7.6 [95% CI 3.2, 11.9] per 100 person-years; n=12/310, 3.9%), neuropathy peripheral (3.6 [95% CI 0.7, 6.6] per 100 person-years; n=6/310, 1.9%)
- Blood and lymphatic system disorders (8.0 [95% CI 3.6, 12.3] per 100 person-years; n=13/310, 4.2%): neutropenia (4.3 [95% CI 1.1, 7.4] per 100 person-years; n=7/310, 2.3%)
- Respiratory, thoracic and mediastinal disorders (4.8 [95% CI 1.5, 8.2] per 100 person-years; n=8/310, 2.6%)
- Gastrointestinal disorders (4.2 [95% CI 1.1, 7.4] per 100 person-years; n=7/310, 2.3%)
- Cardiac disorders (3.6 [95% CI 0.7, 6.5] per 100 person-years; n=6/310, 1.9%)
- Neoplasms benign, malignant and unspecified (including cysts and polyps) (3.6 [95% CI 0.7, 6.5] per 100 person-years; n=6/310, 1.9 %)
- Renal and urinary disorders (3.2 [95% CI 0.4, 6.1] per 100 person-years; n=5/310, 1.8%)

Differences reported between the prospective and retrospective cohorts are as follows:

Infections and infestations had higher incidence in the prospective cohort (45.6 [95% CI 27.4, 63.8] per 100 person-years) than in the retrospective cohort (18.8 [95% CI 9.6, 27.9] per 100 person-years). Pneumonia had higher incidence in the prospective cohort (15.9 [95% CI 6.1, 25.8] per 100 person-years) than the retrospective cohort (3.2 [95% CI 0.0, 6.8] per 100 person-years); and sepsis only occurred in the prospective cohort (7.2 [95% CI 0.7, 13.7] per 100 person-years).

General disorders and administration site conditions had higher incidence in the prospective cohort (31.7 [95% CI 17.5, 46.0] per 100 person-years) than in the prospective cohort (10.7 [95% CI 4.1, 17.3] per 100 person-years). Pyrexia had higher incidence in the prospective cohort (23.6

[95% CI 11.6, 35.6] per 100 person-years) than the retrospective cohort (6.3 [95% CI 1.2, 11.4] per 100 person-years).

Nervous system disorders had similar incidence between the retrospective cohort (17.3 [95% CI 8.5, 26.1] per 100 person-years) and the prospective cohort (14.2 [95% CI 4.6, 17.3] per 100 person-years), despite having a higher frequency in the retrospective cohort. Within this classification, neuropathy peripheral occurred in the retrospective cohort only (6.3 [95% CI 1.2, 11.5] per 100 person-years). Peripheral sensory neuropathy had higher incidence in the prospective cohort (11.0 [95% CI 2.7, 19.4]) than in the retrospective cohort (incidence=5.3 [95% CI 0.6, 9.9] per 100 person-years).

Blood and lymphatic system disorders had higher incidence in the prospective cohort (10.1 [95% CI 2.4, 17.9] per 100 person-years) than the retrospective cohort (6.4 [95% CI 1.3, 11.5] per 100 person-years). Within this classification, the incidence on neutropenia was nearly identical between cohorts.

Gastrointestinal disorders occurred in the retrospective cohort only (7.4 [95% CI 1.8, 13.0] per 100 person-years).

Cardiac disorders had higher incidence in the prospective cohort (7.1 [95% CI 0.8, 13.5] per 100 person-years) than in the retrospective cohort (1.0 [95% CI 0.0, 3.1] per 100 person-years).

Neoplasms benign, malignant and unspecified (including cysts and polyps) had higher incidence in the prospective cohort (7.2 [95% CI 0.8, 13.5] per 100 person-years) than the retrospective cohort (1.0 [95% CI 0.0, 3.1] per 100 person-years), although this observation is based on few events.

Skin and subcutaneous tissue disorders had higher incidence in the prospective cohort (7.2 [95% CI 0.8, 13.6] per 100 person-years) than the retrospective cohort (1.0 [95% CI 0.0, 3.1] per 100 person-years).

Table 10-15. Summary of Serious Adverse Events Frequently Observed[§]

		Safety Population			Per-protocol Population		
		Prospective Cohort	**Retrospective Cohort**	**Total**	**Prospective Cohort**	**Retrospective Cohort**	**Total**

		Safety Population			Per-protocol Population		
		Prospective Cohort	**Retrospective Cohort**	**Total**	**Prospective Cohort**	**Retrospective Cohort**	**Total**
N		156	154	310	139	145	284
Any SAE	n (%)	59 (37.8%)	50 (32.5%)	109 (35.2%)	57 (41.0%)	48 (33.1%)	105 (37.0%)
Blood and lymphatic system disorders							
SOC	n (%)	7 (4.5%)	6 (3.9%)	13 (4.2%)	7 (5.0%)	6 (4.1%)	13 (4.6%)
	Incidence[1] (95%CI)	10.1 (2.4, 17.9)	6.4 (1.3, 11.5)	8.0 (3.6, 12.3)	10.9 (2.5, 19.3)	6.6 (1.3, 11.9)	8.4 (3.8, 13.0)
Neutropenia	n (%)	3 (1.9%)	4 (2.6%)	7 (2.3%)	3 (2.2%)	4 (2.8%)	7 (2.5%)
	Incidence[1] (95%CI)	4.3 (0.0, 9.3)	4.2 (0.1, 8.4)	4.3 (1.1, 7.4)	4.6 (0.0, 10.0)	4.4 (0.1, 8.7)	4.5 (1.1, 7.8)
Febrile neutropenia[2]	n (%)	3 (1.9%)	1 (0.6%)	4 (1.3%)	3 (2.2%)	1 (0.7%)	4 (1.4%)
	Incidence[1] (95%CI)	4.3 (0.0, 9.3)	1.0 (0.0, 3.1)	2.4 (0.0, 4.8)	4.6 (0.0, 10.0)	1.1 (0.0, 3.2)	2.5 (0.0, 5.1)
Cardiac disorders							
SOC	n (%)	5 (3.2%)	1 (0.6%)	6 (1.9%)	5 (3.6%)	1 (0.7%)	6 (2.1%)
	Incidence[1] (95%CI)	7.1 (0.8, 13.5)	1.0 (0.0, 3.1)	3.6 (0.7, 6.5)	7.6 (0.8, 14.5)	1.1 (0.0, 3.2)	3.8 (0.7, 6.9)
Gastrointestinal disorders							
SOC	n (%)	0	7 (4.5%)	7 (2.3%)	0	7 (4.8%)	7 (2.5%)
	Incidence[1] (95%CI)	0	7.4 (1.8, 13.0)	4.2 (1.1, 7.4)	0	7.7 (1.9, 13.5)	4.5 (1.1, 7.8)
General disorders and administration site conditions							
SOC	n (%)	20 (12.8%)	10 (6.5%)	30 (9.7%)	20 (14.4%)	10 (6.9%)	30 (10.6%)
	Incidence[1] (95%CI)	31.7 (17.5, 46.0)	10.7 (4.1, 17.3)	19.2 (12.2, 26.1)	34.3 (18.8, 49.9)	11.1 (4.2, 17.9)	20.2 (12.9, 27.6)
Pyrexia	n (%)	15 (9.6%)	6 (3.9%)	21 (6.8%)	15 (10.8%)	6 (4.1%)	21 (7.4%)
	Incidence[1] (95%CI)	23.6 (11.6, 35.6)	6.3 (1.2, 11.4)	13.3 (7.6, 19.0)	25.5 (12.5, 38.5)	6.6 (1.3, 11.9)	14.0 (8.0, 20.0)
Infections and infestations							
SOC	n (%)	28 (17.9%)	17 (11.0%)	45 (14.5%)	27 (19.4%)	17 (11.7%)	44 (15.5%)
	Incidence[1] (95%CI)	45.6 (27.4, 63.8)	18.8 (9.6, 27.9)	29.6 (20.5, 38.7)	47.6 (28.0, 67.2)	19.5 (9.9, 29.1)	30.6 (21.0, 40.2)
Pneumonia	n (%)	11 (7.1%)	3 (1.9%)	14 (4.5%)	11 (7.9%)	3 (2.1%)	14 (4.9%)
	Incidence[1] (95%CI)	15.9 (6.1, 25.8)	3.2 (0.0, 6.8)	8.5 (4.0, 13.1)	17.1 (6.4, 27.8)	3.3 (0.0, 7.0)	9.0 (4.2, 13.8)
Sepsis	n (%)	5 (3.2%)	0	5 (1.6%)	5 (3.6%)	0	5 (1.8%)
	Incidence[1] (95%CI)	7.2 (0.7, 13.7)	0	3.0 (0.3, 5.7)	7.7 (0.7, 14.7)	0	3.2 (0.4, 6.0)
Neoplasms benign, malignant and unspecified (including cysts and polyps)							
SOC	n (%)	5 (3.2%)	1 (0.6%)	6 (1.9%)	4 (2.9%)	1 (0.7%)	5 (1.8%)

		Safety Population			Per-protocol Population		
		Prospective Cohort	**Retrospective Cohort**	**Total**	**Prospective Cohort**	**Retrospective Cohort**	**Total**
	Incidence[1] (95%CI)	7.2 (0.8, 13.5)	1.0 (0.0, 3.1)	3.6 (0.7, 6.5)	6.1 (0.1, 12.2)	1.1 (0.0, 3.2)	3.2 (0.4, 6.0)
Nervous system disorders							
SOC	n (%)	9 (5.8%)	16 (10.4%)	25 (8.1%)	9 (6.5%)	14 (9.7%)	23 (8.1%)
	Incidence[1] (95%CI)	14.2 (4.6, 23.8)	17.3 (8.5, 26.1)	16.1 (9.6, 22.5)	15.4 (5.0, 25.8)	15.7 (7.2, 24.2)	15.6 (9.0, 22.1)
Neuropathy peripheral	n (%)	0	6 (3.9%)	6 (1.9%)	0	5 (3.4%)	5 (1.8%)
	Incidence[1] (95%CI)	0	6.3 (1.2, 11.5)	3.6 (0.7, 6.6)	0	5.5 (0.6, 10.3)	3.2 (0.4, 6.0)
Peripheral sensory neuropathy	n (%)	7 (4.5%)	5 (3.2%)	12 (3.9%)	7 (5.0%)	5 (3.4%)	12 (4.2%)
	Incidence[1] (95%CI)	11.0 (2.7, 19.4)	5.3 (0.6, 9.9)	7.6 (3.2, 11.9)	11.9 (2.9, 21.0)	5.4 (0.6, 10.3)	8.0 (3.4, 12.6)
Renal and urinary disorders							
SOC	n (%)	2 (1.3%)	3 (1.9%)	5 (1.6%)	2 (1.4%)	3 (2.1%)	5 (1.8%)
	Incidence[1] (95%CI)	2.9 (0.0, 6.9)	3.2 (0.0, 6.8)	3.1 (0.4, 5.7)	3.2 (0.0, 7.5)	3.3 (0.0, 7.0)	3.2 (0.4, 6.1)
Respiratory, thoracic and mediastinal disorders							
SOC	n (%)	3 (1.9%)	5 (3.2%)	8 (2.6%)	3 (2.2%)	5 (3.4%)	8 (2.8%)
	Incidence[1] (95%CI)	4.3 (0.0, 9.2)	5.2 (0.6, 9.8)	4.8 (1.5, 8.2)	4.6 (0.0, 9.9)	5.4 (0.6, 10.2)	5.1 (1.5, 8.6)
Skin and subcutaneous tissue disorders							
SOC	n (%)	5 (3.2%)	1 (0.6%)	6 (1.9%)	5 (3.6%)	1 (0.7%)	6 (2.1%)
	Incidence[1] (95%CI)	7.2 (0.8, 13.6)	1.0 (0.0, 3.1)	3.6 (0.7, 6.6)	7.7 (0.9, 14.6)	1.1 (0.0, 3.2)	3.8 (0.7, 6.9)

Abbreviations: AESI= adverse event of special interest; CI= confidence interval; SAE= serious adverse event; SOC= system organ class; PT= preferred term
[§] SOCs and PTs reported in 5 or more patients
[1] Incidence density rate (per 100 person-years)
[2] Febrile neutropenia is a form of neutropenia and specified as an AESI, it was therefore included if neutropenia was presented
Note(s): Percentages are based on total number of patients N.
Time at risk was defined as between the first dose of brentuximab vedotin and: event start date, last dose plus 30 days, date of death, study completion/ discontinuation, data base lock, whichever occurred first.
Source: EOT Table 14.2.1.1, EOT Table 14.2.1.1_pp

10.4.3.1.2 **Treatment-related Serious Adverse Events**

The most commonly reported treatment-related SAEs (SOCs and PTs reported in 5 or more patients in the Safety Population) are presented in Table 10-16. In order of decreasing incidence these were:

- Nervous system disorders (15.4 [95% CI 9.1, 21.8] per 100 person-years; n=24/310, 7.7%): neuropathy peripheral (3.6 [95% CI 0.7, 6.6] per 100 person-years; n=6/310, 1.9%), peripheral sensory neuropathy (7.6 [95% CI 3.2, 11.9] per 100 person-years; n=12/310, 3.9%)
- Infections and infestations (12.8 [95% CI 7.1, 18.4] per 100 person-years; n=20/310, 6.5%): pneumonia (3.6 [95% CI 0.7, 6.6] per 100 person-years; n=6/310, 1.9%)
- General disorders and administration site conditions (10.0 [95% CI 5.1, 15.0] per 100 person-years; n=16/310, 5.2%): pyrexia (9.4 [95% CI 4.6, 14.2] per 100 person-years; n=15/310, 4.8%)
- Blood and lymphatic system disorders (5.5 [95% CI 1.9, 9.1] per 100 person-years; n=9/310, 2.9%): neutropenia (4.3 [95% CI 1.1, 7.4] per 100 person-years; n=7/310, 2.3%)
- Skin and subcutaneous tissue disorders (3.6 [95% CI 0.7, 6.6] per 100 person-years; n=6/310, 1.9%)

Differences reported between the prospective and retrospective cohorts are the following:

Nervous system disorders had similar incidence between the retrospective cohort (16.2 [95% CI 7.7, 24.7] per 100 person-years) and the prospective cohort (14.2 [95% CI 4.6, 23.8] per 100 person-years), despite having higher frequency in the retrospective cohort. Within this classification, neuropathy peripheral occurred in the retrospective cohort only (6.3 [95% CI 1.2, 11.5] per 100 person-years). Peripheral sensory neuropathy had higher incidence in the prospective cohort (11.0 [95% CI 2.7, 19.4]) than in the retrospective cohort (5.3 [95% CI 0.6, 9.9] per 100 person-years).

Infections and infestations had higher incidence in the prospective cohort (20.5 [95% CI 8.8, 32.2] per 100 person-years) than in the retrospective cohort (7.5 [95% CI 2.0, 13.0] per 100 person-years). Pneumonia had higher incidence in the prospective cohort (5.8 [95% CI 0.0, 11.6] per 100 person-years) than the retrospective cohort (2.1 [95% CI 0.0, 5.0] per 100 person-years).

General disorders and administration site conditions had higher incidence in the prospective cohort (20.3 [95% CI 9.3, 31.3] per 100 person-years) than in the prospective cohort (3.1 [95% CI 0.0, 6.7] per 100 person-years). Pyrexia had higher incidence in the prospective cohort (20.3 [95% CI 9.3, 31.3] per 100 person-years) than the retrospective cohort (2.1 [95% CI 0.0, 5.0] per 100 person-years).

Skin and subcutaneous tissue disorders had higher incidence in the prospective cohort (7.2 [95% CI 0.8, 13.6] per 100 person-years) than the retrospective cohort (1.0 [95% CI 0.0, 3.1] per 100 person-years).

Table 10-16. Summary of Treatment-related Serious Adverse Events Frequently Observed[§]

		Safety Population		
		Prospective Cohort	**Retrospective Cohort**	**Total**
N		156	154	310
Treatment-related[2] SAE	n (%)	37 (23.7%)	31 (20.1%)	68 (21.9%)
Blood and lymphatic system disorders				
SOC	n (%)	4 (2.6%)	5 (3.2%)	9 (2.9%)
	Incidence[1] (95%CI)	5.8 (0.0, 11.6)	5.3 (0.6, 9.9)	5.5 (1.9, 9.1)
Neutropenia	n (%)	3 (1.9%)	4 (2.6%)	7 (2.3%)
	Incidence[1] (95%CI)	4.3 (0.0, 9.3)	4.2 (0.1, 8.4)	4.3 (1.1, 7.4)
Febrile neutropenia[3]	n (%)	2 (1.3%)	1 (0.6%)	3 (1.0%)
	Incidence[1] (95%CI)	2.9 (0.0, 6.9)	1.0 (0.0, 3.1)	1.8 (0.0, 3.9)
General disorders and administration site conditions				
SOC	n (%)	13 (8.3%)	3 (1.9%)	16 (5.2%)
	Incidence[1] (95%CI)	20.3 (9.3, 31.3)	3.1 (0.0, 6.7)	10.0 (5.1, 15.0)
Pyrexia	n (%)	13 (8.3%)	2 (1.3%)	15 (4.8%)
	Incidence[1] (95%CI)	20.3 (9.3, 31.3)	2.1 (0.0, 5.0)	9.4 (4.6, 14.2)
Infections and infestations				
SOC	n (%)	13 (8.3%)	7 (4.5%)	20 (6.5%)
	Incidence[1] (95%CI)	20.5 (8.8, 32.2)	7.5 (2.0, 13.0)	12.8 (7.1, 18.4)
Pneumonia	n (%)	4 (2.6%)	2 (1.3%)	6 (1.9%)
	Incidence[1] (95%CI)	5.8 (0.0, 11.6)	2.1 (0.0, 5.0)	3.6 (0.7, 6.6)
Sepsis	n (%)	3 (1.9%)	0	3 (1.0%)
	Incidence[1] (95%CI)	4.3 (0.0, 9.3)	0	1.8 (0.0, 3.9)

		Safety Population		
		Prospective Cohort	**Retrospective Cohort**	**Total**
Nervous system disorders				
SOC	n (%)	9 (5.8%)	15 (9.7%)	24 (7.7%)
	Incidence[1] (95%CI)	14.2 (4.6, 23.8)	16.2 (7.7, 24.7)	15.4 (9.1, 21.8)
Neuropathy peripheral	n (%)	0	6 (3.9%)	6 (1.9%)
	Incidence[1] (95%CI)	0	6.3 (1.2, 11.5)	3.6 (0.7, 6.6)
Peripheral sensory neuropathy	n (%)	7 (4.5%)	5 (3.2%)	12 (3.9%)
	Incidence[1] (95%CI)	11.0 (2.7, 19.4)	5.3 (0.6, 9.9)	7.6 (3.2, 11.9)
Skin and subcutaneous tissue disorders				
SOC	n (%)	5 (3.2%)	1 (0.6%)	6 (1.9%)
	Incidence[1] (95%CI)	7.2 (0.8, 13.6)	1.0 (0.0, 3.1)	3.6 (0.7, 6.6)

Abbreviations: AESI= adverse event of special interest; CI= confidence interval; n/N= number of patients; SAE= serious adverse event; SOC= system organ class; PT= preferred term
[§] SOCs reported in 5 or more patients. For all SOC that were reported as treatment-related in at least 5 patients, the PT that were included in Table 10-15 were retained for comparison.
[1] Incidence density rate (per 100 person-years)
[2] Treatment-related adverse events were determined to be related to brentuximab vedotin by the treating physician
[3] Febrile neutropenia is a form of neutropenia and specified as an AESI, it was therefore included if neutropenia was presented
Note(s): Percentages are based on total number of patients N.
Time at risk was defined as between the first dose of brentuximab vedotin and: event start date, last dose plus 30 days, date of death, study completion/ discontinuation, data base lock, whichever occurred first.
Source: EOT Table 14.2.2

10.4.3.2 Serious Adverse Events by Subgroups

The frequency of SAEs was also described by subgroups of interest, including age group (EOT Table 14.2.1.2), sex (EOT Table 14.2.1.3), CD30+ lymphoma type (EOT Table 14.2.1.4), ALK positivity (EOT Table 14.2.1.5), long-term treatment (EOT Table 14.2.1.6), and post-autologous SCT status (EOT Table 14.2.1.7)

10.4.3.2.1 **Serious Adverse Events by Age group (<65 years vs. ≥65 years)**

In the Safety Population there were 234 patients <65 years (n=234/310, 75.5%) and 76 patients ≥65 years (n=76/310, 24.5%). In the prospective cohort, 114 patients were <65 years (n=114/156, 73.1%) and 42 patients were ≥65 years (n=42/156, 26.9%). In the retrospective cohort, 120 patients were <65 years (n=120/154, 77.9%) and 34 patients were ≥65 years (n=34/154, 22.1%).

Slightly more patients aged ≥65 years than patients aged <65 years reported SAEs (44.7% vs. 32.1%). Of the patients aged ≥65 years, 34 reported at least one SAE (n=34/76, 44.7%), the frequency was slightly higher in the prospective cohort (n=20/42, 47.6%) than in the

retrospective cohort (n=14/34, 41.2%). Of the patients aged <65 years, 75 reported at least one SAE (n=75/234, 32.1%), the frequency was similar between the prospective cohort (n=39/114, 34.2%) and the retrospective cohort (n=36/120, 30.0%).

Infections and infestations were more frequent in the ≥65 years group (n=16/76, 21.1%) than in the <65 years group (n=29/234, 12.4%). Blood and lymphatic system disorders were similar between the age groups, including neutropenia, but febrile neutropenia was more frequent in the ≥65 years group (n=3/76, 3.9%) than in the <65 years group (n=1/234, 0.4%).

The time at risk was notably different between the age groups, with patients ≥65 years having approximately 40 person-years and patients aged <65 years having approximately 125 person-years of on-treatment follow-up. Using incidence of events, infections and infestations were higher in patients ≥65 years (41.9 [95% CI 19.0, 64.9] per 100 person-years) than in patients <65 years (25.5 [95% CI 15.9, 35.0] per 100 person-years), which were primarily due to higher rates of pneumonia in patients ≥65 years (15.2 [95% CI 2.5, 27.9] per 100 person-years) than in patients <65 years (6.4 [95% CI 1.9, 11.0] per 100 person-years). Blood and lymphatic system disorders were higher in patients ≥65 years (15.4 [95% CI 2.8, 28.0] per 100 person-years) than in patients <65 years (5.6 [95% CI 1.4, 9.8] per 100 person-years). This was primarily due to higher incidence of febrile neutropenia in patients ≥65 years (7.5 [95% CI 0.0, 16.1] per 100 person-years) than in patients <65 years (0.8 [95% CI 0.0, 2.4] per 100 person-years), as well as higher neutropenia rates in patients ≥65 years (7.6 [95% CI 0.0, 16.3] per 100 person-years) than in patients <65 years (3.2 [95% CI 0.0, 6.4] per 100 person-years). Respiratory, thoracic and mediastinal disorders were slightly higher in patients ≥65 years (7.4 [95% CI 0.0, 16.0] per 100 person-years) than in patients <65 years (4.0 [95% CI 0.5, 7.5] per 100 person-years).

