OBSERVATIONAL STUDY PROTOCOL MA25101

Brentuximab vedotin

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

Protocol Number:	MA25101
Indication:	Relapsed or Refractory CD30+ Hodgkin Lymphoma and Relapsed or Refractory Systemic Anaplastic Large Cell Lymphoma
Phase:	Post-Authorisation
Study Sponsor:	Millennium Pharmaceuticals, Inc. 40 Landsdowne Street, Cambridge, MA 02139 USA
Marketing Authorisation Holder:	Takeda Global Research and Development Centre (Europe) 61 Aldwych London WC2B 4AE United Kingdom
Therapeutic area:	Oncology

Protocol history

Original	06 April 2012	Version 1.0
Revised	14 June 2012	Version 1.1
Amendment 1	05 December 2013	Version 2.0
Amendment 2	11 March 2014	

Approved by:

Note: If this document was approved electronically, the electronic approval signatures may be found at the end of the document.

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Dominic Beale, MBBS, BSc, MSc, FFPM, Senior Medical Director, EU QPPV 21 March 2014

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Protocol Amendment 2

I have read and understand the protocol and agree that it contains the ethical, legal and scientific information necessary to participate in this study. My signature confirms the agreement of both parties that the study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to Good Pharmacoepidemiology Practices (GPP), the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, the ethical principles that have their origins in the Declaration of Helsinki and applicable privacy laws.

I will provide copies of this protocol as needed to all physicians, nurses, and other professional personnel responsible to me who will participate in the Study. I will discuss the protocol with them to assure myself that they are sufficiently informed regarding the conduct of the Study. I am aware that this protocol will need to be approved by an appropriate Ethics Committee prior to any patients being enrolled and that I am responsible for verifying whether that requirement is met. I agree to adhere to the attached protocol and if requested to provide copies of medical information for the purpose of verification of submitted information, I will comply.

Since the information in this protocol is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

Investigator:

_____
Print Name

_____ _____
Signature Date

_____
Print Name of Institution or Practice and Location

RETURN ORIGINAL TO Quintiles (CRO)
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LIST OF ABBREVIATIONS

AE	Adverse event
AESI	Adverse events of special interest
sALCL	Anaplastic large cell lymphoma (systemic)
ALK	Anaplastic lymphoma kinase
ASCT	Autologous stem cell transplant
BMI	Body mass index
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CRF	Case report form
CRO	Contract research organization
CT	Computed tomography
DMP	Data management plan
eCRF	Electronic case report form
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	U.S. Food and Drug Administration
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HL	Hodgkin lymphoma
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	International ethics committee
ISPE	International Society for Pharmacoepidemiology
JCV	John Cunningham virus
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NPP	Named Patient Program
PASS	Post-authorisation safety study
PET	Positive emission tomography
PV & RM	Pharmacovigilance and Risk Management
SAE	Serious adverse event
SAP	Statistical analysis plan
SmPC	Summary of Product Characteristics
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology

STUDY SYNOPSIS

<table>
<tr><td colspan="4">Full 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
Protocol amendment 2 dated 11 March 2014</td></tr>
<tr><td>Phase:</td><td>Post-authorisation</td><td>Type:</td><td>Observational</td></tr>
<tr><td colspan="2">Number of Patients: 500</td><td colspan="2">Duration of Patient Participation: Maximum of 5 years</td></tr>
<tr><td colspan="2">Number of Sites: 75-100</td><td colspan="2">Duration of Study: 5 years</td></tr>
<tr><td colspan="4">Background/Rationale: Relapsed and refractory CD30+ Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (sALCL) are rare conditions. Although at initial presentation both HL and sALCL are potentially curable types of lymphoma when conventional chemotherapy regimens and radiation therapy are used, not all patients are cured with currently available regimens and many go on to require additional therapies. For patients with CD30+ HL and sALCL who subsequently relapse, or have refractory disease and fail to respond to first- or second-line therapies, treatment options have typically included additional combination chemotherapy, stem cell transplant or investigational agents.