10.4.3.2.2 **Serious Adverse Events by Sex**

In the Safety Population there were 190 males (n=190/310, 61.3%) and 120 females (n=120/310, 38.7%). In the prospective cohort, 93 patients were male (n=93/156, 59.6%) and 63 patients were female (n=63/156, 40.4%). In the retrospective cohort, 97 patients were male (n=97/154, 63.0%) and 57 patients were female (n=57/154, 37.0%).

Serious adverse events were reported about equally between males and females (34.2% vs. 36.7%, respectively): 65 males and 44 females had at least one SAE.

Blood and lymphatic system disorders (including neutropenia and febrile neutropenia) were more frequent in males (n=10/190, 5.3%) than in females (n=3/120, 2.5%). Cardiac disorders were only reported in males (n=6/190, 3.2%).

The time at risk was different between the groups, with male patients having approximately 102 person-years and female patients having approximately 63 person-years of on-treatment follow-up. Using incidence of events, overall blood and lymphatic system disorders were higher in males (9.9 [95% CI 3.6, 16.2] per 100 person-years) than in females (4.8 [95% CI 0.0, 10.2] per 100 person-years). This was primarily due to reporting of febrile neutropenia in males only (3.9 [95% CI 0.0, 7.8] per 100 person-years), as well as a higher neutropenia rate in males (4.9

[95% CI 0.5, 9.3] per 100 person-years) than in females (3.2 [95% CI 0.0, 7.6] per 100 person-years). Cardiac disorders were reported in males only (5.8 [95% CI 1.1, 10.5]). Infections and infestations (primarily pneumonia) were slightly higher in females (33.6 [95% CI 17.7, 49.5] per 100 person-years) than in males (27.2 [95% CI 16.2, 38.3] per 100 person-years). Nervous system disorders were slightly higher in females (19.2 [95% CI 7.4, 30.9] per 100 person-years) than in males (14.2 [95% CI 6.6, 21.9] per 100 person-years); however, neuropathy peripheral and peripheral sensory neuropathy were similar between males and females. Renal and urinary disorders were slightly more common in females (5.0 [95% CI 0.0, 10.5] per 100 person-years) than in males (1.9 [95% CI 0.0, 4.7] per 100 person-years).

10.4.3.2.3 **Serious Adverse Events by Lymphoma Type (CD30+ HL and sALCL)**

In the Safety Population there were 252 patients with CD30+ HL (n=252/310, 81.3%) and 58 patients with sALCL (n=58/310, 18.7%). In the prospective cohort, 120 patients had CD30+ HL (n=120/156, 76.9%) and 36 patients had sALCL (n=36/156, 23.1%). In the retrospective cohort, 132 patients had CD30+ HL (n=132/154, 85.7%) and 22 patients had sALCL (n=22/154, 14.3%).

Serious adverse events occurred about equally between CD30+ HL and sALCL patients (34.9% vs. 36.2%, respectively): 88 CD30+ HL patients and 21 sALCL patients had at least one SAE.

Blood and lymphatic system disorders (neutropenia and febrile neutropenia were only reported in CD30+ HL patients) were more frequent in CD30+ HL patients (n=12/252, 4.8%) than in sALCL patients (n=1/58, 1.7%). Cardiac disorders were only reported in CD30+ HL patients (n=6/252, 2.4%). Gastrointestinal disorders were only reported in CD30+ HL patients (n=7/252, 2.8%). General disorders and administration site conditions (primarily pyrexia) were more frequent in sALCL patients (n=8/58, 13.8%) than in CD30+ HL patients (n=22/252, 8.7%). Nervous system disorders were slightly more frequent in sALCL patients (n=6/58, 10.3%) than in CD30+ HL patients (n=19/252, 7.5%). Skin and subcutaneous disorders only occurred in CD30+ HL patients (n=6/252, 2.4%). Vascular disorders only occurred in CD30+ HL patients (n=4/252, 1.6%).

The time at risk was notably different between the groups, with CD30+ HL patients having approximately 135 person-years and sALCL patients having approximately 31 person-years of on-treatment follow-up. Using incidence of events, overall blood and lymphatic system disorders were higher in CD30+ HL patients (9.1 [95% CI 3.9, 14.3] per 100 person-years) than sALCL patients (3.2 [95% CI 0.0, 9.7] per 100 person-years). This was primarily due to febrile neutropenia and neutropenia being reported in CD30+ HL patients only (3.0 [95% CI 0.0, 5.9] per 100 person-years and 5.3 [95% CI 1.3, 9.2] per 100 person-years, respectively). Cardiac disorders were reported in CD30+ HL patients only (4.4 [95% CI 0.9, 8.0] per 100 person-years). Gastrointestinal disorders were reported in CD30+ HL patients only (5.2 [95% CI 1.3, 9.2] per 100 person-years). General disorders and administration site conditions (primarily pyrexia) were higher in sALCL patients (31.0 [95% CI 8.5, 53.5] per 100 person-years) than CD30+ HL patients (16.8 [95% CI 9.8, 23.9] per 100 person-years). Infections and infestations (primarily

pneumonia) were higher in sALCL patients (34.8 [95% CI 10.9, 58.6] per 100 person-years) than CD30+ HL patients (28.5 [95% CI 18.7, 38.4] per 100 person-years). Nervous system disorders were higher in sALCL patients (24.7 [95% CI 4.7, 44.7 per 100 person-years) than CD30+ HL patients (14.5 [95% CI 7.7, 21.2] per 100 person-years), however peripheral sensory neuropathy was similar between the groups. Skin and subcutaneous tissue disorders were reported in CD30+ HL patients only (4.5 [95% CI 0.9, 8.1] per 100 person-years). Vascular disorders were reported in CD30+ HL patients only (3.0 [95% CI 0.1, 5.9] per 100 person-years).

10.4.3.2.4 **Serious Adverse Events by ALK Positivity (sALCL Only)**

In the Safety Population only 17 patients were AKL+, out of 58 sALCL patients.

Amongst the ALK+ sALCL patients, only 3 patients reported at least 1 SAE (n=3/17, 17.6%), however the small sample size of ALK+ patients prevents meaningful interpretation. The SAEs reported were multiple organ dysfunction syndrome, hyperglycaemia, groin pain, anaplastic large cell lymphoma T- and null-cell types, T-cell lymphoma, and neuropathy peripheral (n=1/17, 5.9%, each).

10.4.3.2.5 **Serious Adverse Events by Long-Term Treatment (>16 Cycles vs. ≤16 Cycles)**

In the Safety Population there were 9 patients with >16 cycles (n=9/310, 2.9%) and 301 patients with ≤16 cycles (n=301/310, 97.1%) of treatment with brentuximab vedotin. In the prospective cohort, 2 patients had >16 cycles (n=2/156, 1.3%) and 154 patients had ≤16 cycles (n=154/156, 98.7%). In the retrospective cohort, 7 patients had >16 cycles (n=7/154, 4.5%) and 147 patients had ≤16 cycles (n=147/154, 95.5%). The time at risk was notably different between the groups, with patients with >16 cycles having approximately 17 person-years and patients with ≤16 cycles having approximately 148 person-years of on-treatment follow-up.

Two patients with >16 cycles (n=2/9, 22.2%) and 107 patients with ≤16 cycles (n=107/301, 35.5%) reported at least one SAE.

Within the group with >16 cycles, 1 patient reported general disorders and administration site conditions, specifically pyrexia (7.3 [95% CI 0.0, 22.8] per 100 person-years) and 1 patient reported infections and infestations, specifically lower respiratory tract infection (7.3 [95% CI 0.0, 23.0] per 100 person-years). The small sample size of patients with >16 cycles prevents meaningful interpretation.

10.4.3.2.6 **Serious Adverse Events by Post-Autologous SCT status**

In the Safety Population there were 150 patients post-ASCT (n=150/310, 48.4%). In the prospective cohort, 63 patients were post-ASCT (n=63/156, 40.4%) and in the retrospective cohort, 87 patients were post-ASCT (n=87/154, 56.5%). The time at risk was almost identical between the post-ASCT and overall population (approximately 165 per 100 person-years in both). Overall, 37 patients post-ASCT reported at least one SAE (n=37/150, 24.7%).

Infections and infestations were less frequent in patients post-ASCT (n=16/150, 10.7%) than the population overall (n=95/310, 30.6%). General disorders and administration site conditions (primarily pyrexia) were similar between post-ASCT patients (n=11/150, 7.3%) and the population overall (n=30/310, 9.7%) patients. Nervous system disorders were slightly less frequent in patients post-ASCT (n=9/150, 6.0%) than the population overall (n=25/310, 8.1%). No conditions appeared to be more frequent in post-ASCT patients than in the population overall.

10.4.3.3 Treatment Modifications and Discontinuations

The summary of SAEs resulting in dose modifications and discontinuations are presented in Table 10-17.

Dose Reductions

Overall 6 patients had dose reductions due to an SAE (n=6/310, 1.9%), 2 patients from the prospective cohort (n=2/156, 1.3%), and 4 patients from the retrospective cohort (n=4/154, 2.6%).

Dose reductions were due to:

- Infections and infestations in 1 patient (n=1/310, 0.3%): herpes zoster cutaneous disseminated
- Metabolism and nutrition disorders in 1 patient (n=1/310, 0.3%): hyperglycaemia
- Nervous system disorders in 5 patients (n=5/310, 1.6%): neuropathy peripheral (n=2), peripheral sensory neuropathy (n=2), polyneuropathy (n=1)

Dose Hold, Delay, or Interruption

Overall 11 patients had dose hold, delay, or interruption due to an SAE (n=11/310, 3.5%), 5 patients from the prospective cohort (n=5/156, 3.2%), and 6 patients from the retrospective cohort (n=6/154, 3.9%). Distributions were identical in the Per-protocol Population.

Dose hold, delay or interruption were due to:

- Blood and lymphatic disorders in 4 patients (n=4/310, 1.3%): neutropenia (n=3), febrile neutropenia (n=1)
- General disorders and administration site conditions in 2 patients (n=2/310, 0.6%): general physical health deterioration, pyrexia (n=1 each)
- Infections and infestations in 6 patients (n=6/310, 1.9%): herpes zoster, lower respiratory tract infection, lung infection, pneumonia, pneumonia fungal, salmonellosis (n=1 each)
- Metabolism and nutrition disorders in 2 patients (n=2/310, 0.6%): diabetic ketoacidosis, hyperglycaemia (n=1 each)
- Nervous system disorders in 1 patient (n=1/310, 0.3%): neuropathy peripheral
- Renal and urinary disorders in 1 patient (n=1/310, 0.3%): renal pain

Dose Permanently Discontinued

Overall 26 patients had dose permanently discontinued due to an SAE (n=26/310, 8.4%), 16 patients from the prospective cohort (n=16/156, 10.6%), and 10 patients from the retrospective cohort (n=10/154, 6.5%). Per-protocol, these patients should have remained on follow-up until the end of the study despite discontinuing treatment.

Dose discontinuations were due to:

- Blood and lymphatic disorders in 1 patient (n=1/310, 0.3%): lymph node pain
- Cardiac disorders in 2 patients (n=2/310, 0.6%): atrioventricular block complete, myocardial infarction (n=1 each)
- General disorders and administration site conditions in 5 patients (n=5/310, 1.6%): pyrexia (n=3), multiple organ dysfunction syndrome (n=2)
- Hepatobiliary disorders in 1 patient (n=1/310, 0.3%): cholangitis
- Immune system disorders in 1 patient (n=1/310, 0.3%): anaphylactic reaction
- Infections and infestations in 10 patients (n=10/310, 3.2%): pneumonia (n=5), enterococcal infection, lung infection, pneumonia bacterial, sepsis, vulvovaginal candidiasis (n=1 each)
- Musculoskeletal and connective tissue disorders in 2 patients (n=2/310, 0.6%): groin pain, pain in extremity (n=1 each)
- Neoplasms benign, malignant and unspecified (including cysts and polyps) in 3 patients (n=3/310, 1.0%): Hodgkin's disease, T-cell lymphoma, tumour haemorrhage (n=1 each)
- Nervous system disorders in 5 patients (n=5/310, 1.6%): neuropathy peripheral, hypoaesthesia, neurotoxicity, peripheral sensory neuropathy, polyneuropathy
- Renal and urinary disorders in 1 patient (n=1/310, 0.3%): acute kidney injury
- Respiratory, thoracic and mediastinal disorders in 3 patients (n=3/310, 1.0%): dyspnoea, pneumonitis, respiratory failure (n=1 each)
- Skin and subcutaneous tissue disorders in 1 patient (n=1/310, 0.3%): drug eruption

Discontinuation from Study

Overall 17 patients were discontinued from the study due to an SAE (n=17/310, 5.5%), 12 patients from the prospective cohort (n=12/156, 7.7%), and 5 patients from the retrospective cohort (n=5/154, 3.2%).

Discontinuations from study were due to:

- Cardiac disorders in 2 patients (n=2/310, 0.6%): acute myocardial infarction, cardiac arrest (n=1 each)
- General disorders and administration site conditions in 4 patients (n=4/310, 1.3%): multiple organ dysfunction syndrome (n=3), general physical health deterioration (n=1)
- Immune system disorders in 1 patient (n=1/310, 0.3%): anaphylactic reaction
- Infections and infestations in 6 patients (n=6/310, 1.9%): pneumonia (n=4), bacterial sepsis, sepsis (n=1 each)

- Neoplasms benign, malignant and unspecified (incl. cysts and polyps) in 3 patients (n=3/310, 1.0%): Hodgkin's disease, meningioma, tumour haemorrhage (n=1 each)
- Nervous system disorders in 1 patient (n=1/310, 0.3%): polyneuropathy
- Respiratory, thoracic and mediastinal disorders in 1 patient (n=1/310, 0.3%): respiratory failure

Table 10-17. Summary of Study Discontinuations and Dose Modifications due to Serious Adverse Events by System Organ Class

		Safety Population		
		Prospective Cohort	**Retrospective Cohort**	**Total**
N		156	154	310
SAE leading to dose reduction	n (%)	2 (1.3%)	4 (2.6%)	6 (1.9%)
SAE leading to dose held, delay, and interruption	n (%)	5 (3.2%)	6 (3.9%)	11 (3.5%)
SAE leading to dose permanently discontinued	n (%)	16 (10.3%)	10 (6.5%)	26 (8.4%)
SAE leading to discontinuation from study	n (%)	12 (7.7%)	5 (3.2%)	17 (5.5%)
Blood and lymphatic system disorders				
Dose reduction	n (%)	0	0	0
Dose held, delay, and interruption	n (%)	1 (0.6%)	3 (1.9%)	4 (1.3%)
Dose permanently discontinued	n (%)	1 (0.6%)	0	1 (0.3%)
Discontinuation from study	n (%)	0	0	0
Cardiac disorders				
Dose reduction	n (%)	0	0	0
Dose held, delay, and interruption	n (%)	0	0	0
Dose permanently discontinued	n (%)	2 (1.3%)	0	2 (0.6%)
Discontinuation from study	n (%)	1 (0.6%)	1 (0.6%)	2 (0.6%)
General disorders and administration site conditions				
Dose reduction	n (%)	0	0	0
Dose held, delay, and interruption	n (%)	1 (0.6%)	1 (0.6%)	2 (0.6%)
Dose permanently discontinued	n (%)	4 (2.6%)	1 (0.6%)	5 (1.6%)
Discontinuation from study	n (%)	3 (1.9%)	1 (0.6%)	4 (1.3%)

		Safety Population		
		Prospective Cohort	**Retrospective Cohort**	**Total**
Infections and infestations				
Dose reduction	n (%)	1 (0.6%)	0	1 (0.3%)
Dose held, delay, and interruption	n (%)	3 (1.9%)	3 (1.9%)	6 (1.9%)
Dose permanently discontinued	n (%)	9 (5.8%)	1 (0.6%)	10 (3.2%)
Discontinuation from study	n (%)	6 (3.8%)	0	6 (1.9%)
Metabolism and nutrition disorders				
Dose reduction	n (%)	0	1 (0.6%)	1 (0.3%)
Dose held, delay, and interruption	n (%)	0	2 (1.3%)	2 (0.6%)
Dose permanently discontinued	n (%)	0	0	0
Discontinuation from study	n (%)	0	0	0
Nervous system disorders				
Dose reduction	n (%)	1 (0.6%)	4 (2.6%)	5 (1.6%)
Dose held, delay, and interruption	n (%)	0	1 (0.6%)	1 (0.3%)
Dose permanently discontinued	n (%)	1 (0.6%)	4 (2.6%)	5 (1.6%)
Discontinuation from study	n (%)	0	1 (0.6%)	1 (0.3%)
Renal and urinary disorders				
Dose reduction	n (%)	0	0	0
Dose held, delay, and interruption	n (%)	1 (0.6%)	0	1 (0.3%)
Dose permanently discontinued	n (%)	1 (0.6%)	0	1 (0.3%)
Discontinuation from study	n (%)	0	0	0
Hepatobiliary disorders				
Dose reduction	n (%)	0	0	0
Dose held, delay, and interruption	n (%)	0	0	0
Dose permanently discontinued	n (%)	0	1 (0.6%)	1 (0.3%)
Discontinuation from study	n (%)	0	0	0
Immune system disorders				
Dose reduction	n (%)	0	0	0
Dose held, delay, and interruption	n (%)	0	0	0
Dose permanently discontinued	n (%)	0	1 (0.6%)	1 (0.3%)
Discontinuation from study	n (%)	0	1 (0.6%)	1 (0.3%)
Musculoskeletal and connective tissue disorders				

		Safety Population		
		Prospective Cohort	**Retrospective Cohort**	**Total**
Dose reduction	n (%)	0	0	0
Dose held, delay, and interruption	n (%)	0	0	0
Dose permanently discontinued	n (%)	1 (0.6%)	1 (0.6%)	2 (0.6%)
Discontinuation from study	n (%)	0	0	0
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)				
Dose reduction	n (%)	0	0	0
Dose held, delay, and interruption	n (%)	0	0	0
Dose permanently discontinued	n (%)	2 (1.3%)	1 (0.6%)	3 (1.0%)
Discontinuation from study	n (%)	2 (1.3%)	1 (0.6%)	3 (1.0%)
Respiratory, thoracic and mediastinal disorders				
Dose reduction	n (%)	0	0	0
Dose held, delay, and interruption	n (%)	0	0	0
Dose permanently discontinued	n (%)	1 (0.6%)	2 (1.3%)	3 (1.0%)
Discontinuation from study	n (%)	1 (0.6%)	0	1 (0.3%)
Skin and subcutaneous tissue disorders				
Dose reduction	n (%)	0	0	0
Dose held, delay, and interruption	n (%)	0	0	0
Dose permanently discontinued	n (%)	1 (0.6%)	0	1 (0.3%)
Discontinuation from study	n (%)	0	0	0

Abbreviations: n/N= number of patients; SAE= serious adverse event
Note(s): Percentages are based on total number of patients N.
Source: EOT Table 14.4.1.2, EOT Table 14.4.1.3, EOT Table 14.4.1.4, EOT Table 14.4.1.5

10.5 **Other Analyses**

There were no other analyses performed.

10.6 **Protocol-specified Adverse Events of Special Interest**

The following protocol-specified serious and non-serious AESIs were evaluated as part of the PASS: peripheral neuropathy (using SMQ), neutropenia (including febrile neutropenia), infections (including opportunistic infections), hyperglycaemia, and hypersensitivity reactions (including infusion-related reactions and allergic reactions).

10.6.1 Summary by Classification

A summary of the frequencies of AESIs, and dose modifications and discontinuations due to AESI are summarised in Table 10-18.

Protocol-specified AESIs were reported in 213 patients (n=213/310, 68.7%), including peripheral neuropathy in 131 patients (113.6 [95% CI 93.3, 133.9] per 100 person-years; n=131/310, 42.3%), infections in 97 patients (76.0 [95% CI 60.1, 92.0] per 100 person-years; n=97/310, 31.3%), neutropenia in 54 patients (37.2 [95% CI 26.3, 48.0] per 100 person-years; n=54/310, 17.4%), hypersensitivity reactions in 34 patients (22.5 [95% CI 14.7, 30.4] per 100 person-years; n=34/310, 11.0%), and hyperglycaemia in 4 patients (2.4 [95% CI 0.0, 4.9] per 100 person-years; n=4/310, 1.3%).

The incidence of peripheral neuropathy (sensory, motor, or other) was similar between the retrospective cohort (117.3 [95% CI 89.9, 144.8] per 100 person-years; n=78/154, 50.6%) and the prospective cohort (108.5 [95% CI 78.4, 138.7] per 100 person-years; n=53/156, 34.0%), and the incidence of neutropenia was higher in the prospective cohort (53.3 [95% CI 31.7, 75.0] per 100 person-years; n=32/156, 20.5%) than in the retrospective cohort (25.8 [95% CI 14.5, 37.1] per 100 person-years; n=22/154, 14.3%). Infections (including opportunistic infections) had higher incidence in the prospective cohort (96.7 [95% CI 69.1, 124.3] per 100 person-years; n=51/156, 32.7%) than in the retrospective cohort (61.4 [95% CI 42.8, 80.1] per 100 person-years; n=46/154, 29.9%). Hyperglycaemia was reported in the retrospective cohort only (4.3 [0.0, 8.5] per 100 person-years; n=4/154, 2.6%). The incidence of hypersensitivity reactions (including infusion-related reactions and allergic reactions) was similar between the prospective cohort (23.3 [11.0, 35.6] per 100 person-years; n=15/154, 9.6%) and the retrospective cohort (21.9 [11.7, 32.2] per 100 person-years; n=19/154, 12.3%).

Overall 35 patients discontinued treatment due to an AESI (n=35/310, 11.3%), this was slightly higher in the retrospective cohort than in the prospective cohort (13.0% vs. 9.6%, respectively). Another 60 patients had dose modification due to an AESI (n=60/310, 19.4%), this was also higher in the retrospective cohort than in the prospective cohort (26.0% vs. 12.8%).

The results were almost identical in the Per-protocol Population.

Table 10-18. Overview of Adverse Events of Special Interest

		Safety Population			Per-protocol Population		
		Prospective Cohort	Retrospective Cohort	Total	Prospective Cohort	Retrospective Cohort	Total

		Safety Population			Per-protocol Population		
		Prospective Cohort	**Retrospective Cohort**	**Total**	**Prospective Cohort**	**Retrospective Cohort**	**Total**
N		156	154	310	139	145	284
Patients with any AESI							
n	n (%)	97 (62.2%)	116 (75.3%)	213 (68.7%)	93 (66.9%)	114 (78.6%)	207 (72.9%)
Peripheral neuropathy[2]	n (%)	53 (34.0%)	78 (50.6%)	131 (42.3%)	52 (37.4%)	76 (52.4%)	128 (45.1%)
	Incidence[1] (95%CI)	108.5 (78.4, 138.7)	117.3 (89.9, 144.8)	113.6 (93.3, 133.9)	117.8 (84.1, 151.6)	119.1 (90.7, 147.5)	118.6 (96.9, 140.3)
Neutropenia[3]	n (%)	32 (20.5%)	22 (14.3%)	54 (17.4%)	32 (23.0%)	21 (14.5%)	53 (18.7%)
	Incidence[1] (95%CI)	53.3 (31.7, 75.0)	25.8 (14.5, 37.1)	37.2 (26.3, 48.0)	57.9 (33.9, 81.9)	25.5 (14.1, 36.9)	38.5 (27.1, 50.0)
Infections[4]	n (%)	51 (32.7%)	46 (29.9%)	97 (31.3%)	49 (35.3%)	46 (31.7%)	95 (33.5%)
	Incidence[1] (95%CI)	96.7 (69.1, 124.3)	61.4 (42.8, 80.1)	76.0 (60.1, 92.0)	101.1 (71.5, 130.7)	64.4 (44.7, 84.1)	79.3 (62.4, 96.2)
Hyperglycaemia	n (%)	0	4 (2.6%)	4 (1.3%)	0	4 (2.8%)	4 (1.4%)
	Incidence[1] (95%CI)	0	4.3 (0.0, 8.5)	2.4 (0.0, 4.9)	0	4.4 (0.0, 8.8)	2.6 (0.0, 5.1)
Hypersensitivity reactions[5]	n (%)	15 (9.6%)	19 (12.3%)	34 (11.0%)	14 (10.1%)	18 (12.4%)	32 (11.3%)
	Incidence[1] (95%CI)	23.3 (11.0, 35.6)	21.9 (11.7, 32.2)	22.5 (14.7, 30.4)	23.4 (10.6, 36.2)	21.5 (11.2, 31.8)	22.3 (14.3, 30.3)
Patients with any treatment-emergent[6] AESI							
n	n (%)	97 (62.2%)	115 (74.7%)	212 (68.4%)	93 (66.9%)	113 (77.9%)	206 (72.5%)
Patients with any treatment-related[7] AESI							
n	n (%)	83 (53.2%)	94 (61.0%)	177 (57.1%)	81 (58.3%)	92 (63.4%)	173 (60.9%)
Patients with any treatment-emergent[6] treatment-related[7] AESI							
n	n (%)	83 (53.2%)	92 (59.7%)	175 (56.5%)	81 (58.3%)	90 (62.1%)	171 (60.2%)
Dose Modifications and Discontinuations							
Patient discontinued treatment[8] due to AESI	n (%)	15 (9.6%)	20 (13.0%)	35 (11.3%)	14 (10.1%)	20 (13.8%)	34 (12.0%)
Patient with dose modification[9] due to AESI	n (%)	20 (12.8%)	40 (26.0%)	60 (19.4%)	19 (13.7%)	38 (26.2%)	57 (20.1%)

		Safety Population			Per-protocol Population		
		Prospective Cohort	**Retrospective Cohort**	**Total**	**Prospective Cohort**	**Retrospective Cohort**	**Total**
Abbreviations: AESI= adverse event of special interest; n/N= number of patients *Manually calculated for consistency between tables [1] Incidence density rate (per 100 person-years) [2] Including sensory, motor or other (See Section 9.8 for list of terms) [3] Including febrile neutropenia and neutrophil count decreased [4] Including opportunistic infections [5] Including infusion-related reactions and allergic reactions [6] Treatment-emergent adverse events started or worsened on or after the first dose of brentuximab vedotin and within 30 days after the last dose of brentuximab vedotin [7] Treatment-related adverse events were determined to be related to brentuximab vedotin by the treating physician [8] Discontinued includes "action taken"= "discontinued from study" and "dose permanently discontinued" [9] Dose modification includes "action taken"= "dose increased", "dose reduced", "dose held", "dose interrupted" and "dose delayed" Note(s): Percentages are based on total number of patients N. Source: EOT Table 13, EOT Table 13_pp, EOT Table 14.3.1.1, EOT Table 14.3.1.1_pp, EOT Table 15.3, EOT Table 15.3_pp							

10.6.2 Treatment Modifications and Discontinuations

Table 10-19 presents dose modifications due AESIs. Overall 29 (n=29/310, 9.4%) patients had dose reductions due to an AESI, 8 (n=8/156, 5.1%) from the prospective cohort, and 21 (n=21/154, 13.6%) patients from the retrospective cohort. Thirty-nine (n=39/310, 12.6%) patients had dose holding, delay, or interruption due to an AESI, 16 (n=16/156, 10.3%) from the prospective cohort, and 23 (n=23/154, 14.9%) patients from the retrospective cohort. Thirty-one (n=31/310, 10.0%) patients had dose holding, delay, or interruption due to an AESI, 12 (n=12/156, 7.7%) from the prospective cohort, and 19 (n=19/154, 12.3%) patients from the retrospective cohort. Eight patients (n=8/310, 2.6%) were discontinued from the study due to an AESI, 5 (n=5/156, 3.2%) from the prospective cohort, and 3 (n=3/154, 1.9%) patients from the retrospective cohort.

Table 10-19 Summary of Study Discontinuations and Dose Modifications due to Adverse Events of Special Interest

		Safety Population		
		Prospective Cohort	**Retrospective Cohort**	**Total**
N		156	154	310
AESI leading to dose reduction	n (%)	8 (5.1%)	21 (13.6%)	29 (9.4%)
AESI leading to dose held, delay, and interruption	n (%)	16 (10.3%)	23 (14.9%)	39 (12.6%)
AESI leading to dose permanently discontinued	n (%)	12 (7.7%)	19 (12.3%)	31 (10.0%)
AESI leading to discontinuation from study	n (%)	5 (3.2%)	3 (1.9%)	8 (2.6%)

Abbreviations: AESI= adverse event of special interest; n/N= number of patients
Note(s): Percentages are based on total number of patients N.
Source: EOT Table 14.4.2.2, EOT Table 14.4.2.3, EOT Table 14.4.2.4, EOT Table 14.4.2.5

10.6.3 Peripheral Neuropathy

Peripheral neuropathy (using SMQ, see Section 9.8 for details) was the most common AESI, occurring in 131 patients (n=131/310, 42.3%), and is summarised in Table 10-20. Almost all peripheral neuropathy events were considered treatment-related, 128 patients had treatment-related events (n=128/310, 41.3%). Almost all peripheral neuropathy events were treatment-emergent, 127 patients had treatment-emergent events (n=127/310, 41.0%). Four patients developed peripheral neuropathy more than 30 days after discontinuing treatment with brentuximab vedotin.

The incidence of peripheral neuropathy was 113.6 (95% CI 93.3, 133.9) per 100 person-years. The incidence was similar between the prospective cohort (108.5 [95% CI 78.4, 138.7] per 100 person-years) and the retrospective cohort (117.3 [95% CI 89.9, 144.8] per 100 person-years). The frequency of peripheral neuropathy was 50.6% in the retrospective cohort and 34.0% in the prospective cohort, possibly owing to longer at-risk periods in the retrospective cohort (ie, higher number of treatment cycles, Section 10.4.1). The Per-protocol Population had a slightly higher incidence of 118.6 (95% CI 96.9, 140.3) per 100 person-years. This could be attributed to early discontinuation of patients with protocol deviations that had shorter at-risk periods.

Peripheral neuropathy was reported as serious in 22 patients (n=22/310, 7.1%) with an incidence of (14.1 [95% CI 8.1, 20.2] per 100 person-years). Following additional SAE reconciliation, it was found that 2 patients had SMQ peripheral neuropathy reported as serious in the clinical database when they should have been reported as non-serious. Therefore, 20 patients (n=20/310, 6.5%) actually experienced serious peripheral neuropathy events. The following reporting of results remains consistent with the original results, and has not been altered to reflect the findings of the SAE reconciliation since they do not affect interpretation of the results. It was reported as serious with similar incidence between the retrospective cohort (15.2 [95% CI 7.0, 23.4] per 100 person-years) and the prospective cohort (12.6 [95% CI 3.6, 21.6] per 100 person-years).

The incidence of treatment-related peripheral neuropathy was 110.0 (95% CI 90.1, 129.8) per 100 person-years. It was reported as treatment-related with similar incidence between the prospective cohort (108.5 [95% CI 78.4, 138.7] per 100 person-years) and the retrospective cohort (111.0 [95% CI 84.6, 137.4] per 100 person-years). There were 3 patients with peripheral neuropathy that was not considered treatment-related, 1 in each of dysesthesia, neuropathy peripheral, and paraesthesia.

10.6.3.1 Treatment-emergent events

Most of the 131 patients with peripheral neuropathy had events occur on-treatment, 127 patients (n=127/310, 41.0%) with an incidence of 111.1 (95% CI 90.9, 131.3). The treatment-emergent incidence was slightly higher in the retrospective cohort (114.5 [95% CI 87.4, 141.6] per 100 person-years) than the prospective cohort (106.3 [95% CI 75.9, 136.8] per 100 person-years). Post-treatment, 8 patients reported peripheral neuropathy events (EOT Table 14.3.1.1.b).

Table 10-20. Summary of Peripheral Neuropathy Events

		Safety Population			Per-protocol Population		
		Prospective Cohort	**Retrospective Cohort**	**Total**	**Prospective Cohort**	**Retrospective Cohort**	**Total**
N		156	154	310	139	145	284
Peripheral neuropathy[2] (sensory, motor, other)							
Any	n (%)	53 (34.0%)	78 (50.6%)	131 (42.3%)	52 (37.4%)	76 (52.4%)	128 (45.1%)
	Incidence[1] (95%CI)	108.5 (78.4, 138.7)	117.3 (89.9, 144.8)	113.6 (93.3, 133.9)	117.8 (84.1, 151.6)	119.1 (90.7, 147.5)	118.6 (96.9, 140.3)
Serious	n (%)	8 (5.1%)	14 (9.1%)	22 (7.1%)	8 (5.8%)	13 (9.0%)	21 (7.4%)
	Incidence[1] (95%CI)	12.6 (3.6, 21.6)	15.2 (7.0, 23.4)	14.1 (8.1, 20.2)	13.7 (3.9, 23.4)	14.6 (6.4, 22.8)	14.2 (8.0, 20.5)
Treatment-emergent[3]	n (%)	51 (32.7%)	76 (49.4%)	127 (41.0%)	---	---	---
	Incidence[1] (95%CI)	106.3 (75.9, 136.8)	114.5 (87.4, 141.6)	111.1 (90.9, 131.3)	---	---	---
Treatment-related[4]	n (%)	53 (34.0%)	75 (48.7%)	128 (41.3%)	52 (37.4%)	73 (50.3%)	125 (44.0%)
	Incidence[1] (95%CI)	108.5 (78.4, 138.7)	111.0 (84.6, 137.4)	110.0 (90.1, 129.8)	117.8 (84.1, 151.6)	112.5 (85.2, 139.8)	114.7 (93.5, 135.8)

Abbreviations: AESI= adverse event of special interest; CI= confidence interval; n/N= number of patients
[1] Incidence density rate (per 100 person-years)
[2] Includes PT: peripheral sensory neuropathy, neuropathy peripheral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, polyneuropathy, and symptoms of neuropathy such as hypoesthesia, paraesthesia, and pain in extremity (Section 9.8)
[3] Treatment-emergent adverse events started or worsened on or after the first dose of brentuximab vedotin and within 30 days after the last dose of brentuximab vedotin
[4] Treatment-related adverse events were determined to be related to brentuximab vedotin by the treating physician
Note(s): Percentages are based on total number of patients N. Time at risk was defined as between the first dose of brentuximab vedotin and: event start date, last dose plus 30 days, date of death, study completion/ discontinuation, data base lock, whichever occurred first.
Source: EOT Table 14.3.1.1, EOT Table 14.3.1.1_pp, EOT Table 14.3.1.2, EOT Table 14.3.1.2_pp, EOT Table 14.3.1.1.a, EOT Table 14.3.3.2, EOT Table 14.3.3.2_pp

10.6.3.2 Maximum Severity of Events

The reporting of peripheral neuropathy varied as the Investigators were requested to report whether an event was an AESI and then used free-text to specify. Treatment-related peripheral neuropathy was reported as follows (patients could be in more than one category), and is summarised by severity in Table 10-21 and by PT in EOT Table 14.3.3.1:

- Peripheral sensory neuropathy was reported for 72 patients (n=72/310, 23.2%), which was evenly split between the prospective (n=37/156, 23.7%) and retrospective (n=35/154, 22.7%) cohorts.

  There were 42 patients with Grade 1 (n=42/310, 13.5%), 25 patients with Grade 2 (n=25/310, 8.1%), and 5 patients with Grade 3 (n=5/310, 1.6%) maximum severity peripheral sensory neuropathy; with a trend for higher severity in the retrospective cohort.

- Neuropathy peripheral was reported for 39 patients (n=39/310, 12.6%), which was more frequent in the retrospective cohort (n=28/154, 18.2%) than in the prospective cohort (n=11/156, 7.1%).

  There were 23 patients with Grade 1 (n=23/310, 7.4%), 10 patients with Grade 2 (n=10/310, 3.2%), 5 patients with Grade 3 (n=5/310, 1.6%), and 1 patient with Grade 4 (n=1/310, 0.3%) maximum severity neuropathy peripheral, with even proportions in each cohort.

- Peripheral motor neuropathy (including peripheral sensorimotor neuropathy) was reported for 7 patients (n=7/310, 2.3%), which was evenly split between the prospective (n=4/156, 2.6%) and retrospective (n=3/154, 1.9%) cohorts.

  There were 2 patients with Grade 1 (n=2/310, 0.6%), 2 patients with Grade 2 (n=2/310, 0.6%), and 3 patients with Grade 3 (n=3/310, 1.0%) maximum severity peripheral motor/sensorimotor neuropathy; with approximately even proportions in each cohort.

- Polyneuropathy was reported for 3 patients (n=3/310, 1.0%), all of whom were in the retrospective cohort.

  There was 1 patient each with Grade 1, Grade 2, and Grade 3 (n=1/310, 0.3%) maximum severity polyneuropathy.

- The remaining terms were symptoms of neuropathy (such as hypoesthesia, hyperesthesia, paraesthesia, discomfort, a burning sensation, neuropathic pain, or weakness), and were considered as peripheral neuropathy events. The most frequently reported was paraesthesia (n=12/310, 3.9%).

  There were 12 patients with Grade 1 (n=12/310, 3.9%), 5 patients with Grade 2 (n=5/310, 1.6%), and 1 patient with Grade 3 (n=1/310, 0.3%) maximum severity symptoms of peripheral neuropathy.

Most treatment-related peripheral neuropathy were <Grade 3 (n=113/310, 36.5%). A higher proportion of treatment-related peripheral neuropathy were <Grade 3 in the prospective cohort than the retrospective cohort (90.5% vs. 86.7%, respectively).

Table 10-21. Overview of Peripheral Neuropathy Events and Maximum Severity

		Safety Population			Per-protocol Population		
		Prospective Cohort	**Retrospective Cohort**	**Total**	**Prospective Cohort**	**Retrospective Cohort**	**Total**
N		156	154	310	139	145	284
Patients with any peripheral neuropathy[1] (sensory, motor, other)							
n	n (%)	53 (34.0%)	78 (50.6%)	131 (42.3%)	52 (37.4%)	76 (52.4%)	128 (45.1%)
Grade 1	n (%)	34 (64.2%)	41 (52.6%)	75 (57.3%)	34 (65.4%)	39 (51.3%)	73 (57.0%)
Grade 2	n (%)	14 (26.4%)	27 (34.6%)	41 (31.3%)	13 (25.0%)	27 (35.5%)	40 (31.3%)
Grade 3	n (%)	5 (9.4%)	9 (11.5%)	14 (10.7%)	5 (9.6%)	9 (11.8%)	14 (10.9%)
Grade 4	n (%)	0	1 (1.3%)	1 (0.8%)	0	1 (1.3%)	1 (0.8%)
Patients with any treatment-emergent[2] peripheral neuropathy and highest severity							
n	n (%)	51 (32.7%)	76 (49.4%)	127 (41.0%)	50 (36.0%)	74 (51.0%)	124 (43.7%)
<Grade 3	n (%)	47 (30.1%)	68 (44.2%)	115 (37.1%)	46 (33.1%)	66 (45.5%)	112 (39.4%)
≥Grade 3*	n (%)	4 (2.6%)	8 (5.2%)	12 (3.9%)	4 (2.9%)	8 (5.5%)	12 (9.4%)
≤Grade 3	n (%)	51 (32.7%)	75 (48.7%)	126 (40.6%)	50 (36.0%)	73 (50.3%)	123 (43.3%)
Patients with any treatment-related[3] peripheral neuropathy and highest severity							
n	n (%)	53 (34.0%)	75 (48.7%)	128 (41.3%)	52 (37.4%)	73 (50.3%)	125 (44.0%)
<Grade 3	n (%)	48 (30.8%)	65 (42.2%)	113 (36.5%)	47 (33.8%)	63 (43.4%)	110 (38.7%)
≥Grade 3*	n (%)	5 (3.2%)	10 (6.5%)	15 (4.8%)	5 (3.6%)	10 (6.9%)	15 (11.7%)
≤Grade 3	n (%)	53 (34.0%)	74 (48.1%)	127 (41.0%)	52 (37.4%)	72 (49.7%)	124 (43.7%)
Patients with any treatment-emergent[2] treatment-related[3] peripheral neuropathy							
n	n (%)	51 (32.7%)	73 (47.4%)	124 (40.0%)	50 (36.0%)	71 (49.0%)	121 (42.6%)

Abbreviations: AESI= adverse event of special interest; n/N= number of patients; PN= peripheral neuropathy
*Manually calculated for consistency between tables
[1] Includes PT: peripheral sensory neuropathy, neuropathy peripheral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, polyneuropathy, and symptoms of neuropathy such as hypoesthesia, paraesthesia, and pain in extremity (Section 9.8)
[2] Treatment-emergent adverse events started or worsened on or after the first dose of brentuximab vedotin and within 30 days after the last dose of brentuximab vedotin
[3] Treatment-related adverse events were determined to be related to brentuximab vedotin by the treating physician
Note(s): Percentages are based on total number of patients N.
Source: EOT Table 14.3.3.1, EOT Table 14.3.3.1_pp, EOT Table 15.1, EOT Table 15.1_pp, EOT Listing 7.3

10.6.3.3 Treatment Modifications and Discontinuations

Table 10-22 presents a summary of the dose changes resulted from peripheral neuropathy AESIs.

Dose Reductions due to:

- Nervous system disorders in 25 patients (n=25/310, 8.1%): peripheral sensory neuropathy (n=14), neuropathy peripheral (n=9), paraesthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, polyneuropathy (n=1 each)

Dose Hold, Delay, or Interruption due to:

- Nervous system disorders in 6 patients (n=6/310, 1.9%): neuropathy peripheral (n=4), peripheral sensory neuropathy (n=2)

Dose Permanently Discontinued due to:

- Nervous system disorders in 20 patients (n=20/310, 6.5%): neuropathy peripheral (n=9), peripheral sensory neuropathy (n=7), hypoaesthesia, neurotoxicity, paraesthesia, polyneuropathy (n=1 each)
- Musculoskeletal and connective tissue disorders 1 patient (n=1/310, 0.3%): pain in extremity

Discontinuation from Study due to:

- Nervous system disorders in 2 patients (n=2/310, 1.6%): neuropathy peripheral, paraesthesia, polyneuropathy (n=1 each)

Table 10-22. Summary of Study Discontinuations and Dose Modifications due to Neuropathy Peripheral Adverse Events of Special Interest

		Safety Population		
		Prospective Cohort	**Retrospective Cohort**	**Total**
N		156	154	310
Peripheral neuropathy[1] (sensory, motor, other)				
Dose reduction	n (%)	6 (3.8%)	19 (12.3%)	25 (8.1%)
Dose held, delay, and interruption	n (%)	1 (0.6%)	5 (3.2%)	6 (1.9%)
Dose permanently discontinued	n (%)	5 (3.2%)	15 (9.7%)	20 (6.5%)
Discontinuation from study	n (%)	0	2 (1.3%)	2 (0.6%)

Abbreviations: n/N= number of patients
[1] Includes PT: peripheral sensory neuropathy, neuropathy peripheral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, polyneuropathy, and symptoms of neuropathy such as hypoesthesia, paraesthesia, and pain in extremity (Section 9.8)
Note(s): Percentages are based on total number of patients N.
Source: EOT Table 14.4.2.2, EOT Table 14.4.2.3, EOT Table 14.4.2.4, EOT Table 14.4.2.5

10.6.3.4 Time to First Peripheral Neuropathy

Time-to-event analysis was carried out for peripheral neuropathy using Kaplan-Meier analysis. The occurrence of the first on-study reported peripheral neuropathy event is presented in Table 10-23.

All patients were considered at risk at enrolment regardless of whether peripheral neuropathy had been reported in their medical history (ie, diagnosed prior to initiating treatment with brentuximab vedotin). Overall 35 (n=35/310, 11.3%) patients had peripheral neuropathy in their medical history and 25 (n=25/310, 8.1%) had ongoing peripheral neuropathy at enrolment (see Section 10.2.2). Review of the database found that of the 25 patients with ongoing peripheral neuropathy at enrolment, 11 patients (n=11/25, 44%) patients experienced a peripheral neuropathy event during the study; additionally, of the 131 patients who experienced peripheral neuropathy during the study, 15 patients (n=15/131, 11.5%) had any (resolved or ongoing) history of peripheral neuropathy at enrolment.

Figure 2 shows the cumulative event free probability of peripheral neuropathy by time since enrolment, showing that most events occurred in the first months of treatment. Figure 3 shows the same by cohort, which shows a greater cumulative event probability in the retrospective cohort. The retrospective cohort also had a slightly steeper curve than the prospective cohort, but this could be due to the recording of events following enrolment as retrospective patients had longer exposure to brentuximab vedotin, making the accumulation of events appear more rapid early on.