CD30, a member of the tumor necrosis factor superfamily, 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. Brentuximab vedotin (Millennium Pharmaceuticals, Inc. and Seattle Genetics), a novel antibody drug conjugate directed against the CD30 surface antigen, was recently approved by the European Medicines Agency (EMA) for the treatment of relapsed or refractory CD30+ HL and sALCL. Brentuximab vedotin is a CD30-directed antibody-drug conjugate consisting of IgG1 antibody cAC10, specific for CD30, and the microtubule disrupting agent, monomethyl auristatin E (MMAE, or vedotin). During clinical development prior to approval, the safety of brentuximab vedotin was evaluated in more than 300 patients with relapsed or refractory CD30+ HL, sALCL, and other CD30+ haematologic malignancies. Analyses of the available safety data indicate that brentuximab vedotin has a manageable and tolerable safety profile in the studied populations. As is common with new therapies for rare conditions, the EMA has required a post-authorisation safety study (PASS) to further evaluate the safety profile of brentuximab vedotin. Specifically, this PASS is designed as a prospective, observational cohort study of patients prescribed brentuximab vedotin as part of routine clinical care.</td></tr>
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The objectives of the study are to:
Evaluate the occurrence of serious adverse events (SAEs) and specified adverse events of special interest (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.</td></tr>
</table>

Study design: This is a multi-centre prospective, observational cohort study of the safety of brentuximab vedotin treatment in patients who have been diagnosed with relapsed or refractory CD30+ HL or relapsed or refractory sALCL. The study will target the enrolment of approximately 500 patients (at least 50 of whom have a diagnosis of sALCL), who are treated with brentuximab vedotin at approximately 75-100 sites in Europe and potentially other countries outside of Europe. Patients will be enrolled over an approximate 3-year enrolment period and the total study duration will be five years from the date of first patient enrolled. Patients already being treated with brentuximab vedotin at the time of enrolment will be considered to be retrospectively enrolled for purposes of analysis and inclusion in the PASS.

Study population:

Inclusion criteria

- Age at enrolment ≥ 18 years
- Clinical diagnosis (with histologic confirmation) of relapsed or refractory CD 30+ HL or relapsed or refractory sALCL
- Patient is planned to start or is already receiving single agent therapy with brentuximab vedotin as part of routine clinical care
- Willing and able to provide informed consent

Exclusion criteria

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

Data collection: Data elements will be collected from information routinely recorded in the medical record. No study visits or examinations, laboratory tests or procedures are mandated by the study. Baseline patient and disease characteristics, relevant medical history and all initial and subsequent treatment for relapsed or refractory CD30+ HL or relapsed or refractory sALCL will be recorded. Follow-up will include changes in patient status and disease management, treatment with brentuximab and any other medications, SAEs and both serious and non-serious AESI [i.e., peripheral neuropathy, neutropenia (including febrile neutropenia), infections (including opportunistic infections), hyperglycaemia and hypersensitivity reactions (including infusion-related reactions or allergic reactions)], as assessed by the treating physician. Patients will remain under follow-up until death, withdrawal of consent, loss of follow-up or study closure, whichever comes first. Follow-up data will be collected in conjunction with all routine care visits, typically every three months.

Data Management and Quality Assurance: All study data will be entered directly into the electronic data capture (EDC) system. Participating sites will only have access to those data entered by their own institution. All sites will be fully trained on using the on line data capture system, including electronic case report form (eCRF) completion guidelines and help files. The eCRFs will include programmable edits to deliver immediate feedback if data are missing, out of range, illogical or potentially erroneous. A study monitoring plan, including for-cause monitoring, that is appropriate for the study design will be developed and implemented. Site monitoring will be performed by clinical research associates (CRAs) 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. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data.

Safety: All SAEs and both serious and non-serious AESI will be recorded in the eCRF, from the patient's first dose of brentuximab vedotin (which may be prior to enrolment) through 30 days after the patient's last dose of brentuximab vedotin. After that time point, only SAEs and both serious and non-serious AESI considered related to brentuximab vedotin will be recorded in the eCRF.

Statistical Considerations:

Sample size

The sample size for this study was based on the need for more information regarding the occurrence of AESI, both serious and non-serious, relative to the size of the current safety database. Evaluation of the sample size for the study objectives was performed based on the expected rate of AESI, both serious and non-serious, in patients with relapsed or refractory CD30+ HL or relapsed or refractory sALCL treated with brentuximab vedotin to ensure sufficient enrolment. The targeted sample size of 500 was determined to provide an adequate level of precision to achieve the first safety objective of this study through estimating the proportion of patients experiencing an individual AESI. The sample size of 500 includes the patients already being treated with brentuximab vedotin at the time of enrolment, the retrospective patients. It is assumed that approximately 15 to 20% (75 to 100 patients) of the study population will be retrospectively enrolled.