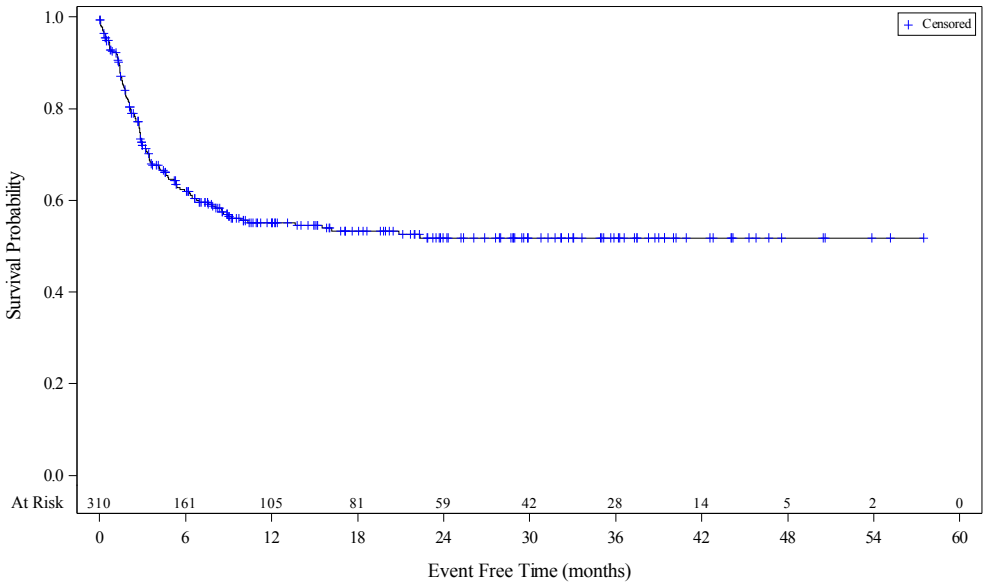

Figure 2. Kaplan-Meier Plot of Time to Onset of Peripheral Neuropathy

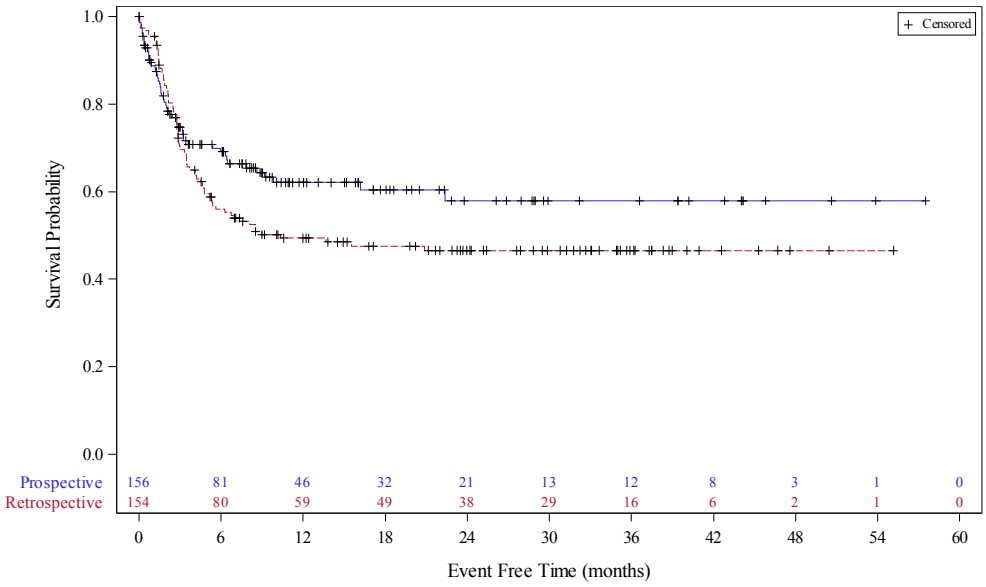

Figure 3. Kaplan-Meier Plot of Time to Onset of Peripheral Neuropathy by Cohort

The Kaplan-Meier plots are summarised in Table 10-23. By month 6, 110 patients (n=110/310, 35.5%) had developed peripheral neuropathy, this was higher in the retrospective cohort (n=66/154, 42.9%) than the prospective cohort (n=44/156, 28.2%). The cumulative event free probability was 61.9% (95% CI 56.0%, 67.3%) overall, 69.1% (95% CI 60.7%, 76.1%) in the prospective cohort and 56.0% (95% CI 47.7%, 63.5%) in the retrospective cohort.

By month 12, 126 patients (n=126/310, 40.6%) had developed peripheral neuropathy, this was higher in the retrospective cohort (n=75/154, 48.7%) than the prospective cohort (n=51/156, 32.7%). The cumulative event free probability was 55.1% (95% CI 49.0%, 60.8%) overall, 62.1% (95% CI 53.0%, 69.9%) in the prospective cohort and 49.4% (95% CI 41.0%, 57.2%) in the retrospective cohort.

By month 24, 131 patients (n=131/310, 42.3%) had developed peripheral neuropathy, this was higher in the retrospective cohort (n=78/154, 50.6%) than the prospective cohort (n=53/156, 34.0%). The cumulative event free probability was 51.8% (95% CI 45.4%, 57.9%) overall, 57.9% (95% CI 47.4%, 66.9%) in the prospective cohort and 46.5% (95% CI 38.1%, 54.5%) in the retrospective cohort.

The greatest difference in the occurrence of peripheral neuropathy between cohorts occurred during the period Enrolment to Month 6, in which the retrospective cohort had 50% (n=66/44, 150%) more events than the prospective cohort. In the later follow-up periods, the differences in occurrence diminished dramatically. Between Month 6 and Month 12, 7 prospective patients and 9 retrospective patients had new occurrences of peripheral neuropathy; between Month 12 and Month 18 these were 2 patients and 1 patient, respectively; and between Month 18 and Month 24 each cohort had 1 patient with a new occurrence.

Table 10-23. Kaplan-Meier Estimates of First Peripheral Neuropathy Event After Baseline

		Safety Population		
		Prospective Cohort	**Retrospective Cohort**	**Total**
N		156	154	310
Enrolment to Month 6				
Patients at risk at enrolment	n (%)	156 (100%)	154 (100%)	310 (100%)
Patients with PN by Month 6[1]	n (%)	44 (28.2%)	66 (42.9%)	110 (35.5%)
Cumulative event free probability	Probability (95% CI)	69.1% (60.7%, 76.1%)	56.0% (47.7%, 63.5%)	61.9% (56.0%, 67.3%)
Month 6 to Month 12				
Patients at risk at Month 6	n (%)	81 (51.9%)	80 (51.9%)	161 (51.9%)
Patients with PN by Month 12	n (%)	51 (32.7%)	75 (48.7%)	126 (40.6%)
Cumulative event free probability	Probability (95% CI)	62.1% (53.0%, 69.9%)	49.4% (41.0%, 57.2%)	55.1% (49.0%, 60.8%)
Month 12 to Month 18				
Patients at risk at Month 12	n (%)	46 (29.5%)	59 (38.3%)	105 (33.9%)
Patients with PN by Month 18	n (%)	52 (33.3%)	77 (50.0%)	129 (41.6%)
Cumulative event free probability	Probability (95% CI)	60.4% (50.9%, 68.6%)	47.6% (39.2%, 55.5%)	53.3% (47.1%, 59.2%)
Month 18 to Month 24				
Patients at risk at Month 18	n (%)	32 (20.5%)	49 (31.8%)	81 (26.1%)
Patients with PN by Month 24	n (%)	53 (34.0%)	78 (50.6%)	131 (42.3%)
Cumulative event free probability	Probability (95% CI)	57.9% (47.4%, 66.9%)	46.5% (38.1%, 54.5%)	51.8% (45.4%, 57.9%)

Abbreviations: CI= confidence interval; n/N= number of patients; PN= peripheral neuropathy; SMQ= standardised MedDRA query

[1] Cumulative number of patients with SMQ peripheral neuropathy between initiation of treatment with brentuximab vedotin and the end of the interval

Note(s): Patients with peripheral neuropathy at enrolment were included as at-risk, worsening of the event was recorded as an AESI

Source: EOT Table 16

10.6.4 Neutropenia

Neutropenia (including febrile neutropenia and neutrophil count decreased) occurred in 54 patients (n=54/310, 17.4%), with an incidence of 37.2 (95% CI 26.3, 48.0) per 100 person-years. The incidence was higher in the prospective cohort (53.3 [95% CI 31.7, 75.0] per 100 person-years) than the retrospective cohort (25.8 [95% CI 14.5, 37.1] per 100 person-years). The frequency of neutropenia was 20.5% in the prospective cohort and 14.3% in the retrospective cohort. The Per-protocol Population had an almost identical incidence of 38.5 (95% CI 27.1, 50.0) per 100 person-years.

Table 10-24 presents the incidence of neutropenia events. Neutropenia was reported as serious in 11 patients (n=11/310, 3.5%), with an incidence of 6.7 (95% CI 2.7, 10.8) per 100 person-years. It was reported as serious with similar incidence between the prospective cohort (7.2 [95% CI 0.7, 13.7] per 100 person-years) and the retrospective cohort (6.4 [95% CI 1.2, 11.5] per 100 person-years).

Most of the reported neutropenia were considered treatment-related, reported for 42 patients (n=42/310, 13.5%), with an incidence of 27.9 (95% CI 18.8, 37.0) per 100 person-years. It was reported as treatment-related with higher incidence in the prospective cohort (44.6 [95% CI 025.3, 63.8] per 100 person-years) than in the retrospective cohort (16.7 [95% CI 8.0, 25.4] per 100 person-years).

All reported neutropenia events were treatment-emergent (n=54/310, 17.4%), with an incidence of 37.2 (95% CI 26.3, 48.0) per 100 person-years. Post-treatment, 2 patients reported neutropenia events (EOT Table 14.3.1.1.b).

Table 10-24. Summary of Neutropenia Events

		Safety Population			Per-protocol Population		
		Prospective Cohort	**Retrospective Cohort**	**Total**	**Prospective Cohort**	**Retrospective Cohort**	**Total**
N		156	154	310	139	145	284
Neutropenia (including febrile neutropenia) [2]							
Any	n (%)	32 (20.5%)	22 (14.3%)	54 (17.4%)	32 (23.0%)	21 (14.5%)	53 (18.7%)
	Incidence[1] (95%CI)	53.3 (31.7, 75.0)	25.8 (14.5, 37.1)	37.2 (26.3, 48.0)	57.9 (33.9, 81.9)	25.5 (14.1, 36.9)	38.5 (27.1, 50.0)
Serious	n (%)	5 (3.2%)	6 (3.9%)	11 (3.5%)	5 (3.6%)	6 (4.1%)	11 (3.9%)
	Incidence[1] (95%CI)	7.2 (0.7, 13.7)	6.4 (1.2, 11.5)	6.7 (2.7, 10.8)	7.8 (0.8, 14.8)	6.6 (1.3, 11.9)	7.1 (2.8, 11.3)
Treatment-emergent[3]	n (%)	32 (20.5%)	22 (14.3%)	54 (17.4%)	---	---	---
	Incidence[1] (95%CI)	53.3 (31.7, 75.0)	25.8 (14.5, 37.1)	37.2 (26.3, 48.0)	---	---	---
Treatment-related[4]	n (%)	27 (17.3%)	15 (9.7%)	42 (13.5%)	27 (19.4%)	14 (9.7%)	41 (14.4%)
	Incidence[1] (95%CI)	44.6 (25.3, 63.8)	16.7 (8.0, 25.4)	27.9 (18.8, 37.0)	48.4 (27.1, 69.7)	16.1 (7.4, 24.8)	28.7 (19.2, 38.3)

Abbreviations: AESI= adverse event of special interest; CI= confidence interval; n/N= number of patients
[1] Incidence density rate (per 100 person-years)
[2] Includes also neutrophil count decreased
[3] Treatment-emergent adverse events started or worsened on or after the first dose of brentuximab vedotin and within 30 days after the last dose of brentuximab vedotin
[4] Treatment-related adverse events were determined to be related to brentuximab vedotin by the treating physician
Note(s): Percentages are based on total number of patients N. Time at risk was defined as between the first dose of brentuximab vedotin and: event start date, last dose plus 30 days, date of death, study completion/ discontinuation, data base lock, whichever occurred first.
Source: EOT Table 14.3.1.1, EOT Table 14.3.1.1_pp, EOT Table 14.3.1.2, EOT Table 14.3.1.2_pp, EOT Table14.3.1.1.a, EOT Table 14.3.3.2, EOT Table 14.3.3.2_pp

10.6.4.1 Treatment Modifications and Discontinuations

Table 10-25 presents a summary of the dose changes resulted from neutropenia AESIs.

Dose Reductions due to:

- Blood and lymphatic disorders in 1 patient (n=1/310, 0.3%): neutropenia

Dose Hold, Delay, or Interruption due to:

- Blood and lymphatic disorders in 14 patients (n=14/310, 4.5%): neutropenia (n=13), febrile neutropenia (n=1)
- Investigations in 1 patient (n=1/310, 0.3%): neutrophil count decreased

Dose Permanently Discontinued due to:

- Blood and lymphatic disorders in 1 patient (n=1/310, 0.3%): neutropenia

Table 10-25. Summary of Study Discontinuations and Dose Modifications due to Neutropenia Adverse Events of Special Interest

		Safety Population		
		Prospective Cohort	**Retrospective Cohort**	**Total**
N		156	154	310
Neutropenia (including febrile neutropenia)[1]				
Dose reduction	n (%)	0	1 (0.6%)	1 (0.3%)
Dose held, delay, and interruption	n (%)	4 (2.6%)	10 (6.5%)	14 (4.5%)
Dose permanently discontinued	n (%)	1 (0.6%)	0	1 (0.3%)
Discontinuation from study	n (%)	0	0	0

Abbreviations: n/N= number of patients
[1] Includes also neutrophil count decreased
Note(s): Percentages are based on total number of patients N.
Source: EOT Table 14.4.2.2, EOT Table 14.4.2.3, EOT Table 14.4.2.4, EOT Table 14.4.2.5

10.6.4.2 Time to First Neutropenia

Figure 4 shows the cumulative event free probability of neutropenia by time since enrolment. Neutropenia occurred at relatively consistent rates throughout the study period.

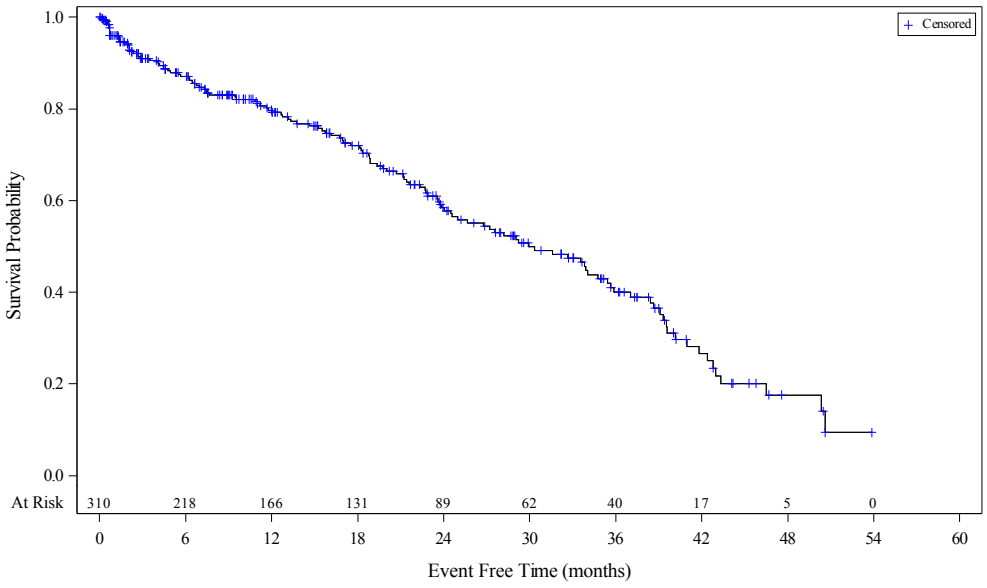

Figure 4. Kaplan-Meier Plot of Time to Onset of Neutropenia

10.6.5 Infections

Infections (including opportunistic infections) occurred in 97 patients (n=97/310, 31.3%), with an incidence of 76.0 (95% CI 60.1, 92.0) per 100 person-years. The incidence was higher in the prospective cohort (96.7 [95% CI 69.1, 124.3] per 100 person-years) than and retrospective cohort (61.4 [95% CI 42.8, 80.1] per 100 person-years). The Per-protocol Population had an almost identical incidence of 79.3 (95% CI 62.4, 96.2) per 100 person-years.

Table 10-26 presents the incidence of infections. Infections were reported as serious in 42 patients (n=42/310, 13.5%), with an incidence of serious neutropenia of 27.2 (95% CI 18.8, 35.7) per 100 person-years. It was reported as serious with higher incidence in the prospective cohort (32.8 [95% CI 22.4, 54.1] per 100 person-years) than the retrospective cohort (19.7 [95% CI 10.4, 28.9] per 100 person-years).

About half of the reported infections were considered treatment-related, reported for 53 patients (n=53/310, 17.1%), with an incidence of 36.1 (95% CI 26.1, 46.1) per 100 person-years. They were reported as treatment-related with higher incidence in the prospective cohort (52.9 [95% CI 33.6, 72.3] per 100 person-years) than the retrospective cohort (24.9 [95% CI 14.4, 35.4] per 100 person-years).

All but 1 of the reported infections events occurred on-treatment, 96 patients (n=96/310, 31.0%) had a treatment-emergent infection with an incidence of 75.3 (95% CI 59.4, 91.1). The treatment-emergent incidence was higher in the prospective cohort (95.0 [95% CI 67.5, 122.4] per 100 person-years) than the retrospective cohort (61.4 [95% CI 42.8, 80.1] per 100 person-years).

Table 10-26. Summary of Infections as Events

		Safety Population			Per-protocol Population		
		Prospective Cohort	Retrospective Cohort	Total	Prospective Cohort	Retrospective Cohort	Total
N		156	154	310	139	145	284
Infections (including opportunistic infections)							
Any	n (%)	51 (32.7%)	46 (29.9%)	97 (31.3%)	49 (35.3%)	46 (31.7%)	95 (33.5%)
	Incidence[1] (95%CI)	96.7 (69.1, 124.3)	61.4 (42.8, 80.1)	76.0 (60.1, 92.0)	101.1 (71.5, 130.7)	64.4 (44.7, 84.1)	79.3 (62.4, 96.2)
Serious	n (%)	24 (15.4%)	18 (11.7%)	42 (13.5%)	23 (16.5%)	18 (12.4%)	41 (14.4%)
	Incidence[1] (95%CI)	38.2 (22.4, 54.1)	19.7 (10.4, 28.9)	27.2 (18.8, 35.7)	39.6 (22.6, 56.6)	20.5 (10.8, 30.1)	28.1 (19.2, 37.0)
Treatment-emergent[2]	n (%)	50 (32.1%)	46 (29.9%)	96 (31.0%)	---	---	---
	Incidence[1] (95%CI)	95.0 (67.5, 122.4)	61.4 (42.8, 80.1)	75.3 (59.4, 91.1)	---	---	---
Treatment-related[3]	n (%)	31 (19.9%)	22 (14.3%)	53 (17.1%)	30 (21.6%)	22 (15.2%)	52 (18.3%)
	Incidence[1] (95%CI)	52.9 (33.6, 72.3)	24.9 (14.4, 35.4)	36.1 (26.1, 46.1)	55.3 (34.7, 76.0)	25.9 (15.0, 36.9)	37.4 (26.9, 47.9)

Abbreviations: AESI= adverse event of special interest; CI= confidence interval; n/N= number of patients
[1] Incidence density rate (per 100 person-years)
[2] Treatment-emergent adverse events started or worsened on or after the first dose of brentuximab vedotin and within 30 days after the last dose of brentuximab vedotin
[3] Treatment-related adverse events were determined to be related to brentuximab vedotin by the treating physician
Note(s): Percentages are based on total number of patients N. Time at risk was defined as between the first dose of brentuximab vedotin and: event start date, last dose plus 30 days, date of death, study completion/ discontinuation, data base lock, whichever occurred first.
Source: EOT Table 14.3.1.1, EOT Table 14.3.1.1_pp, EOT Table 14.3.1.2, EOT Table 14.3.1.2_pp, EOT Table 14.3.1.1.a, EOT Table 14.3.3.2, EOT Table 14.3.3.2_pp

10.6.5.1 Treatment Modifications and Discontinuations

Table 10-27 presents a summary of the dose changes resulted from infection AESIs.

Dose Reductions due to:

- Infections and infestations in 2 patients (n=2/310, 0.6%): fungal infection, herpes zoster cutaneous disseminated (n=1 each)

Dose Hold, Delay, or Interruption due to:

- Infections and infestations in 17 patients (n=17/310, 5.5%): herpes zoster (n=4), conjunctivitis (n=2), lung infection (n=2), upper respiratory tract infection (n=2), fungal

infection, hepatitis C, laryngitis, lower respiratory tract infection, pneumonia, pneumonia fungal, salmonellosis (n=1 each)
- Gastrointestinal disorders in 1 patient (n=1/310, 0.3%): diarrhoea

Dose Permanently Discontinued due to:
- Infections and infestations in 8 patients (n=8/310, 2.6%): pneumonia (n=4), gingivitis, lung infection, pneumonia viral, vulvovaginal candidiasis (n=1 each)
- Hepatobiliary disorders in 1 patient (n=1/310, 0.3%): cholangitis
- Respiratory, thoracic and mediastinal disorders in 1 patient (n=1/310, 0.3%): pneumonitis

Discontinuation from Study due to:
- Infections and infestations in 5 patients (n=5/310, 1.6%): pneumonia (n=3), bacterial sepsis, sepsis (n=1 each)

Table 10-27. Summary of Study Discontinuations and Dose Modifications due to Infection Adverse Events of Special Interest

		Safety Population		
		Prospective Cohort	**Retrospective Cohort**	**Total**
N		156	154	310
Infections (including opportunistic infections)				
Dose reduction	n (%)	2 (1.3%)	0	2 (0.6%)
Dose held, delay, and interruption	n (%)	7 (4.5%)	10 (6.5%)	17 (5.5%)
Dose permanently discontinued	n (%)	6 (3.8%)	2 (1.3%)	8 (2.6%)
Discontinuation from study	n (%)	5 (3.2%)	0	5 (1.6%)

Abbreviations: n/N= number of patients
Note(s): Percentages are based on total number of patients N.
Source: EOT Table 14.4.2.2, EOT Table 14.4.2.3, EOT Table 14.4.2.4, EOT Table 14.4.2.5

10.6.5.2 Time to First Infection

Figure 5 shows the cumulative event free probability of infections by time since enrolment. Infections occurred at relatively consistent rates throughout the study period.

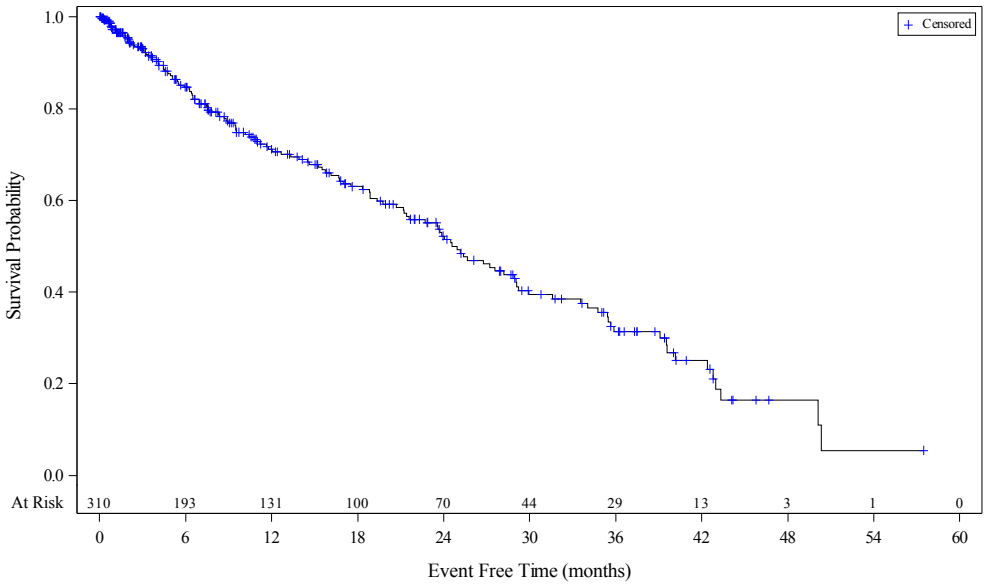

Figure 5. Kaplan-Meier Plot of Time to Onset of Infection

10.6.6 Hyperglycaemia

Hyperglycaemia occurred in 4 patients (n=4/310, 1.3%) with an incidence of 2.4 (95% CI 0.0, 4.9) per 100 person-years, including 1 event of diabetic ketoacidosis, and were all in the retrospective cohort. The Per-protocol Population had an almost identical incidence of 2.6 (95% CI 0.0, 5.1) per 100 person-years. Two of these patients had a medical history of diabetes recorded.

Table 10-28 presents the incidence of hyperglycaemia events. Hyperglycaemia was reported as serious in 2 patients (1 each hyperglycaemia and diabetic ketoacidosis) (n=2/310, 0.6%), with an incidence of 1.2 (95% CI 0.0, 2.9) per 100 person-years.

Treatment-related hyperglycaemia was reported for 2 patients (both without a medical history of diabetes) (n=2/310, 0.6%), with an incidence of 1.2 (95% CI 0.0, 2.9) per 100 person-years.

10.6.6.1 Treatment-related events

Overall 4 hyperglycaemia events occurred on-treatment, with an incidence of 2.4 (95% CI 0.0, 4.9) per 100 person-years.

Table 10-28. Summary of Hyperglycaemia Events

		Safety Population			Per-protocol Population		
		Prospective Cohort	Retrospective Cohort	Total	Prospective Cohort	Retrospective Cohort	Total
N		156	154	310	139	145	284
Hyperglycaemia[2]							
Any	n (%)	0	4 (2.6%)	4 (1.3%)	0	4 (2.8%)	4 (1.4%)
	Incidence[1] (95%CI)	0	4.3 (0.0, 8.5)	2.4 (0.0, 4.9)	0	4.4 (0.0, 8.8)	2.6 (0.0, 5.1)
Serious	n (%)	0	2 (1.3%)	2 (0.6%)	0	2 (1.4%)	2 (0.7%)
	Incidence[1] (95%CI)	0	2.1 (0.0, 5.0)	1.2 (0.0, 2.9)	0	2.2 (0.0, 5.2)	1.3 (0.0, 3.0)
Treatment-emergent[3]	n (%)	0	4 (2.6%)	4 (1.3%)	---	---	---
	Incidence[1] (95%CI)	0	4.3 (0.0, 8.5)	2.4 (0.0, 4.9)	---	---	---
Treatment-related[4]	n (%)	0	2 (1.3%)	2 (0.6%)	0	2 (1.4%)	2 (0.7%)
	Incidence[1] (95%CI)	0	2.1 (0.0, 5.1)	1.2 (0.0, 2.9)	0	2.2 (0.0, 5.3)	1.3 (0.0, 3.1)

Abbreviations: AESI= adverse event of special interest; CI= confidence interval; n/N= number of patients
[1] Incidence density rate (per 100 person-years)
[2] Includes hyperglycaemia (n=3) and diabetic ketoacidosis (n=1)
[3] Treatment-emergent adverse events started or worsened on or after the first dose of brentuximab vedotin and within 30 days after the last dose of brentuximab vedotin
[4] Treatment-related adverse events were determined to be related to brentuximab vedotin by the treating physician
Note(s): Percentages are based on total number of patients N. Time at risk was defined as between the first dose of brentuximab vedotin and: event start date, last dose plus 30 days, date of death, study completion/ discontinuation, data base lock, whichever occurred first.
Source: EOT Table 14.3.1.1, EOT Table 14.3.1.1_pp, EOT Table 14.3.1.2, EOT Table 14.3.1.2_pp, EOT Table 14.3.1.1.a, EOT Table 14.3.3.2, EOT Table 14.3.3.2_pp

10.6.6.2 Treatment Modifications and Discontinuations

Table 10-29 presents a summary of the dose changes resulted from hyperglycaemia AESIs.

Dose Reductions due to:

- Metabolism and nutrition disorders in 2 patients (n=2/310, 0.6%): hyperglycaemia (n=2)

Dose Hold, Delay, or Interruption due to:

- Metabolism and nutrition disorders in 2 patients (n=2/310, 0.6%): diabetic ketoacidosis, hyperglycaemia (n=1 each)

Table 10-29. Summary of Study Discontinuations and Dose Modifications due to Hyperglycaemia Adverse Events of Special Interest

		Safety Population		
		Prospective Cohort	**Retrospective Cohort**	**Total**
N		156	154	310
Hyperglycaemia				
Dose reduction	n (%)	0	2 (1.3%)	2 (0.6%)
Dose held, delay, and interruption	n (%)	0	1 (0.6%)	1 (0.3%)
Dose permanently discontinued	n (%)	0	0	0
Discontinuation from study	n (%)	0	0	0

Abbreviations: n/N= number of patients
Note(s): Percentages are based on total number of patients N.
Source: EOT Table 14.4.2.2, EOT Table 14.4.2.3, EOT Table 14.4.2.4, EOT Table 14.4.2.5

10.6.6.3 Time to First Hyperglycaemia

Figure 6 shows the cumulative event free probability of hyperglycaemia by time since enrolment. Hyperglycaemia had a delay before onset of any events, possibly due to the small number of events overall.

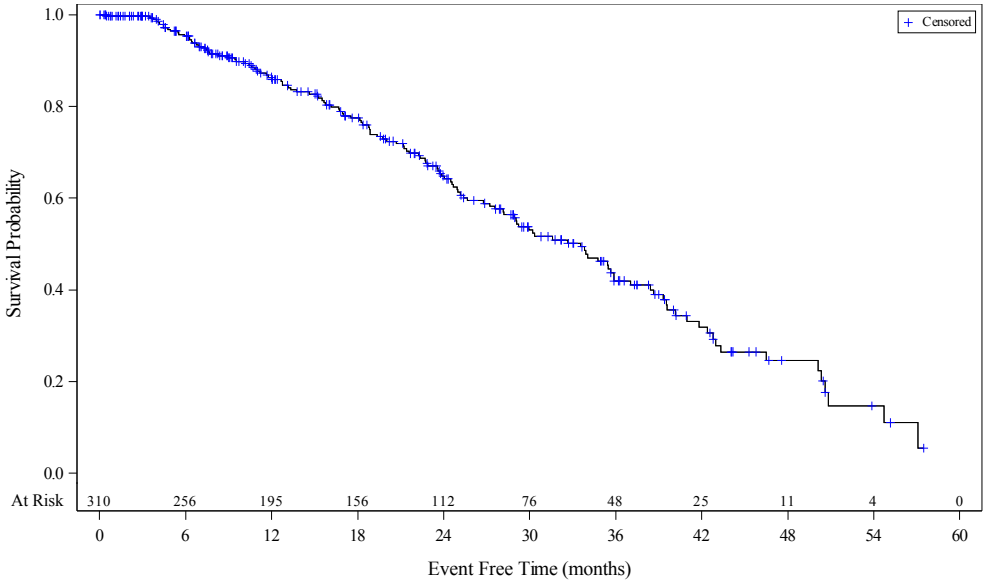

Figure 6. Kaplan-Meier Plot of Time to Onset of Hyperglycaemia

10.6.7 Hypersensitivity Reactions

Hypersensitivity reactions (including infusion-related reactions and allergic reactions) were reported in 34 patients (n=34/310, 11.0%), with an incidence of 22.5 (95% CI 14.7, 30.4) per 100 person-years. The incidence was similar between the prospective and retrospective cohorts. The Per-protocol Population had an almost identical incidence of 22.3 (95% CI 14.3, 30.3) per 100 person-years.

Table 10-30 presents the incidence of hypersensitivity reactions. Hypersensitivity reactions were reported as serious in 7 patients (n=7/310, 2.3%), with an incidence of 4.2 (95% CI 1.1, 7.4) per 100 person-years. They were reported as serious with similar incidence between the prospective and retrospective cohorts.

Most of the reported hypersensitivity reactions were considered treatment-related (n=24/34, 70.6%). Treatment-related hypersensitivity reactions were reported for 24 patients (n=24/310, 7.7%), with an incidence of 15.3 (95% CI 9.0, 21.7) per 100 person-years. They were reported as treatment-related with similar incidence between the prospective and retrospective cohorts.

Table 10-30. Summary of Hypersensitivity Reaction Events

		Safety Population			Per-protocol Population		
		Prospective Cohort	Retrospective Cohort	Total	Prospective Cohort	Retrospective Cohort	Total
N		156	154	310	139	145	284
Hypersensitivity reactions (including infusion-related reactions and allergic reactions)							
Any	n (%)	15 (9.6%)	19 (12.3%)	34 (11.0%)	14 (10.1%)	18 (12.4%)	32 (11.3%)
	Incidence[1] (95%CI)	23.3 (11.0, 35.6)	21.9 (11.7, 32.2)	22.5 (14.7, 30.4)	23.4 (10.6, 36.2)	21.5 (11.2, 31.8)	22.3 (14.3, 30.3)
Serious	n (%)	3 (1.9%)	4 (2.6%)	7 (2.3%)	3 (2.2%)	4 (2.8%)	7 (2.5%)
	Incidence[1] (95%CI)	4.3 (0.0, 9.2)	4.2 (0.0, 8.4)	4.2 (1.1, 7.4)	4.6 (0.0, 9.9)	4.3 (0.0, 8.7)	4.5 (1.1, 7.8)
Treatment-emergent[2]	n (%)	15 (9.6%)	19 (12.3%)	34 (11.0%)	---	---	---
	Incidence[1] (95%CI)	23.3 (11.0, 35.6)	21.9 (11.7, 32.2)	22.5 (14.7, 30.4)	---	---	---
Treatment-related[3]	n (%)	11 (7.1%)	13 (8.4%)	24 (7.7%)	11 (7.9%)	12 (8.3%)	23 (8.1%)
	Incidence[1] (95%CI)	16.7 (6.4, 27.0)	14.4 (6.3, 22.4)	15.3 (9.0, 21.7)	18.0 (6.9, 29.1)	13.7 (5.7, 21.7)	15.5 (8.9, 22.0)

Abbreviations: AESI= adverse event of special interest; CI= confidence interval; n/N= number of patients
[1] Incidence density rate (per 100 person-years)
[2] Treatment-emergent adverse events started or worsened on or after the first dose of brentuximab vedotin and within 30 days after the last dose of brentuximab vedotin
[3] Treatment-related adverse events were determined to be related to brentuximab vedotin by the treating physician
Note(s): Percentages are based on total number of patients N. Time at risk was defined as between the first dose of brentuximab vedotin and: event start date, last dose plus 30 days, date of death, study completion/ discontinuation, data base lock, whichever occurred first.
Source: EOT Table 14.3.1.1, EOT Table 14.3.1.1_pp, EOT Table 14.3.1.2, EOT Table 14.3.1.2_pp, EOT Table 14.3.1.1.a, EOT Table 14.3.3.2, EOT Table 14.3.3.2_pp

10.6.7.1 On-treatment events

Overall 34 patients experienced a hypersensitivity reaction with an incidence of 22.5 (95% CI 14.7, 30.4) per 100 person-years. All events occurred on-treatment.

10.6.7.2 Treatment Modifications and Discontinuations

Table 10-31 presents a summary of the dose changes resulted from hypersensitivity reaction AESIs.

Dose Hold, Delay, or Interruption due to:

- Injury, poisoning and procedural complications in 1 patient (n=1/310, 0.3%): infusion-related reaction

Dose Permanently Discontinued due to:

- Immune system disorders in 1 patient (n=1/310, 0.3%): anaphylactic reaction
- General disorders and administration site conditions in 1 patient (n=1/310, 0.3%): pyrexia

Discontinuation from Study due to:

- Immune system disorders in 1 patient (n=1/310, 0.3%): anaphylactic reaction

Table 10-31. Summary of Study Discontinuations and Dose Modifications due to Hypersensitivity Reaction Adverse Events of Special Interest

		Safety Population		
		Prospective Cohort	**Retrospective Cohort**	**Total**
N		156	154	310
Hypersensitivity reactions (including infusion-related reactions and allergic reactions)				
Dose reduction	n (%)	0	0	0
Dose held, delay, and interruption	n (%)	1 (0.6%)	0	1 (0.3%)
Dose permanently discontinued	n (%)	1 (0.6%)	1 (0.6%)	2 (1.3%)
Discontinuation from study	n (%)	0	1 (0.6%)	1 (0.6%)

Abbreviations: n/N= number of patients
Note(s): Percentages are based on total number of patients N.
Source: EOT Table 14.4.2.2, EOT Table 14.4.2.3, EOT Table 14.4.2.4, EOT Table 14.4.2.5

10.6.8 Potential Risk Factors of Peripheral Neuropathy

Logistic regression analysis was used to identify potential risk factors of peripheral neuropathy in the Safety Population, presented in Table 10-32; and by disease type: CD30+HLand sALCL, presented in Table 10-33.

10.6.8.1 Univariate analysis

Univariate analysis was used to identify potential risk factors of peripheral neuropathy in patients treated with brentuximab vedotin. In the overall population, the crude odds ratio (OR) of variables that had p<0.10 were BMI (OR=1.067 [95% CI 1.023, 1.113]; p=0.003) and presence of extranodal involvement compared with no extranodal involvement at initiation of treatment with brentuximab vedotin (OR=0.559 [95% CI 0.340, 0.918]; p=0.021). Other variables did not meet the cut-off, possibly due to the small number of patients in one of the categories limiting the ability to compare and interpret the results.

Amongst CD30+ HL patients the results were similar, increased BMI (OR=1.083 [95% CI 1.032, 1.137]; p=0.001), presence of extranodal involvement compared with no extranodal involvement (OR=0.553 [95% CI 0.316, 0.968]; p=0.038), and age <65 years compared with ≥65 years

(OR=0.533 [95% CI 0.290, 0.983]; p=0.044). Amongst sALCL patients, no predictor was associated with risk of peripheral neuropathy, likely owing to the small sample size overall (n=58).

Table 10-32. Odds Ratios from Univariate Analysis for Peripheral Neuropathy Events after Enrolment

	Patients with PN	Patients without PN	Odds Ratio (95% CI)	p-value[1]	p-value[2]
Disease type					
CD30+HL	107	145	1.045 (0.586, 1.865)	0.881	0.881
sALCL	24	34	Ref.		
Age by group					
< 65 years	93	141	0.660 (0.392, 1.110)	0.117	0.117
>= 65 years	38	38	Ref.		
Sex					
Male	84	106	1.231 (0.773, 1.960)	0.382	0.382
Female	47	73	Ref.		
BMI as a numeric factor					
BMI (per 1-unit increase)			1.067 (1.023, 1.113)	0.003	0.003
Diabetes mellitus at baseline					
Yes	13	16	1.122 (0.520, 2.422)	0.769	0.769
No	118	163	Ref.		
Disease stage at baseline					
Unknown and other	8	14	0.961 (0.373, 2.474)	0.934	0.532
IV	44	74	Ref.		
III	30	33	1.529 (0.823, 2.840)	0.179	
II	43	53	1.364 (0.788, 2.362)	0.267	
I	6	5	2.018 (0.582, 7.003)	0.269	
Extranodal involvement at baseline					
Unknown	18	15	1.376 (0.649, 2.919)	0.405	0.024
Yes	38	78	0.559 (0.340, 0.918)	0.022	
No	75	86	Ref.		
Neuropathy at baseline					
Yes	19	29	0.877 (0.468, 1.644)	0.683	0.683
No	112	150	Ref.		

	Patients with PN	Patients without PN	Odds Ratio (95% CI)	p-value[1]	p-value[2]
Previous history of peripheral neuropathy					
Yes	15	20	1.028 (0.505, 2.093)	0.939	0.939
No	116	159	Ref.		
Most recent chemotherapy exposure					
Yes	131	177	---	---	---
No	0	0	Ref.		
Number of cycles from prior lines of therapy					
Number of cycles per 1 cycle			1.025 (0.980, 1.071)	0.283	0.283
Impaired renal function at baseline					
Yes	10	8	1.767 (0.677, 4.606)	0.245	0.245
No	121	171	Ref.		
Thyroid dysfunction					
Yes	12	18	0.902 (0.418, 1.944)	0.792	0.792
No	119	161	Ref.		
Impaired hepatic function at baseline					
Yes	2	8	0.331 (0.069, 1.587)	0.167	0.167
No	129	171	Ref.		
Autoimmune disease at baseline					
Yes	3	11	0.358 (0.098, 1.310)	0.121	0.121
No	128	168	Ref.		
Previous exposure to known neurotoxic chemotherapeutics					
Yes	115	160	0.764 (0.370, 1.574)	0.465	0.465
No	16	17	Ref.		
Exposure to granulocyte-colony stimulating factor					
Yes	13	10	1.862 (0.790, 4.388)	0.155	0.155
No	118	169	Ref.		

Abbreviations: BMI= body mass index; CI= confidence interval; HL= Hodgkin's lymphoma; n/N= number of patients; PN= peripheral neuropathy; Ref= reference; sALCL= systemic anaplastic large cell lymphoma
[1] p-value from univariate logistic regression model.
[2] p-value from type 3 analysis of effects based on Wald Test.
Note(s): Patients with peripheral neuropathy at enrolment were included as at risk, worsening of the event was recorded as an AESI. Baseline refers to data collected in the baseline/enrolment form, refer to Section 9.5.1 for further details.
Source: EOT Table 99.2.17.1

Table 10-33. Odds Ratios from Univariate Analysis for Peripheral Neuropathy Events After Enrolment by Cancer Type

	CD30+ HL Patients					sALCL Patients				
	with PN	**no PN**	**Odds Ratio (95% CI)**	**p-value[1]**	**p-value[2]**	**with PN**	**no PN**	**Odds Ratio (95% CI)**	**p-value[1]**	**p-value[2]**
N	107	145				24	34	Ref		
Age by group										
< 65 years	78	121	0.533 (0.290, 0.983)	0.044	0.044	15	20	1.167 (0.399, 3.408)	0.778	0.778
>= 65 years	29	24	Ref.			9	14	Ref.		
Sex										
Male	65	86	1.062 (0.637, 1.768)	0.818	0.818	19	20	2.660 (0.802, 8.820)	0.110	0.110
Female	42	59	Ref.			5	14	Ref.		
BMI as a numeric factor										
BMI (per 1-unit increase)			1.083 (1.032, 1.137)	0.001	0.001			1.004 (0.913, 1.104)	0.938	0.938
Diabetes mellitus at baseline										
Yes	12	13	1.283 (0.561, 2.935)	0.556	0.556	1	3	0.449 (0.044, 4.602)	0.500	0.500
No	95	132	Ref.			23	31	Ref.		
Disease stage at baseline										
Unknown /other	7	7	1.657 (0.536, 5.122)	0.380	0.671	1	7	0.254 (0.027, 2.407)	0.232	0.306
IV	35	58	Ref.			9	16	Ref.		
III	26	29	1.486 (0.756, 2.919)	0.251		4	4	1.778 (0.356, 8.882)	0.483	
II	34	47	1.199 (0.652, 2.204)	0.559		9	6	2.667 (0.715, 9.951)	0.144	
I	5	4	2.071 (0.521, 8.234)	0.301		1	1	1.778 (0.099, 31.976)	0.696	
Extranodal involvement at baseline										
Unknown	17	13	1.522 (0.685, 3.384)	0.303	0.031	1	2	0.536 (0.044, 6.582)	0.626	0.568
Yes	29	61	0.553 (0.316, 0.968)	0.038		9	17	0.567 (0.191, 1.683)	0.307	
No	61	71	Ref.			14	15	Ref.		
Neuropathy at baseline										
Yes	15	24	0.822 (0.408, 1.655)	0.583	0.583	4	5	1.160 (0.277, 4.861)	0.839	0.839
No	92	121	Ref.			20	29	Ref.		
Previous history of peripheral neuropathy										

	CD30+ HL Patients					sALCL Patients				
	with PN	no PN	Odds Ratio (95% CI)	p-value[1]	p-value[2]	with PN	no PN	Odds Ratio (95% CI)	p-value[1]	p-value[2]
Yes	11	17	0.863 (0.386, 1.926)	0.719	0.719	4	3	2.067 (0.418, 10.226)	0.374	0.374
No	96	128	Ref.			20	31	Ref.		
Most recent chemotherapy exposure										
Yes	107	145	---	---	---	24	32	---	---	---
No	0	0	Ref.			0	0	Ref.		
Number of cycles from prior lines of therapy										
Number of cycles			1.030 (0.981, 1.082)	0.234	0.234			1.000 (0.889, 1.124)	0.995	0.995
Impaired renal function at baseline										
Yes	10	6	2.388 (0.840, 6.790)	0.102	0.102	0	2	<0.001 (<0.001,>999.99)	0.981	0.981
No	97	139	Ref.			24	32	Ref.		
Thyroid dysfunction										
Yes	10	14	0.965 (0.411, 2.264)	0.934	0.934	2	4	0.682 (0.114, 4.061)	0.674	0.674
No	97	131	Ref.			22	30	Ref.		
Impaired hepatic function at baseline										
Yes	2	8	0.326 (0.068, 1.568)	0.162	0.162	0	0	---	---	---
No	105	137	Ref.			24	34	Ref.		
Autoimmune disease at baseline										
Yes	1	7	0.186 (0.023, 1.535)	0.118	0.118	2	4	0.682 (0.114, 4.061)	0.674	0.674
No	106	138	Ref.			22	30	Ref.		
Previous exposure to known neurotoxic chemotherapeutics										
Yes	94	134	0.594 (0.255, 1.382)	0.226	0.226	21	26	1.615 (0.360, 7.243)	0.531	0.531
No	13	11	Ref.			3	6	Ref.		
Exposure to granulocyte-colony stimulating factor										
Yes	10	9	1.558 (0.610, 3.978)	0.354	0.354	3	1	4.714 (0.459, 48.374)	0.192	0.192
No	97	136	Ref.			21	33	Ref.		