Interim and Final Analyses:

Details of the statistical analysis will be fully described in a written and approved statistical analysis plan (SAP). Frequency and incidence proportion for all reported SAEs and AESI will be reported for patients enrolled and receiving at least one dose of treatment. Incidence rates and 95% confidence interval (CI) will also be reported for selected events. Time at risk will be defined in the SAP. Analyses will be conducted on the enrolled population, including all patients exposed to brentuximab vedotin. In addition, analyses will be presented separately for patients prospectively and retrospectively enrolled to account for potential differences in the data reported, in particular the volume and nature of adverse events.

Subgroup safety analyses will be performed by indication and other characteristics of interest (e.g., by age at enrolment < 65 or ≥ 65 years, number of treatment cycles). All dose modifications including dose delays, temporary interruptions and permanent interruptions, and reported reason for change(s) will be summarised, and where possible the effect of modifications on safety will be explored.

An interim analysis will be performed approximately 2.5 years after the first patient is enrolled. A final analysis and study report will be generated after all data collection is complete and will encompass all planned analyses, including a description of the complete study population, as described above and in the SAP. All reporting will be consistent with the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) Initiative checklist for cohort studies.

Ethical and Regulatory Considerations:

The study will be conducted in compliance with all applicable legislation, and national regulations, directives and guidelines regarding the conduct of post-authorisation safety studies (PASS), including Good Pharmacovigilance Practices (GVP) Module VIII – Post-marketing Authorisation Studies. To ensure the quality and integrity of research, this study will be conducted under the Guidelines for Good Pharmacoepidemiology Practices (GPPs) issued by the International Society for Pharmacoepidemiology (ISPE), the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, the Declaration of Helsinki and its amendments, and any applicable national guidelines. Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing patient data. Every effort will be made to protect participant confidentiality according to the Directive 95/46/EC on the protection of individuals, and in compliance with Safe Harbor privacy principles.

Milestones
Anticipated start of data collection (first patient enrolled): March 2013
Actual start of data collection (first patient enrolled): June 2013
Date of study progress reports: As agreed upon with the relevant competent authorities: included in the annual renewal of conditional marketing authorisation (currently, each April), RMP and PSUR (currently, each April and October).
Interim analysis with data cut September 2015; Interim analysis report in April 2016
Anticipated end of data collection (availability of final analytic dataset): March 2018
Final study report: December 2018

Documentation of Protocol Amendments

Number	Date	Section of Study Protocol	Amendment or update	Reason
2	11 March 2014	Section 4., Table 1 and text	Add expected frequency of visits. Minor wording and clarifications, including additional footnotes	Address PRAC's concern 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 two 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

Study Milestones

The planned dates for key study milestones are:

Anticipated start of data collection (first patient enrolled)	March 2013
Actual start of data collection (first patient enrolled)	June 2013
Date of study progress reports	As agreed upon with the relevant competent authorities: included in the annual renewal of conditional marketing authorisation (currently, each April), RMP and PSUR (currently, each April and October)
Interim report of study results	Interim analysis data cut September 2015; Interim analysis report in April 2016
Anticipated end of data collection (availability of final analytic dataset)	March 2018
Final study report	December 2018

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, not all patients are cured with currently available front-line regimens and go on to require additional therapies.

Hodgkin Lymphoma

There is wide international variation for both males and females in HL incidence, with the highest rates in Southern Europe and Northern America. The annual age-adjusted incidence of HL in Europe in males and females is estimated at 2.1/100,000 per year [IARC 2008]. In many parts of Asia and Africa, incidence rates for Hodgkin lymphoma 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 [Ferlay 2010]. HL occurs in patients in all age groups and presents a bimodal distribution with peaks at 15 to 35 years of age and over the age of 60 [Cartwright 2004]. Classical HL is defined histopathologically by the presence of malignant 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, cyclophosphamide, Oncovin®, propcarbazine, prednisone), but other older options (e.g., MOPP – mechlorethamine, Oncovin, procarbazine, prednisone) and alternating regimens may be used [Furtado 2012]. Approximately 10 to 20% of patients presenting with HL will become 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, and it is only effective in half of such patients [Sureda 2005, Majhail 2005]. Patients who subsequently relapse after stem cell transplant have an extremely poor prognosis [Moscowitz 2004, Horning 2008].

Systemic Anaplastic Large Cell Lymphoma

Primary sALCL represents only 2-8% of adult non-Hodgkin lymphoma cases and as many as 30% of childhood non-Hodgkin lymphoma cases [Lister 2000]. 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) infusion proteins, with ALK- ALCL tending to be more aggressive and more likely to relapse than ALK+ ALCL. The malignant cells in all types of ALCL strongly express the CD30 antigen on cell membranes, and histologic review reveals the characteristic tumor 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 tumor 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. A combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), or similar, is the standard first-line treatment for sALCL. 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 stem cell transplant, although this is less common in sALCL.