Abbreviations: BMI= body mass index; CI= confidence interval; HL= Hodgkin's lymphoma; n/N= number of patients; PN= peripheral neuropathy; Ref= reference; sALCL= systemic anaplastic large cell lymphoma
[1] p-value from univariate logistic regression model.
[2] p-value from type 3 analysis of effects based on Wald Test.
Note(s): Patients with peripheral neuropathy at enrolment were included as at risk, worsening of the event was recorded as an AESI. Baseline refers to data collected in the baseline/enrolment form, refer to Section 9.5.1 for further details.
Source: EOT Table 99.2.17.2, EOT Table 99.2.17.3

10.6.8.2 Multivariate Analysis

Multivariate analysis included age, sex, and any variables with p<0.10 from univariate analysis to predict the risk of peripheral neuropathy, overall and by disease type. The results are presented in Table 10-34 and Table 10-35.

Multivariate analysis was performed using age (<65 years and ≥65 years), sex, and the variables that had p<0.01 in univariate analysis (ie, BMI and evidence of extranodal involvement) to identify potential risk factors of peripheral neuropathy in patients treated with brentuximab vedotin. Increased BMI remained associated with increased risk of peripheral neuropathy with a similar effect as in the univariate analysis (OR=1.061 [95% CI 1.016, 1.108]; p=0.007). The presence of extranodal involvement compared with no extranodal involvement gave an indication of being protective with a similar effect as in the univariate analysis (OR= 0.605 [95% CI 0.364, 1.005]; p=0.052).

Amongst CD30+ HL patients the results were similar to the overall population; however, in the age and sex adjusted model (Model 1), age <65 years compared with ≥65 years was protective against peripheral neuropathy (OR=0.538 [95% CI 0.292-0.992]; p=0.047), consistent with the univariate results. Amongst the sALCL patients, no predictor seems to be associated with risk of peripheral neuropathy. However, consistent with the univariate analyses in Table 10-33, there was an indication that age may play less of a role in sALCL patients than that in CD30+ HL patients.

Table 10-34. Odds Ratios from Multivariate Analysis for Peripheral Neuropathy Events After Enrolment

	Patients with PN	Patients without PN	Model 1[1] Odds Ratio (95% CI)	p-value[3]	p-value[4]	Model 2[2] Odds Ratio (95% CI)	p-value[3]	p-value[4]
N	131	178						
Age by group								
<65 years	93	140	0.665 (0.395, 1.120)	0.125	0.125	0.700 (0.410, 1.195)	0.192	0.192
≥65 years	38	38	Ref.			Ref.		
Sex								
Male	84	105	1.241 (0.778, 1.980)	0.365	0.365	1.207 (0.747, 1.950)	0.442	0.442
Female	47	73	Ref.			Ref.		
BMI as a numeric factor								
BMI (per 1-unit increase)			---			1.061 (1.016, 1.108)	0.007	0.007
Evidence of extranodal involvement at baseline								
Unknown	18	15	---			1.313 (0.606, 2.841)	0.490	0.071
Yes	38	77	---			0.605 (0.364, 1.005)	0.052	
No	75	86	---			Ref.		

Abbreviations: BMI= body mass index; CI= confidence interval; HL= Hodgkin's lymphoma; n/N= number of patients; PN= peripheral neuropathy; Ref= reference; sALCL= systemic anaplastic large cell lymphoma
[1] Adjusted for sex and age only
[2] Fully adjusted for all variables included in table
[3] p-value from multivariate logistic regression model based on Wald Chi-Square test for each comparison.
[4] p-value from type 3 analysis of effects based on Wald Test.
Note(s): Patients with peripheral neuropathy at enrolment were included as at-risk, worsening of the event was recorded as an AESI. The fully adjusted model included sex, age, and all variables from the univariate analysis with a p-value <0.10 (refer to Table 10-32). Baseline refers to data collected in the baseline/enrolment form, refer to Section 9.5.1 for further details.
Source: EOT Table 99.2.18.1

Table 10-35. Odds Ratios from Multivariate Analysis for Peripheral Neuropathy Events After Enrolment by Cancer Type

CD30+ HL Patients								
	Patients with PN	**Patients without PN**	**Model 1[1] Odds Ratio (95% CI)**	**p-value[3]**	**p-value[4]**	**Model 2[2] Odds Ratio (95% CI)**	**p-value[3]**	**p-value[4]**
N	107	144						
Age by group								
<65 years	78	120	0.538 (0.292, 0.992)	0.047	0.047	0.596 (0.318, 1.120)	0.108	0.108
≥65 years	29	24	Ref.			Ref.		
Sex								
Male	65	85	1.072 (0.640, 1.794)	0.792	0.792	1.039 (0.610, 1.772)	0.887	0.887
Female	42	59	Ref.			Ref.		
BMI as a numeric factor								
BMI (per 1-unit increase)			---			1.075 (1.024, 1.129)	0.004	0.004
Evidence of extranodal involvement								
Unknown	17	13	---			1.491 (0.653, 3.406)	0.343	0.076
Yes	29	60	---			0.600 (0.338, 1.067)	0.082	
No	61	71	---			Ref.		
sALCL Patients								
	Patients with PN	**Patients without PN**	**Model 1[1] Odds Ratio (95% CI)**	**p-value[3]**	**p-value[4]**	**Model 2[2] Odds Ratio (95% CI)**	**p-value[3]**	**p-value[4]**
N	24	34	-			-		
Age by group								
<65 years	15	20	1.138 (0.380, 3.410)	0.818	0.818	1.463 (0.441, 4.852)	0.534	0.534
≥65 years	9	14	Ref.			Ref.		
Sex								
Male	19	20	2.650 (0.799, 8.793)	0.111	0.111	2.911 (0.841, 10.070)	0.092	0.092
Female	5	14	Ref.			Ref.		
BMI as a numeric factor								
BMI (per 1-unit increase)			---			0.979 (0.878, 1.090)	0.696	0.696

CD30+ HL Patients								
	Patients with PN	**Patients without PN**	**Model 1[1] Odds Ratio (95% CI)**	**p-value[3]**	**p-value[4]**	**Model 2[2] Odds Ratio (95% CI)**	**p-value[3]**	**p-value[4]**
Evidence of extranodal involvement at baseline								
Unknown	1	2	---			0.527 (0.036, 7.802)	0.641	0.447
Yes	9	17	---			0.473 (0.145, 1.537)	0.213	
No	14	15				Ref.		

Abbreviations: BMI= body mass index; CI= confidence interval; HL= Hodgkin's lymphoma; n/N= number of patients; PN= peripheral neuropathy; Ref= reference; sALCL= systemic anaplastic large cell lymphoma
[1] Adjusted for sex and age only
[2] Fully adjusted for all variables included in table
[3] p-value from multivariate logistic regression model based on Wald Chi-Square test for each comparison.
[4] p-value from type 3 analysis of effects based on Wald Test.
Note(s): Patients with peripheral neuropathy at enrolment were included as at-risk, worsening of the event was recorded as an AESI. The fully adjusted model included sex, age, and all variables from the univariate analysis with a p-value < 0.10 (refer to Table 10-32). Baseline refers to data collected in the baseline/enrolment form, refer to Section 9.5.1 for further details.
Source: EOT Table 99.2.18.2; EOT Table 99.2.18.3

10.6.8.3 Post-hoc analysis

Following the observed association between increased BMI and the development of peripheral neuropathy, a post-hoc analysis was performed to further assess BMI as a categorical factor. Univariate analyses are presented in Table 10-36, and multivariate analyses are presented in Table 10-37.

Comparing BMI as a categorical variable also found that there was an increased risk of peripheral neuropathy with higher BMI categories (p=0.007). Compared with patients in the normal range of BMI, underweight subjects had a lower risk (OR=0.226 [95% CI 0.064, 0.796]; p=0.021), while patients categorised as overweight (OR=1.520 [95% CI 0.897, 2.577]; p=0.120) and obese (OR=1.849 [95% CI 0.971, 3.523]; p=0.062) had increased risk.

Multivariate analysis was performed using the same models as previously, replacing BMI as a continuous variable with BMI as a categorical variable. The results were very similar, categorical BMI remained associated with increased risk of peripheral neuropathy (p=0.015), following the same trend as observed in the univariate analysis.

Table 10-36. Odds Ratios from Univariate Analysis for Peripheral Neuropathy Events After Enrolment – post-hoc analyses of BMI

	Patients with PN	Patients without PN	Odds Ratio (95% CI)	p-value[1]	p-value[2]
BMI as a categorical factor					
Underweight (<18.5 kg/m^2)	3	21	0.226 (0.064, 0.796)	0.021	0.007
Normal (18.5 to <25 kg/m^2)	53	84	Ref.		
Overweight (25 to <30 kg/m^2)	47	49	1.520 (0.897, 2.577)	0.120	
Obese (≥30 kg/m^2)	28	24	1.849 (0.971, 3.523)	0.062	

Abbreviations: BMI= body mass index; CI= confidence interval; PN= peripheral neuropathy; Ref= reference
[1] p-value from univariate logistic regression model.
[2] p-value from type 3 analysis of effects based on Wald Test.
Source: EOT Table 99.1.17.1

Table 10-37. Odds Ratios from Multivariate Analysis for Peripheral Neuropathy Events After Enrolment – post-hoc analyses of BMI

	Patients with PN	Patients without PN	Odds Ratio (95% CI)	p-value[1]	p-value[2]
Treatment					
Brentuximab vedotin	131	178	--		
Age by group					
<65 years	93	140	0.707 (0.411, 1.216)	0.211	0.211
≥65 years	38	38	Ref.		
Sex					
Male	84	105	1.115 (0.682, 1.823)	0.664	0.664
Female	47	73	Ref.		
BMI as a categorical factor					
Underweight (<18.5 kg/m^2)	3	21	0.228 (0.064, 0.810)	0.022	0.015
Normal (18.5 to <25 kg/m^2)	53	84	Ref.		
Overweight (25 to <30 kg/m^2)	47	49	1.421 (0.828, 2.439)	0.202	
Obese (≥30 kg/m^2)	28	24	1.723 (0.894, 3.320)	0.104	
Evidence of extranodal involvement at baseline					
Unknown	18	15	1.384 (0.637, 3.010)	0.412	0.063
Yes	38	77	0.607 (0.364, 1.012)	0.056	
No	75	86	Ref.		

Abbreviations: BMI= body mass index; CI= confidence interval; PN= peripheral neuropathy; Ref= reference
[1] p-value from multivariate logistic regression model based on Wald Chi-Square test for each comparison.
[2] p-value from type 3 analysis of effects based on Wald Test.
Note(s): Baseline refers to data collected in the baseline/enrolment form, refer to Section 9.5.1 for further details.
Source: EOT Table 99.1.18.2

Further exploratory analyses were performed using a backward stepwise logistic selection model applying a retention criterion of p<0.1, presented in Table 10-38 and Table 10-39. The results for BMI and extranodal involvement remained approximately the same as in earlier models.

Table 10-38. Odds Ratios from Backward Logistic Stepwise Regression for Peripheral Neuropathy Events After Enrolment – Continuous BMI

	Patients with PN	Patients without PN	Odds Ratio (95% CI)	p-value[1]	p-value[2]
Treatment					
Brentuximab vedotin	131	178	--		
Age by group					
<65 years	93	140	0.655 (0.380, 1.128)	0.127	0.127
≥65 years	38	38	Ref.		
BMI as a numeric factor					
BMI (per 1-unit increase)			1.062 (1.017, 1.109)	0.007	0.007
Evidence of extranodal involvement at baseline					
Unknown	18	15	1.319 (0.607,2.867)	0.485	0.085
Yes	38	77	0.618 (0.371, 1.028)	0.064	
No	75	86	Ref.		
Autoimmune disease at baseline					
Yes	3	11	0.332 (0.087, 1.264)	0.106	0.106
No	128	167	Ref.		

Abbreviations: BMI= body mass index; CI= confidence interval; PN= peripheral neuropathy; Ref= reference
Variables are selected by logistic backward selection model with p-value <0.1.
Baseline refers to data collected in the baseline/enrolment form, refer to Section 9.5.1 for further details.
[1] p-value from multivariate logistic regression model based on Wald Chi-Square test for each comparison.
[2] p-value from type 3 analysis of effects based on Wald Test.
Source: EOT Table 99.1.18.1

Table 10-39. Odds Ratios from Backward Logistic Stepwise Regression for Peripheral Neuropathy Events After Enrolment – Categorical BMI

	Patients with PN	Patients without PN	Odds Ratio (95% CI)	p-value[1]	p-value[2]
Treatment					
Brentuximab vedotin	131	178	--		
Age by group					
<65 years	93	140	0.664 (0.382, 1.152)	0.145	0.145
≥65 years	38	38	Ref.		
BMI as a categorical factor					
Underweight (<18.5 kg/m^2)	3	21	0.238 (0.067, 0.850)	0.027	0.014
Normal (18.5 to <25 kg/m^2)	53	84	Ref.		
Overweight (25 to <30 kg/m^2)	47	49	1.506 (0.877, 2.586)	0.138	
Obese (≥30 kg/m^2)	28	24	1.747 (0.903, 3.377)	0.097	
Evidence of extranodal involvement at baseline					
Unknown	18	15	1.396 (0.640, 3.047)	0.402	0.074
Yes	38	77	0.619 (0.370, 1.035)	0.067	
No	75	86	Ref.		
Autoimmune disease at baseline					
Yes	3	11	0.340 (0.086, 1.338)	0.123	0.123
No	128	167	Ref.		

Abbreviations: BMI= body mass index; CI= confidence interval; PN= peripheral neuropathy; Ref= reference
Variables were selected by logistic backward selection model with p-value <0.1.
Baseline refers to data collected in the baseline/enrolment form, refer to Section 9.5.1 for further details.
[1] p-value from multivariate logistic regression model based on Wald Chi-Square test for each comparison.
[2] p-value from type 3 analysis of effects based on Wald Test.
Source: EOT Table 99.1.18.1

11 DISCUSSION

An interim study report (dated 04 March 2016) (Annex 1 Number 12) was prepared using results from a data cut on 31 August 2015, at which 108 eligible patients (66 prospective, 42 retrospective) were enrolled at 41 sites in 10 European countries. All 108 patients were included in the Safety Population, however the time on-treatment was much shorter, the median time since first dose of brentuximab vedotin was 0.6 years, (range: 0.0-2.2 years), and interpretation was limited.

These final results provide much longer follow-up on a population of 310 patients (156 prospective, 154 retrospective), providing more robust results. The median time since first dose of brentuximab vedotin was 1.5 years (IQR: 0.7, 2.5 years; range: 0.0-4.8 years), and the median number of treatment cycles per patient was 6.0 cycles (IQR: 4.0, 9.0 cycles; range: 1.0-41.0 cycles). The retrospective cohort had a slightly higher number of treatment cycles per patient than the prospective cohort (7.5 vs. 5.0 cycles). This sample size was sufficient to detect events occurring in 3% of the population (9 patients), with a 95% CI of (1.4%, 5.6%).

11.1 Key Results

11.1.1 Population Characteristics

MA25101 was a multi-centre, observational cohort study on the safety of brentuximab vedotin treatment in patients who had been diagnosed with relapsed or refractory CD30+ HL or relapsed or refractory sALCL. The objectives were to evaluate safety outcomes in patients who were treated with brentuximab vedotin in routine clinical practice, in particular protocol-specified AESI, and to identify and describe potential risk factors for peripheral neuropathy.

This final analysis includes data on 310 patients who were included in the Safety Population, with relevant comparisons to 284 patients who were in the Per-protocol Population. The Safety Population included 252 CD30+ HL patients and 58 CD30+ sALCL patients, with 156 patients in the prospective cohort (of whom 36 [23.1%] patients had a diagnosis of sALCL) and 154 patients in the retrospective cohort (of whom 22 [14.3%] patients had a diagnosis of sALCL).

The median age at study enrolment was 44.0 years (range: 18-87 years), with 24.5% of patients ≥65 years old. A slight majority of patients in the overall population were male (61%). Overall, the patient demographics of the prospective and retrospective cohorts were similar; however, the median age was slightly higher in the prospective cohort than the retrospective cohort (46.0 years vs. 42.5 years, respectively)

The median time since diagnosis was 21.4 months, which was similar between cohorts: 20.8 months (IQR: 10.1, 41.9 months) in the prospective cohort and 22.2 months (IQR: 11.5, 50.5 months) in the retrospective cohort. Overall, most patients had Stage IV lymphoma (n=118/310, 38.1%) or Stage II lymphoma (n=96/310, 31.0%) at initiation of treatment with brentuximab vedotin. A similar distribution of disease stage was observed in both cohorts.

The median time since first dose of brentuximab vedotin was 1.5 years (IQR: 0.7, 2.5 years; range: 0.0-4.8 years). The median number of treatment cycles per patient was 6.0 cycles (IQR: 4.0, 9.0 cycles; range: 1.0-41.0 cycles). The retrospective cohort had a slightly longer time since first dose of brentuximab vedotin with a median of 2.0 years (IQR: 1.0, 2.9 years; range: 0.1-4.6 years), which coincided with higher number of treatment cycles per patient. The retrospective cohort had a median 7.5 cycles (IQR: 5.0, 11.0 cycles; range:1.0-23.0 cycles), and the prospective cohort had a median 5.0 cycles (IQR: 3.0, 8.0 cycles; range:1.0-41.0). Only 9 patients received >16 treatment cycles.

11.1.2 Medical History

Medical history included conditions that were diagnosed prior to initiating treatment with brentuximab vedotin.

The most commonly reported medical history was abnormal blood counts for 44.5% of patients (n=138/310, 44.5%), which was more common in the prospective cohort than the retrospective cohort (53.8% vs. 35.1%, respectively). Specifically, a history of neutropenia was reported for 11.0% of patients, which was approximately twice as common in the prospective cohort than the retrospective cohort (14.1% vs. 7.8%, respectively). Ongoing neutropenia at enrolment was reported for 3.2% of patients (n=10/310, 3.2%).

History of cardiovascular disease was reported for 26.8% of patients (n=83/310, 26.8%), with similar distributions between the prospective and retrospective cohorts (26.3% vs. 27.3%, respectively). Rhythm abnormalities and congestive heart failure were reported for 5.2% and 1.3% of the population, respectively, most of which were ongoing at enrolment (4.5% and 1.0%, respectively).

History of pulmonary disease was reported for 15.2% of patients (n=47/310, 15.2%), which was more common in the prospective cohort than the retrospective cohort (17.9% vs. 12.3%, respectively). Chronic obstructive pulmonary disease was reported for 3.9% of patients (n=12/310, 3.9%), with 3.5% ongoing at enrolment (n=11/310, 3.5%).

History of diabetes mellitus was reported for 9.4% of patients (n=29/310, 9.4%), which was slightly more common in the retrospective cohort than the prospective cohort (11.0% vs. 7.7%, respectively); 9.0% of patients had ongoing disease at enrolment (n=28/310, 9.0%).

History of renal impairment was reported for 5.8% of patients (n=18/310, 5.8%), which was similar between the retrospective cohort and the prospective cohort (5.1% vs. 6.5%, respectively); 3.5% of patients had ongoing disease at enrolment (n=11/310, 3.5%).

History of hepatic impairment was reported for 3.2% of patients (n=10/310, 3.2%), which was more common in the retrospective cohort than the prospective cohort (5.1% vs. 1.3%, respectively); 1.9% of patients had ongoing disease at enrolment (n=6/310, 1.9%).

Overall 11.3% of patients had a history of peripheral neuropathy diagnosed prior to initiating treatment with brentuximab vedotin (n=35/310, 11.3%), and 8.1% of patients had ongoing

peripheral neuropathy at enrolment (n=25/310, 8.1%). History of peripheral neuropathy was more common in the prospective cohort than the retrospective cohort (12.8% vs. 9.7%, respectively); but of those with a history, ongoing peripheral neuropathy was more common in the retrospective cohort than the prospective cohort (80.0% vs. 65.0%, respectively). The median time since onset of peripheral neuropathy was 14.8 months (IQR: 3.8, 25.6 months; range: 0.6-108.8 months); the median time since onset was much longer in the retrospective cohort (25.6 months [range: 0.6-108.8 months]) than in the prospective cohort (13.5 months [range: 2.0-57.5 months]). In both cohorts most patients had a history of mild or moderate (<Grade 3) peripheral neuropathy at initiation of treatment with brentuximab vedotin, except for 2 prospective patients with a history of severe (Grade 3) sensory peripheral neuropathy. History of peripheral neuropathy means that it was a result of a previous round of chemotherapy treatment, this difference in time since onset between cohorts could be at least partly explained by the longer follow-up in the retrospective cohort.

Overall 308 patients received a prior line of chemotherapy which ended prior to beginning treatment with brentuximab vedotin (n=308/310, 99.4%), 154 patients in the prospective cohort (n=154/156, 98.7%) and all patients in the retrospective cohort. The most commonly prescribed previous regimen was ABVD (n=209/310, 67.9%), however a variety of previous treatments were recorded. The median number of previous treatment cycles was 8.0 cycles (IQR: 6.0, 10.0 cycles; range: 1.0-44.0 cycles), this was 8.0 cycles (IQR: 6.0, 10.0 cycles) in the prospective cohort, and 9.0 cycles (IQR: 6.0, 10.0 cycles) in the retrospective cohort.

During study follow-up 93 (n=93/310, 30.0%) patients received at least one line of another chemotherapy (in addition to brentuximab vedotin), the most common being 'other' (n=49/93, 52.7%), followed by bendamustine (n=37/93, 39.8%). The median number of additional on-study treatment cycles was 3.0 cycles (IQR: 2.0, 4.0 cycles; range: 0-19 cycles), the median was 3.0 cycles in both cohorts however the range of cycles was 1 to 19 in the prospective cohort and 0 to 10 in the retrospective cohort.

11.1.3 AEs by Severity and System Organ Class

In this study, only SAE and protocol-specified AESI were included in the results, these were further classified as treatment-emergent (occurring between the first dose and up to 30 days after the final dose of brentuximab vedotin) and treatment-related.

Overall, 230 patients experienced at least one SAE and/or AESI (n=230/310, 74.2%), which was similar between cohorts, 110 patients in the prospective cohort (n=110/156, 70.5%) and 120 patients in the retrospective cohort (n=120/154, 77.9%).

The severity of the AEs had approximately even distribution between <Grade 3 (mild or moderate) and ≥Grade 3 (severe or life-threatening) in the prospective cohort (53.6% vs. 46.4%, respectively), whereas the retrospective cohort had more patients with <Grade 3 than ≥Grade 3 (63.3% vs. 36.7%, respectively). Most of the observed AEs were treatment-emergent, occurring in 228 of the 230 patients who experienced any AE. Treatment-related AEs occurred in 186 of the 230 patients who experienced any AE. Two thirds of the patients with treatment-related AEs

had a maximum severity of <Grade 3 (n=124/186, 66.7%), which was similar between the cohorts.

Of the 310 patients in the Safety Population the most frequent AEs (by MedDRA SOC) experienced were nervous system disorders (n=133, 42.9%), infections and infestations (n=95, 30.6%), blood and lymphatic system disorders (n=53, 17.1%), and general disorders and administration site conditions (n=38, 12.3%). The most frequently observed AEs within these SOC were peripheral sensory neuropathy (n=72, 23.3%), and neuropathy peripheral (n=40, 12.9%); pneumonia (n=16, 5.2%), and a collection of respiratory tract/lung infections (n=26, 8.4%); neutropenia (n=46, 14.8%); and pyrexia (n=27, 8.7%). Assessments of treatment-relatedness varied between SOC. Most nervous system disorders and blood and lymphatic system disorders were considered treatment-related, while only approximately half of infections and infestations and general disorders and administration site conditions were considered treatment-related.

Overall, AEs were more frequent in patients aged ≥65 years than patients <65 years, including infections (including upper respiratory tract infections and pneumonia) (36.8% vs. 28.6%, respectively), blood and lymphatic system disorders (including neutropenia) (26.3% vs. 14.1%, respectively), and nervous system disorders (including peripheral sensory neuropathy) (51.3% vs. 40.2%, respectively).

Blood and lymphatic system disorders (including neutropenia) were more frequent in females than males (21.7% vs. 14.2%, respectively), and in CD30+ HL patients than sALCL patients (18.3% vs. 12.1%, respectively). Patients who were post-ASCT experienced fewer AEs compared to the overall population, including blood and lymphatic system disorders (including neutropenia) (12.6% vs. 17.1%, respectively), infections (23.2% vs. 30.6%, respectively), and nervous system disorders (37.1% vs. 42.9%, respectively).

Overall, 109 patients experienced at least one SAE (n=109/310, 35.2%). Following additional SAE reconciliation, it was found that 2 patients were reported as experiencing an SAE in the clinical database, when they should have been reported as non-serious, both in the retrospective cohort. Therefore, 107 patients actually experienced at least one SAE (n=107/310, 34.5%). The following reporting of results remains consistent with the original reporting and interpretation of the results. This was similar between cohorts, 59 patients in the prospective and 50 patients in the retrospective cohort experienced at least one SAE (37.8% and 32.5%, respectively). More than half (61.5%) of patients with SAEs had a maximum severity of ≥Grade 3 (severe or life-threatening) (n=67/109, 61.5%), which was identical between the cohorts.

Most of the SAEs were treatment-emergent, occurring in 106 of the 109 patients who experienced an SAE (n=106/310, 34.2%). This was similar between cohorts, 57 patients in the prospective and 49 patients in the retrospective cohort (36.5% and 31.8%, respectively). More than half of the patients with treatment-emergent SAEs had a maximum severity of ≥Grade 3 (n=65/310, 21.0%), which was identical between the cohorts. Treatment-related SAEs occurred in 68 of the 109 patients who experienced any SAE (n=68/310, 21.9%), with similar rates of

occurrence between the prospective and retrospective cohorts (23.7% and 20.1%, respectively). Overall, half of patients with treatment-related SAEs had a maximum severity of <Grade 3 (n=34/310, 11.0%). The retrospective cohort had more treatment-related SAEs ≥Grade 3 than the prospective cohort (11.7% vs. 10.3%, respectively). Treatment-emergent treatment-related SAEs occurred in 64 (n=64/310, 20.6%) patients overall, with similar rates of occurrence between the prospective and retrospective cohorts (21.8% and 19.5%, respectively).

Serious adverse events were reported as both frequency and incidence density (95% CI) per 100 person-years, which accounts for the longer follow-up in the retrospective cohort. The most common SAEs were infections and infestations (29.6 [95% CI 20.5, 38.7] per 100 person-years, n=45/310, 14.5%), general disorders and administration site conditions (19.2 [95% CI 12.2, 26.1] per 100 person-years, n=30/310, 9.7%), nervous system disorders (16.1 [95% CI 9.6, 22.5] per 100 person-years, n=25/310, 8.1%), and blood and lymphatic system disorders (8.0 [95% CI 3.6, 12.3] per 100 person-years, n=13/310, 4.2%).

The SAEs observed with highest incidence within each of these SOC were peripheral sensory neuropathy (7.6 [95% CI 3.2, 11.9] per 100 person-years) and neuropathy peripheral (3.6 [95% CI 0.7, 6.6] per 100 person-years); pneumonia (8.5 [95% CI 4.0, 13.1] per 100 person-years), and sepsis (3.0 [95% CI 0.3, 5.7] per 100 person-years); neutropenia (4.3 [95% CI 1.1, 7.4] per 100 person-years] and febrile neutropenia [2.4 [95% CI 0.0, 4.8] per 100 person-years]); and pyrexia (13.3 [95% CI 7.6, 19.0] per 100 person-years).

The time at risk was notably different between the age groups, with patients aged ≥65 years having approximately 40 person-years and patients aged <65 years having approximately 125 person-years of on-treatment follow-up. Using incidence of events, blood and lymphatic system disorders were higher in patients aged ≥65 years (15.4 [95% CI 2.8, 28.0] per 100 person-years) than in patients <65 years (5.6 [95% CI 1.4, 9.8] per 100 person-years). This was primarily due to higher incidence of febrile neutropenia in patients aged ≥65 years (7.5 [95% CI 0.0, 16.1] per 100 person-years) than in patients <65 years (0.8 [95% CI 0.0, 2.4] per 100 person-years), as well as higher incidence of neutropenia in patients aged ≥65 years (7.6 [95% CI 0.0, 16.3] per 100 person-years) than in patients <65 years (3.2 [95% CI 0.0, 6.4] per 100 person-years). Infections and infestations were more common in patients aged ≥65 years (41.9 [95% CI 19.0, 64.9] per 100 person-years) than in patients <65 years (25.5 [95% CI 15.9, 35.0] per 100 person-years), which were primarily due to higher rates of pneumonia in patients aged ≥65 years (15.2 [95% CI 2.5, 27.9] per 100 person-years) than in patients <65 years (6.4 [95% CI 1.9, 11.0] per 100 person-years). Respiratory, thoracic and mediastinal disorders were slightly higher in patients aged ≥65 years (7.4 [95% CI 0.0, 16.0] per 100 person-years) than in patients <65 years (4.0 [95% CI 0.5, 7.5] per 100 person-years). Skin and subcutaneous tissue disorders only occurred in patients aged <65 years (4.8 [95% CI 0.9, 8.7] per 100 person-years).

11.1.4 Discontinuation and Deaths

Overall 42 patients discontinued treatment due to an SAE or AESI (n=42/310, 13.5%), which was identical between cohorts; of which 32 patients discontinued treatment due to an SAE

(n=32/310, 10.3%). Almost twice as many patients in the prospective cohort discontinued treatment due to an SAE than in the retrospective cohort (13.5% vs. 7.1%, respectively). Amongst the 167 patients that discontinued the study, 16 patients discontinued due to an AE (n=16/167, 9.6%), representing 5.2% of the Safety Population (n=16/310, 5.2%). Fifteen patients had at least one dose modification due to an SAE (n=15/310, 4.8%), which was similar between prospective and retrospective cohorts (3.8% vs. 5.8%, respectively). Dose modifications due to SAEs were generally associated with protocol-specified AESI, which are discussed in Section 10.6.2.

A total of 88 patients died during the study (n=88/310, 28.4%), of whom 13 patients (n=13/310, 4.2%) died while on-study (ie, within 30 days of the last dose of brentuximab vedotin), and 75 patients (n=75/310, 24.2%) died during post-treatment follow-up (ie, 31 days or more following the last dose of brentuximab vedotin). There were more deaths overall in the prospective cohort compared to the retrospective cohort (35.3% vs. 21.4%, respectively).

There were 72 patient deaths amongst the 230 patients who had an SAE or AESI (n=72/310, 23.2%), with 45 deaths in the prospective cohort and 27 deaths in the retrospective cohort (28.8% vs. 17.5%, respectively). The AE outcome was listed as death for 12 patients overall (n=12/310, 5.2%), 11 of whom were in the prospective cohort and 1 in the retrospective cohort. There were 3 deaths due to treatment-related SAEs (n=3/310, 1.0%), with 2 deaths in the prospective cohort and 1 death in the retrospective cohort.

11.1.5 Adverse Events of Special Interest

Protocol-specified AESIs occurred in 213 patients (n=213/310, 68.7%), these included peripheral neuropathy in 131 patients (n=131/310, 42.3%), infections in 97 patients (n=97/310, 31.3%), neutropenia in 54 patients (n=54/310, 17.4%), hypersensitivity reactions in 34 patients (n=34/310, 11.0%), and hyperglycaemia in 4 patients (n=4/310, 1.3%).

11.1.5.1 Peripheral neuropathy

Peripheral neuropathy (using SMQ) occurred in 131 patients (n=131/310, 42.3%), with an incidence of 113.6 (95% CI 93.3, 133.9) per 100 person-years. The incidence was similar between the retrospective and prospective cohorts (117.3 [95% CI 89.9, 144.8] vs. 108.5 [95% CI 78.4, 138.7] per 100 person-years, respectively), however events were more frequent in the retrospective cohort than in the prospective cohort (50.6% vs. 34.0%, respectively). Almost all peripheral neuropathy was treatment-related (n=128/310, 41.3%) with an incidence of 110.0 (95% CI 90.1, 129.8) per 100 person-years, and treatment-emergent (n=127/310, 41.0%) with an incidence of 111.1 (95% CI 90.9, 131.3) per 100 person-years, and was predominantly sensory neuropathy.

Serious SMQ peripheral neuropathy events occurred in 22 patients (n=22/310, 7.1%) with an incidence of 14.1 (95% CI 8.1, 20.2) per 100 person-years, the incidence was similar between cohorts. Following additional SAE reconciliation, it was found that overall 2 patients had SMQ peripheral neuropathy reported as serious in the clinical database when they should have been

reported as non-serious. Therefore, 20 patients (n=20/310, 6.5%) actually experienced serious peripheral neuropathy events. The following reporting of results remains consistent with the original reporting and interpretation of the results.

The maximum severity of treatment-related peripheral neuropathy (using SMQ) events was mostly <Grade 3 (n=113/310, 36.5%), and 14 patients had Grade 3 peripheral neuropathy (n=14/310, 4.5%). Only 1 patient had Grade 4 peripheral neuropathy, an elderly patient with reported neurotoxicity occurring during the first cycle. The distribution of severity was similar between the cohorts.

Dose modifications and discontinuations due to peripheral neuropathy occurred in 53 patients (n=53/310, 17.1%): dose reduction (n=25/310, 8.1%), dose held, delay, or interruption (n=6/310, 1.9%), dose discontinued (n=20/310, 6.5%), and patient discontinued from study (n=2/310, 0.6%).

The recommendation is that patients with Grade 2 or Grade 3 peripheral neuropathy may require a dose delay followed by a dose reduction of brentuximab vedotin to 1.2 mg/kg; and that patients with Grade 4 peripheral neuropathy discontinue treatment. The frequency of severe peripheral neuropathy events (n=15/310; 4.8% with ≥Grade 3) possibly indicates a compliance with the treatment modification recommendations (n=31/310, 10.0%) and discontinuations (n=20/310, 6.5%) in relation to peripheral neuropathy.

The frequency of SMQ peripheral neuropathy in this study was lower than treatment-emergent events observed in the pivotal phase 2 studies of brentuximab vedotin monotherapy (SG035-0003 with relapsed or refractory HL had received a median of 9 treatment cycles, and SG035-0004 with sALCL had received a median of 7 treatment cycles) in which 56% of patients had peripheral neuropathy (55% in SG035-0003 and 57% in SG035-0004), which was predominantly (45%) peripheral sensory neuropathy. The maximum severity was Grade 3 in 13% of patients, led to treatment discontinuation for 12% of patients, and dose modifications (reduction, delay, or interruption) for 18% of patients. The majority of treatment-emergent PN events were considered to be related to treatment.

In the AETHERA study, post-ASCT patients received a median of 15 treatment cycles of brentuximab vedotin monotherapy. The peripheral neuropathy SMQ included PTs for both sensory and motor neuropathy, and terms that had both sensory and motor components. Treatment-emergent and treatment-related peripheral neuropathy occurred in 67% and 66% of patients, respectively, which was predominantly peripheral sensory neuropathy. The maximum severity of treatment-emergent and treatment-related events was Grade 2 in 37% of patients, and Grade 3 in 13% of patients. Peripheral neuropathy led to either a dose reduction or dose delay for 31% of patients, and treatment discontinuation of 23% of patients.

The frequency of peripheral neuropathy was lower in this study than in the phase 2 population and in the AETHERA study, and a smaller proportion of the population had severity of Grade 3. This may be attributable to the lower median number of treatment cycles in this study (6 cycles in this study vs. 7 cycles in SG035-0003, 9 cycles in SG035-0004 and 15 cycles in AETHERA).

However, in this study the retrospective cohort had a median of 7.5 treatment cycles and a frequency of peripheral neuropathy of 50.6%, which was still lower than the 55% observed in the phase 2 population with a similar number of treatment cycles. The frequency of dose modifications and discontinuations was also consistently lower in this study owing to the lower frequency of events. The higher frequency of peripheral neuropathy in the retrospective cohort could be tied to the higher number of treatment cycles in the retrospective cohort compare to the prospective cohort (median [IQR]: 7.5 [5.0, 11.0] vs. 5.0 [3.0, 8.0] cycles). This follows the known pattern of cumulative effects of chemotherapy exposure on peripheral neuropathy.

11.1.5.2 Neutropenia

Neutropenia occurs as a result of myelosuppression due to decreased bone marrow activity and is a known effect of some cancer treatments. Neutropenia is associated with a diminished immunity to infection; febrile neutropenia includes development of fever and signs of infection.

Neutropenia (including febrile neutropenia and neutrophil count decreased) occurred in 54 patients (n=54/310, 17.4%), with an incidence of 37.2 (95% CI 26.3, 48.0) per 100 person-years. The incidence was approximately double in the prospective cohort (53.3 [95%CI 31.7, 75.0] per 100 person-years) than in the retrospective cohort (25.8 [95%CI 14.5, 37.1] per 100 person-years), and events were more frequent in the prospective cohort than in the retrospective cohort (20.5% vs. 14.3%, respectively). Most events were considered treatment-related (n=42/310, 13.5%) with an incidence of 44.6 (95% CI 25.3, 63.8) per 100 person-years, and all were treatment-emergent. Serious neutropenia occurred in 11 patients (n=11/310, 3.5%) with an incidence of 6.7 (95% CI 2.7, 10.8) per 100 person-years, the incidence and frequency of events was similar between the prospective and retrospective cohorts.

The maximum severity of neutropenia (including neutrophil count decrease) was approximately twice as frequently ≥Grade 3 (n=32/310, 10.3%) than <Grade 3 (n=16/310, 5.2%), while febrile neutropenia was always ≥Grade 3 (n=6/310, 1.9%). The pattern of distributions was similar between the cohorts. Neutropenia was more frequent in elderly patients (≥65 years: 26.3% vs. <65 years: 14.1%), and in CD30+ HL patients than sALCL patients (18.3% vs. 12.1%, respectively). Febrile neutropenia occurred almost exclusively in elderly patients (≥65 years: 5.3% vs. <65 years: 0.9%).

Dose modifications and discontinuations due to neutropenia occurred in 16 patients (n=16/310, 5.2%): dose reduction (n=1/310, 0.3%), dose held, delayed or interrupted (n=14/310, 4.5%), dose discontinued (n=1/310, 0.3%). No patients were discontinued from the study due to neutropenia.

The recommendation is that patients with ≥Grade 3 neutropenia have their dose held and/or be administered a prophylaxis treatment of granulocyte-colony-stimulating factor until improvement, recurrent Grade 4 should have their dose held and consider discontinuation. The maximum severities (n=32 patients with ≥Grade 3) indicated about half of patients were treated through dose modifications.

The frequency of neutropenia was lower than observed in the pivotal phase 2 studies of brentuximab vedotin monotherapy (SG035-0003 and SG035-0004), in which 21% of patients had neutropenia. The maximum severity was ≥Grade 3 for 20% of patients (Grade 3: 13%, Grade 4: 7%). However, febrile neutropenia was not observed in the phase 2 populations, possibly due to the limited number of patients ≥65 years. Neutropenia led to dose modifications (delay) for 13% of patients. Additionally, 11% of patients received prophylaxis treatment with granulocyte-colony-stimulating factor. There were no dose discontinuations or study discontinuations due to neutropenia in the phase 2 population.

In the AETHERA study of post-ASCT patients on brentuximab vedotin monotherapy, treatment-emergent and treatment-related neutropenia occurred in 35% and 32% of patients, respectively. The maximum severity was ≥Grade 3 for 29% of patients, which were considered treatment-related for 26% of patients. Neutropenia led to dose delay for 22% of patients, there were no dose reductions or discontinuations.

The frequency of neutropenia was higher in the prospective cohort than the retrospective cohort, but similar between cohorts for serious events. This could indicate some bias from exclusion of patients who may have discontinued treatment due to neutropenia prior to enrolment in the retrospective cohort. The frequency of neutropenia in the prospective cohort was similar to the phase 2 population, but lower that in the AETHERA study. The severity of neutropenia events observed in this study were lower than previously observed, with about half as many patients with ≥Grade 3 compared to the phase 2 population and about a third compared to the AETHERA population. The frequency of dose modifications was also consistently lower in this study and likely due to the lower frequency of ≥Grade 3 neutropenia in this study.

11.1.5.3 Infections

Infections are a known side effect of chemotherapy, owing to the previously mentioned myelosuppression.

Infections (including opportunistic infections) occurred in 97 patients (n=97/310, 31.3%), with an incidence of 76.0 (95% CI 60.1, 92.0) per 100 person-years. The incidence was higher in the prospective cohort (96.7 [95% CI 69.1, 124.3] per 100 person-years) than and retrospective cohort (61.4 [95% CI 42.8, 80.1] per 100 person-years)). About half of infections were considered treatment-related (n=53/310, 17.1%) with an incidence of 36.1 (95% CI 26.1, 46.1) per 100 person-years, and nearly all were treatment-emergent (n=96/310, 31.0%) with an incidence of 75.3 (95% CI 59.4, 91.1) per 100 person-years. The incidence of treatment-related infections was more than double in the prospective cohort (52.9 [95% CI 33.6, 72.3] per 100 person-years) than in the retrospective cohort (24.9 [95% CI 14.4, 35.4] per 100 person-years).

The most commonly observed infections (>2% by SOCs and PTs in 5 or more patients) were pneumonia (n=16/310, 5.2%), upper respiratory tract infection (n=11/310, 3.5%), herpes zoster (n=5/310, 1.6%), lower respiratory tract infection (n=5/310, 1.6%), lung infection (n=5/310, 1.6%), respiratory tract infection (n=5/310, 1.6%), and sepsis (n=5/310, 1.6%).

Infections were more frequent in the patients ≥65 years (n=28/76, 36.8%) than patients <65 years (n=67/234, 28.6%), specifically pneumonia (9.2% vs. 3.8%, respectively), whereas upper respiratory tract infections only occurred in patients <65 (4.7%). Infections were also less frequent in post-ASCT patients (n=35/150, 23.2%) than the overall population (n=95/310, 30.6%).

Dose modifications and discontinuations due to infections occurred in 32 patients (n=32/310, 10.3%): dose reduction (n=2/310, 0.6%), dose held, delayed or interrupted (n=17/310, 5.5%), dose discontinued (n=8/310, 2.6%), and discontinued from study (n=5/310, 1.6%). There are no dose modification recommendations associated with infections.

The frequency of treatment-emergent infections was lower than observed in the pivotal phase 2 studies of brentuximab vedotin monotherapy (SG035-0003 and SG035-0004), in which 61% of patients had at least 1 infection. The most commonly observed infections (≥5% of patients) were upper respiratory tract infection (31%), sinusitis (8%), bronchitis (8%), urinary tract infection (6%), and herpes zoster (5%). Treatment-related infections were observed with the same frequency as in the phase 2 population (17%), these included upper respiratory tract infection (8%), herpes zoster (3%), pneumonia (2%), folliculitis (1%), and urinary tract infection (1%). Infections led to dose delay for 4% of patients (upper respiratory tract infection, herpes zoster, influenza).

In the AETHERA study of post-ASCT patients on brentuximab vedotin monotherapy, treatment-emergent infections occurred in 60% of patients. Upper respiratory tract infection was the most commonly observed infection (26% of patients), and pneumonia was the most commonly observed SAE (4%); the most commonly observed opportunistic infection was herpes zoster (7%).

Serious infections were observed in 42 patients (n=42/310, 13.5%), which was more frequent in the prospective than in the retrospective cohort (15.4% vs. 11.7%, respectively), these were primarily pneumonia (n=14/310, 4.5%) and sepsis (n=5/310, 1.6%). Serious infections were also more frequent in patients ≥65 years than <65 years (21.1% vs. 12.4%) and were less frequent in post-ASCT patients than overall (23.2% vs. 30.6%).

The frequency of infections was lower in this population than in the phase 2 population and AETHERA study but reported the same common infections: upper respiratory tract infections, pneumonia, and herpes zoster. Unsurprisingly, infections were found to be more common in the elderly population. The difference in frequency could be attributed to the reporting of infections as AESIs, which was at the Investigator's discretion. Serious infections occurred more frequently in this study than AETHERA, which could be attributed to the greater proportion of elderly patients in this study, and the apparent lower infection rates in post-ASCT patients.

11.1.5.4 Hyperglycaemia

Hyperglycaemia occurred in 4 patients in this study (n=4/310, 1.3%), with an incidence of 2.4 (95% CI 0.0, 4.9) per 100 person-years, 2 of whom did not have a history of diabetes and for

whom the events were considered treatment-related. All events were treatment-emergent. There were 2 events reported as serious with ≥Grade 3, one of which was diabetic ketoacidosis in a diabetic patient.

The frequency of hyperglycaemia was lower than observed in the pivotal phase 2 studies of brentuximab vedotin monotherapy (SG035-0003 and SG035-0004), in which 4% of patients had Grade 3 hyperglycaemia.