Safety Profile for Brentuximab Vedotin

CD30, a member of the tumor 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 [Falini 1995]. A novel antibody drug conjugate directed against the CD30 surface antigen, brentuximab vedotin (Millennium Pharmaceuticals, Inc. and Seattle Genetics), was approved by the US Food and Drug Administration (FDA) and by the EMA for the treatment of relapsed or refractory CD30+ HL and sALCL. Brentuximab vedotin is a CD30-directed antibody-drug conjugate consisting of IgG1 antibody cAC10, specific for CD30, the microtubule disrupting agent, monomethyl auristatin E (MMAE, or vedotin) and a protease-cleavable linker that covalently attaches MMAE to cAC10.

During the clinical development program, the safety (and efficacy) of brentuximab vedotin was evaluated in more than 300 patients with relapsed or refractory CD30+ HL, sALCL, and other CD30+ haematologic malignancies as per the clinical trial dossier for the market authorisation application. Clinical data were collected from two completed phase 1 dose escalation 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 a phase 1 drug-drug interaction study (SG035-008A). Analyses of safety data indicate that brentuximab vedotin has a manageable and tolerable safety profile in the studied populations.

In Study SG035-0001, a total of 45 patients with CD30+ haematologic malignancies (42 with HL, two with sALCL, one with angioimmunoblastic T-cell lymphoma) were treated with brentuximab vedotin at dose levels of 0.1 to 3.6 mg/kg administered intravenously every 3 weeks. The primary objectives of the study were to establish a maximum tolerated dose of brentuximab vedotin and to assess the associated toxicity profile. The most common adverse events (AEs) reported were fatigue, pyrexia, diarrhea, nausea, peripheral neuropathy and neutropenia. Notable serious adverse events (SAEs) considered at least possibly related to treatment included anaphylaxis, myocardial infarction and peripheral neuropathy [Younes 2010].

In Study SG035-0002, 44 patients with CD30+ haematologic malignancies (38 with HL, 5 with sALCL, and 1 with peripheral T-cell lymphoma) were treated with brentuximab vedotin at dose levels of 0.4 to 1.4 mg/kg administered intravenously weekly for 3 of 4 weeks. The primary objectives explored in this study were to establish the safety profile and maximum tolerated dose of weekly brentuximab vedotin monotherapy in patients with relapsed or refractory CD30+ haematologic malignancies. 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. The most common adverse events were peripheral sensory neuropathy, fatigue, nausea, diarrhoea, arthralgia, pyrexia, decreased appetite, myalgia, and upper respiratory tract infection. Treatment discontinuations due to adverse events (AEs) were observed in 30% of patients. The most frequent AE that led to dose modification or delay was peripheral sensory neuropathy. Acute infusion reactions, all reported as mild or moderate, occurred in six patients [Fanale 2012].

In SG035-0003, a phase 2, single-arm, open-label study in patients with relapsed or refractory HL postASCT, and in SG035-0004, a phase 2 trial conducted in patients with relapsed or refractory sALCL, brentuximab vedotin was administered at a dose of 1.8 mg/kg every 3 weeks. One hundred two patients with relapsed and refractory HL and 58 patients with relapsed and refractory sALCL were exposed for a median duration of approximately 27 weeks (9 cycles) and 20 weeks (6 cycles), respectively. The primary endpoint of both studies was overall response rate. Treatment-emergent AEs occurring in ≥ 20% of patients in phase 2 were peripheral sensory neuropathy (44%), fatigue (42%), nausea (41%), diarrhoea (34%), pyrexia (31%), upper respiratory tract infection (28%), neutropenia (21%) and vomiting (20%). These events were primarily mild to moderate in severity and reversible. Approximately half of patients had treatment-emergent peripheral neuropathy, predominantly sensory neuropathy, with an onset and severity pattern consistent with a cumulative effect of exposure. Dose delay and subsequent reduction to 1.2 mg/kg was generally effective in managing peripheral neuropathy. Moderate or severe neutropenia occurred in 13% and 7% of patients, respectively; these events were typically of short duration and well managed by brief dose delays with growth factor support in some cases. Infusion-related reactions occurred in approximately 10% of patients and were typically managed by dose delay or reduction. The clinical laboratory parameters for which the most patients had new or worsening findings were low neutrophils, low lymphocytes, low platelets, low leukocytes and elevated glucose [Younes 2012].