In the AETHERA study of post-ASCT patients on brentuximab vedotin monotherapy, treatment-emergent hyperglycaemia occurred in 3% of patients. Events of hyperglycaemia were rare and generally observed in patients with co-morbidities or other risk factors.

11.1.5.5 Hypersensitivity reactions

Treatment infusions can result in hypersensitivity reactions that may be fatal if not rapidly and appropriately managed. Infusion-related reactions can lead to a range of symptoms, ranging from mild discomfort (such as itching, nausea, or chills) to anaphylaxis requiring immediate medical therapy. Hypersensitivity reactions were diverse and included infusion-related reactions and allergic reactions (eg, pyrexia, rash, pruritus, erythema, infusion site extravasation, catheter site inflammation, hypersensitivity, anaphylactic/anaphylactoid reaction).

Hypersensitivity reactions (including infusion-related reactions and allergic reactions) occurred in 34 patients (n=34/310, 11.0%), with an incidence of 22.5 (95% CI 14.7, 30.4) per 100 person-years. The incidence was similar between the retrospective and prospective cohorts, however events were more frequent in the retrospective cohort than the prospective cohort (12.3% vs. 9.6%, respectively). The majority of the observed hypersensitivity reactions were considered treatment-related (n=24/34, 70.6%), with an incidence of 15.3 (95% CI 9.0, 21.7) per 100 person-years, and all were treatment-emergent. Serious hypersensitivity reactions occurred in 7 patients (n=7/310, 2.3%) with an incidence of 4.2 (95% CI 1.1, 7.4) per 100 patient-years, which was nearly identical between cohorts.

The maximum severity of hypersensitivity reactions was mostly <Grade 3, only 4 patients had events ≥Grade 3 (n=4/310, 1.3%).

Dose modifications and discontinuations due to hypersensitivity reactions occurred in 4 patients (n=4/310, 1.3%): dose held, delayed or interrupted (n=1/310, 0.3%), dose discontinued (n=2/310, 0.6%), and discontinued from study (n=1/310, 0.3%). There were 1 each anaphylactic and anaphylactoid reactions that led to discontinuations.

The frequency of infusion-related reactions (hypersensitivity reactions) was lower than observed in the pivotal phase 2 studies of brentuximab vedotin monotherapy (SG035-0003 and SG035-0004), in which 11% of patients had events. No anaphylactic reactions occurred.

In the AETHERA study of post-ASCT patients on brentuximab vedotin monotherapy, infusion-related reactions occurred in 15% of patients, with ≥Grade 3 in 0.9% of patients, and reported as

serious in 0.6% of patients. No anaphylactic reactions occurred. Infusion-related reactions led to interruption or early stoppage of the infusion for 3.4% of patients.

Notably, premedication before infusion of brentuximab vedotin was not required according to protocol guidelines in any of the previous studies, but was allowed in subsequent cycles, if indicated. The frequency of events was otherwise higher in this study than the AETHERA study for serious events (2.7% vs. 0.6%, respectively) and similar for ≥Grade 3 (1.3% vs. 0.9%, respectively). However, these results are based on a small number of events.

11.1.6 Potential Risk Factors of Peripheral Neuropathy

Kaplan-Meier plots showed that most peripheral neuropathy events occurred within the first 6 months of treatment, during which 110 of the 131 events occurred, the cumulative event free probability at Month 6 was 61.9% (95% CI 56.0%, 67.3%).

Univariate and multivariate logistic regression was used to identify potential risk factors of peripheral neuropathy. Univariate analyses found that BMI increase (per unit) was associated with increased risk of peripheral neuropathy OR=1.067 (95% CI 1.023-1.113) with p-value=0.003; and the presence of extranodal involvement compared with no extranodal involvement had decreased risk of peripheral neuropathy OR=0.559 (95% CI 0.340, 0.918), with p-value=0.022.1.

Multivariate analysis was adjusted for age, sex, BMI, and evidence of extranodal involvement following the univariate analysis. The results were similar to the univariate analysis, increased BMI remained associated with increased risk of peripheral neuropathy (OR=1.061 [95% CI 1.016, 1.108]; p=0.007); and the presence of extranodal involvement compared with no extranodal involvement gave an indication of being protective (OR= 0.605 [95% CI 0.364, 1.005]; p=0.052).

Post-hoc analyses using BMI as a categorical factor also found increased BMI to be associated with increased risk of peripheral neuropathy (p=0.007). Compared to patients with a normal BMI (18.5 to <25 kg/m^2), patients categorised as overweight (25 to <30 kg/m^2) had an increased risk of peripheral neuropathy (OR=1.520 [95% CI 0.897, 2.577]) which increased further in patients classified as obese (≥30 kg/m^2) (OR=1.849 [95% CI 0.971, 3.523]).

11.2 Limitations

One of the initial challenges of this study was the lack of available resources at sites and willingness of sites to participate. Most sites had a very limited number of patients available and in some cases the projected availability was over-estimated, which complicated site initiation and patient recruitment. As a result, the protocol was amended to also include patients already taking brentuximab vedotin at the time of informed consent (Amendment 1), the sample size was decreased from 500 to 300 patients, and the retrospective cohort increased from 15-20% to 50% (Amendment 4).

As a result of increasing the retrospective component, baseline/enrolment data collection for half of the enrolled patients began after treatment with brentuximab vedotin had been initiated and some safety data were collected retrospectively. Due to the nature of the safety data collected (SAEs and protocol-specified AESIs) however, under-reporting of these events in the retrospective cohort was considered unlikely to have been a large source of information bias. Overall, rates of SAEs were similar between the cohorts (prospective: 37.8% vs. retrospective: 32.5%), as were treatment-related SAEs cohorts (prospective: 23.7% vs. retrospective: 20.1%). This is unlikely to indicate reporting bias between the cohorts and could reflect the higher proportion of elderly patients in the prospective cohort. The rates of AESI were slightly higher in the retrospective than the prospective cohort (72.9% vs. 62.2%, respectively), which was driven by peripheral neuropathy events. There was a risk of selection bias in that patients who discontinued brentuximab vedotin treatment early may not have been enrolled (ie, they discontinue brentuximab vedotin treatment before the site was activated) into the retrospective cohort. This appears to have been possible: the retrospective cohort had a greater number of treatment cycles, indicating that patients who tolerated the drug well may have been preferentially enrolled; and the above-mentioned frequency of AEs were slightly higher in the prospective cohort.

The retrospective cohort received more treatment cycles than the prospective cohort (median: 7.5 cycles vs. 5.0 cycles, respectively), resulting in a longer at-risk period for the retrospective cohort. The prospective cohort was on average older than the retrospective cohort and had a greater proportion of elderly patients (26.9% vs. 22.1%, respectively), as well as a higher number of deaths (35.3% vs. 21.4%, respectively), including on-study deaths (20.0% vs. 6.1%, respectively). However, treatment interruptions or modifications were about twice as frequent in the retrospective cohort than the prospective cohort (53.2% vs. 27.6%, respectively).

These factors may have been influenced by the recruitment of the retrospective cohort and may have affected the reporting of results through selection bias. The frequency of any AE (SAEs and AESIs only) was similar between the prospective and retrospective cohorts (70.5% vs. 77.9%), however, a greater proportion of these AEs were mild or moderate (<Grade 3) in the retrospective cohort. Patients in the retrospective cohort were prevalent cases and had not discontinued treatment due to an earlier event (or death), and therefore may have better tolerated brentuximab vedotin than the prospective cohort.

The incidence (per 100 person-years) of SAEs was generally higher in the prospective cohort than in the retrospective cohort (detailed in Section 10.4.3), including infections and infusion-related reactions. Dose discontinuations due to SAEs were higher overall in the prospective cohort, affected primarily by infections and infusion-related reactions. However, there was little difference in incidence of serious neutropenia and serious SMQ peripheral neuropathy between the cohorts.

Neutropenia is generally well managed through dose modifications and occurred at a continuous rate during the study. Neutropenia overall had a higher incidence in the prospective cohort, but serious neutropenia had a similar incidence between the cohorts. The reporting of serious events

therefore may be a product of longer exposure and does not appear to have been biased by the recruitment of the retrospective cohort. Chemotherapy-induced peripheral neuropathy is known to be dose-dependent and result from cumulative exposure, contributing to the higher observed frequency of this AESI in the retrospective cohort. However, after accounting for the exposure period the incidence rates of nervous system disorders were similar between the prospective and retrospective cohorts. Dose modifications and discontinuations due to AESI were higher in the retrospective cohort for peripheral neuropathy and neutropenia.

The presence of selection bias could have had a small effect, however it does not appear to have had a great impact on the reporting of SAEs, nor on events that have a possibility for delayed onset. Potential selection bias did not impact the reporting of peripheral neuropathy since it results from cumulative exposure.

There was also potential bias introduced by the differential exclusion of patients taking concomitant chemotherapies at enrolment between cohorts. Patients in both cohorts initiated another treatment after enrolment at the same frequency, but patients in the prospective cohort could potentially have initiated another treatment earlier in their planned treatment. Patients in the retrospective cohort could not have been taking another treatment for the time between initiation of brentuximab vedotin and enrolment. This could have created a differential pattern of exposure to other chemotherapeutic agents between the groups, which could have potentially contributed to the occurrence of AEs. The time to initiation of an additional chemotherapy was not evaluated in these analyses, and whether this impacted the characteristics of patients enrolled could not be evaluated.

Information bias may have occurred since data collected for the retrospective cohort may be less thorough than for the prospective cohort. This could have resulted in some recall bias or missing data for the reporting of the severity and/or seriousness of SAEs and AESIs. Though it does not appear that there were differential rates of reporting between cohorts for peripheral neuropathy, the level of detail may have been affected. In the retrospective cohort the non-specific neuropathy peripheral was more commonly observed, rather than specifying sensory or motor neuropathy. However, the time since initiation of treatment at enrolment was generally not long, and it does not appear to have impacted the overall reporting of events.

Evaluation of sub-populations was limited by patient numbers, particularly for long-term treatment >16 cycles, and ALK positivity (sALCL patients only). Comparisons were possible for elderly population, post-ASCT status, and lymphoma type. Logistic regression analyses to identify potential predictive factors for peripheral neuropathy were also limited, and there were indications of potential differences in risk factors based on disease type, however there was insufficient power to draw any conclusions.

11.3 **Interpretation**

This study was a PASS requested by EMA as part of the Conditional Marketing Authorisation for ADCETRIS, to better understand the safety profile of brentuximab vedotin.

The objectives of this study were to evaluate the occurrence of SAEs and protocol-specified AESIs, both serious and non-serious, in patients actively treated for relapsed or refractory CD30+ HL or relapsed or refractory sALCL in routine practice with brentuximab vedotin; and to identify and describe potential risk factors for peripheral neuropathy in relapsed or refractory CD30+ HL or relapsed or refractory sALCL patients treated with brentuximab vedotin.

Overall 35% of the population experienced an SAE, which was similar between the prospective and retrospective cohorts. Frequently observed SAEs reflected AESIs. The most commonly observed SAEs by SOC and PT were the following: infections and infestations (29.6 [95% CI 20.5, 38.7] per 100 person-years, 14.5%), particularly pneumonia (8.5 [95% CI 4.0, 13.1] per 100 person-years, 4.5%); general disorders and administration site conditions (19.2 [95% CI 12.2, 26.1] per 100 person-years, 9.7%), particularly pyrexia (13.3 [95% CI 7.6, 19.0] per 100 person-years, 6.8%); nervous system disorders (16.1 [95% CI 9.6, 22.5] per 100 person-years, 8.1%), particularly peripheral sensory neuropathy (7.6 [95% CI 3.2, 11.9] per 100 person-years, 3.9%) and neuropathy peripheral (3.6 [95% CI 0.7, 6.6] per 100 person-years, 1.9%); blood and lymphatic system disorders (8.0 [95% CI 3.6, 12.3] per 100 person-years, 4.2%), particularly neutropenia (4.3 [95% CI 1.1, 7.4] per 100 person-years, 2.3%) and febrile neutropenia (2.4 [95% CI 0.0, 4.8] per 100 person-years, 1.3%).

Peripheral neuropathy was the most common AESI, occurring in 42.3% of patients with an incidence of 113.6 (93.3, 133.9) per 100 person-years, and was reported as serious in 7.1% of patients. It was more frequent in the retrospective cohort than in the prospective cohort (50.6% vs. 34.0%, respectively), but with similar incidence owing to the longer at-risk period in the retrospective cohort. This was lower than the 56% observed in the pivotal phase 2 trials and 67% observed in AETHERA, all studies of monotherapy brentuximab vedotin. Notably the retrospective cohort had similar frequency to previous trials. Peripheral neuropathy was also collected more frequently as the PT term ‘neuropathy peripheral’ a general term that doesn’t distinguish between sensory/motor components. This may be attributed to data collection methods, in the retrospective cohort data was also extracted from patients records, which may have been less precise than prospective data collection.

Neutropenia (including febrile neutropenia and neutrophil count decreased) occurred in 17.4% of patients, with an incidence of 37.2 (95% CI 26.3, 48.0) per 100 person-years, and was reported as serious in 3.5% of patients. It was more frequent in the prospective cohort than in the retrospective cohort (20.5% vs. 14.3%, respectively), with a corresponding doubling of incidence, owing to the shorted at-risk period in the prospective cohort. This was lower overall than the 21% observed in the pivotal phase 2 trials and 35% observed in AETHERA, but the prospective cohort had similar frequency to previous trials.

The ADCETRIS Product Information (EMA website, last updated 13 March 2019) notes that febrile neutropenia was observed in <1% of patients on brentuximab vedotin monotherapy, and in 17% of patients on combination therapy. Advanced age is a noted risk factor for febrile neutropenia. This was consistent for patients aged <65 years (0.9%) and was expectedly higher in elderly patients aged ≥65 years (5.3%).

Infections (including opportunistic infections) occurred in 31.3% of patients, with an incidence of 76.0 (95% CI 60.1, 92.0) per 100 person-years, and were reported as serious in 13.5% of patients. They occurred with similar frequencies between the prospective and retrospective cohorts, and with higher incidence in the prospective cohort than the retrospective cohort. This was lower than the 61% observed in the pivotal phase 2 trials and 60% observed in AETHERA. The reporting of infections as an AESI may have affected reporting rates, but the most commonly observed infections remained consistent between this study and previous trials.

Hypersensitivity reactions (including infusion-related reactions and allergic reactions) occurred in 11.0% of patients, with an incidence of 22.5 (95% CI 14.7, 30.4) per 100 person-years, and were reported as serious in 2.3% of patients. They were more frequent in the retrospective cohort than the prospective cohort (12.3% vs. 9.6%, respectively), but with similar incidence between cohorts. This was consistent with the 11% observed in the pivotal phase 2 trials and lower than the 15% observed in AETHERA.

The frequency of AESIs was generally lower in this study than in the pivotal phase 2 studies and AETHERA. The retrospective cohort could have been a contributing factor if patients that had AEs discontinued treatment and were not eligible for this study, this may have been a factor in neutropenia, in which the prospective cohort had similar results to previous trials. Peripheral neuropathy was more frequent in the retrospective cohort, consistent with the cumulative effect and the higher number of treatment cycles compared to the prospective cohort.

There was an insufficient number of patients to address the effects of long-term treatment (9 patients with >16 cycles). This may have been affected by the planned treatment course used in routine clinical practice, following the indication of a maximum of 16 cycles. The number of elderly patients (24.5% of patients were ≥65 years) allowed for limited interpretation. As expected, elderly patients were found to be at increased risk of SAE and AESIs, particularly infections and febrile neutropenia. About half of the population was post-AST (48.4% of patients), and had a markedly lower frequency of infections, possibly owing to a protective effect of the ASCT.

Overall the occurrence of SAE and AESI were consistent with the known safety profile of brentuximab vedotin. Dose modifications and discontinuations can affect patient response to treatment and prognosis, treatment/study discontinuations were observed for 13.9% of patients overall due to SAEs, which was higher in the prospective cohort than the retrospective cohort (17.9% vs. 9.7%, respectively). Treatment/study discontinuations occurred for 12.6% of patients overall due to AESIs (many of which were also considered SAEs), which was higher in the prospective cohort than in the retrospective cohort (10.9% vs. 14.2%, respectively). The higher

discontinuation rates in the prospective cohort indicate that enrolment the retrospective cohort may have resulted in some selection bias, as would be expected.

Finally, patients were treated in a real-world setting, which included a variety of medical history, prior and concomitant treatments, including other chemotherapeutic agents that could have also affected the incidence and/or severity of SAEs and/or AESIs.

Additional SAE reconciliation following completion of the study had minimal findings and did not affect the interpretation of the overall study results.

11.4 **Generalisability**

The findings from this observational study should provide information relevant to the population treated with brentuximab vedotin in the post-marketing setting, which is likely to be less restricted than the subjects included in clinical trials. This observational study was conducted in 13 European countries with the intention that the data collected will be broadly representative of real-world treatment of relapsed or refractory CD30+ HL and relapsed or refractory sALCL with brentuximab vedotin in the European Union (EU).

Screening logs collected limited information and were used to evaluate the generalisability of the patient population in this study, which found that the enrolled population had fewer elderly patients than the non-enrolled population (23.9% vs. 30.6%, respectively), and likely contained fewer elderly patients than typically observed with CD30+ HL and sALCL based on the known distribution patterns, but did enrol sufficient patients to allow for safety analyses in elderly patients. The enrolled population also had fewer patients with advanced stage disease than the non-enrolled population (42.0% vs. 55.7%, respectively); the study population did however have an approximately even distribution between disease stages, and these differences could also reflect clinical treatment decisions.

Although country selection included different European geographical areas with various incidence rates for CD30+ HL and sALCL in order to maximise the representativeness of the full study population, 29% of the study population was from the UK. This study included sufficient sALCL patients to evaluate whether they had a different risk profile from CD30+ HL patients, and the results can be generally applicable to both of these lymphoma diseases.

12 OTHER INFORMATION

No additional information.

13 CONCLUSION

The final results from this study are consistent with the known safety profile of brentuximab vedotin. No new risks were identified. Increased BMI was found to be a potential risk factor for development of peripheral neuropathy during treatment with brentuximab vedotin; further analyses indicated that overweight or obese patients had a higher risk of developing peripheral neuropathy than normal weight patients. Data from this final analysis continues to support the favourable safety profile in line with the established positive benefit/risk profile of brentuximab vedotin in patients with relapsed or refractory CD30+ HL and sALCL.

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APPENDICES

Annex 1 List of Stand-Alone Documents

Number	Document Reference Number	Date	Title
1	Not applicable	13 June 2019	List of Investigators
2	Not applicable	13 June 2019	List of Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs) submissions and approvals by country
3	Not applicable	13 June 2019	List of Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs) and address by country
4	Not applicable	12 June 2019	Adcetris® Summary of Product Characteristics (Last updated: 13Mar2019 & downloaded 12Jun2019)
5	Not applicable	14 June 2012	Protocol version 1.1
6	Not applicable	05 December 2013	Protocol version 2.0 (amendment 1)
7	Not applicable	11 March 2014	Protocol version 3.0 (amendment 2)
8	Not applicable	07 June 2016	Protocol version 4.0 (amendment 3)
9	Not applicable	27 January 2017	Protocol version 5.0 (amendment 4)
10	Not applicable	19 July 2015	SAP version 1.4 (used for interim report)
11	Not applicable	31 May 2018	SAP version 3.0 (used for final report)
12	Not applicable	04 March 2016	MA25101 Interim Clinical Study Report
13	Not applicable	12 November 2012	Master ICF v1. 1
14	Not applicable	16 November 2012	Master ICF v1.1 approval form
15	Not applicable	14 November 2012	Master ICF v1.1 note to file
16	Not applicable	14 December 2012	Master ICF v2.0
17	Not applicable	14 December 2012	Master ICF v2.0 approval form
18	Not applicable	26 May 2014	Master ICF v3.0
19	Not applicable	28 April 2017	Addendum I to the Patient Information Sheet v1.0
20	Not applicable	14 December 2012	Master patient pregnancy ICF v1.0
21	Not applicable	14 December 2012	Master patient pregnancy ICF v1.0 approval form
22	Not applicable	26 May 2014	Master patient pregnancy ICF v2.0
23	Not applicable	14 December 2012	Master partner pregnancy ICF v1.0
24	Not applicable	14 December 2012	Master partner pregnancy ICF v1.0 approval form
25	Not applicable	27 May 2014	Master partner pregnancy ICF v2.0
26	Not applicable	27 November 2012	CRF v1.0
27	Not applicable	27 November 2012	CRF v1.0 approval form
28	Not applicable	16 January 2013	CRF v2.0
29	Not applicable	16 January 2013	CRF v2.0 approval form
30	Not applicable	05 April 2013	CRF v2.1
31	Not applicable	16 July 2013	CRF v2.1 note to file
32	Not applicable	18 September 2013	CRF v3.0

Number	Document Reference Number	Date	Title
33	Not applicable	18 September 2013	CRF v3.0 approval form
34	Not applicable	05 December 2013	CRF v4.0
35	Not applicable	05 December 2013	CRF v4.0 approval form
36	Not applicable	13 June 2019	CRF v4.0 note to file
37	Not applicable	05 March 2014	CRF v5.0 signed
38	Not applicable	15 May 2014	CRF v6.0 signed
39	Not applicable	11 June 2014	CRF v7.0 signed
40	Not applicable	19 June 2014	CRF v8.0 signed
41	Not applicable	29 June 2015	CRF v9.0 signed
42	Not applicable	13 June 2019	List of Study Personnel (Sponsor & CRO)

Annex 2 Additional Information

Changes made to the Study Report, 27 November 2019.

Following completion of v1.0 of the CSR (dated 13 June 2019, not submitted to the Regulatory Authorities) an additional SAE reconciliation was performed. This did not impact the study results and interpretation, but for full transparency details were added about findings that affected reporting within the CSR. This resulted in preparation of v2.0 (dated 11 October 2019).

The following administrative changes were made to v2.0 (dated 11 October 2019) for accuracy in line with PASS CSR template. Since this amendment is purely administrative in nature, it has not been re-signed by the Principal Investigator (PI). This is consistent with the PASS study template which does not require signature by the PI. This became v3.0 (dated 27 November 2019).

List of administrative changes (v2.0 to v3.0) by section:

- Title page
    - Date of last version of the final study report: changed to 27 November 2019
    - Author section: Paul Dolin specified as the main author
- Milestones (Section 5) added date of final report v2.0 dated 11 October 2019
- Milestones (Section 5) added date of final report v3.0 dated 27 November 2019
- Appendices added headings for Annex 1 and Annex 2
- Table of appendices replaced with Annex 1 List of Stand-Alone Documents
- Appendix replaced with Annex 1 Number in text
- Total number of pages updated from 160 to 162

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
Dolin, Paul	Safety Approval	28-Nov-2019 22:47 UTC