Most patients in the two phase 2 studies were between the ages of 18 and 65 years; as a result, there are limited data available regarding the use of brentuximab vedotin in elderly patients. In addition, the maximum number of cycles administered in the pivotal phase 2 studies was 16 and it is unknown whether there is any change in the safety profile of brentuximab vedotin

with longer term use or with the implementation of the recommended dose reductions in the presence of specific toxicities.

2. RATIONALE

As is common with new therapies for rare conditions, the EMA has required a post-authorisation safety study (PASS) to further evaluate the safety profile of brentuximab vedotin. Specifically, this PASS is designed as a prospective, observational cohort study including patients prescribed brentuximab vedotin as part of routine clinical care and followed for up to five years for the occurrence of selected safety outcomes. In addition to SAEs, the following both serious and non-serious adverse events of special interest (AESI) will specifically be evaluated as part of the PASS: peripheral neuropathy, neutropenia (including febrile neutropenia), infections (including opportunistic infections), hyperglycaemia and hypersensitivity reactions (including infusion-related reactions and allergic reactions). In addition to the overall patient population, to the extent possible, the safety profile of brentuximab vedotin in elderly patients and patients with longer term exposure (i.e., $\geq$ 16 cycles) will also be evaluated. The study is intended to provide important information regarding the safety profile of brentuximab vedotin in a real-world population.

3. OBJECTIVES

The objectives of the study are to:

- Evaluate the occurrence of serious adverse events (SAEs) and specified adverse events of special interest (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.

4. STUDY DESIGN

4.1 Study Description

This is a multi-center international prospective, observational cohort study of patients who have been diagnosed with relapsed or refractory CD30+ HL or relapsed or refractory sALCL and are treated with brentuximab vedotin as part of routine clinical care. The study will target the enrolment of approximately 500 patients (at least 50 of whom have a diagnosis of sALCL), who are initiating or are currently being treated with brentuximab vedotin at approximately 75-100 sites in 12-15 countries in Europe and potentially in other countries outside of Europe. Patients already being treated with brentuximab vedotin at the time of enrolment will be considered to be retrospectively enrolled for purposes of analysis and inclusion in the PASS. The sample size for this study was based on the need for more information regarding the occurrence of both serious and non-serious AESI, relative to the

size of the current safety database. The study will continue for five years from the date of first patient enrolled. The study will be managed by the contract research organization (CRO) Quintiles, with oversight by Millennium Pharmaceuticals, Inc. (Millennium) project team.

Sites that treat patients with relapsed or refractory CD30+ lymphomas including HL and sALCL will be invited to participate in the study. Country and site selection will depend 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 are available for enrolment into the study. The duration of the enrolment period may be extended (or contracted) based on actual patient accrual rates.

Eligible patients will be identified from sites where patients are initiating or already receiving therapy with brentuximab vedotin. No study specific visits or procedures will be required as part of patient participation in the study. Patients will be evaluated according to the physician's standard practice and discretion.

4.2 Study Population

The study will aim to enrol eligible patients with relapsed or refractory CD30+ HL or sALCL, from approximately 75-100 centers in Europe (and possibly additional countries outside of Europe). It is estimated that approximately 500 patients (at least 50 of whom have a diagnosis of sALCL) will be eligible and agree to participate during the planned approximate 3-year enrolment period of the study. The sample size for this study was based on the need for more information regarding the occurrence of both serious and non-serious AESI, relative to the size of the current safety database (refer to Section 5.1 regarding the sample size justification). Patients already being treated with brentuximab vedotin at the time of enrolment will be considered to be retrospectively enrolled for purposes of analysis and inclusion in the PASS.

To the extent possible, enrolment of all eligible patients at each site is expected in order to ensure representativeness of the study population.

4.2.1 Inclusion Criteria

To be eligible for enrolment, patients must meet 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 is planned to start or is already receiving single agent therapy with brentuximab vedotin as part of routine clinical care

- Willing and able to provide informed consent

4.2.2 Exclusion Criteria

Patients meeting ANY of the following criteria are not eligible for participation:

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

4.2.3 Study Enrolment

Oncologists and haematologist-oncologists who are routinely involved in the care and treatment of patients with relapsed or refractory CD30+ HL and sALCL will be targeted for recruitment. Site selection criteria will include the projected availability of eligible patients in a 36-month enrolment period and the capacity of site staff to complete the case report forms (CRFs). Selection criteria and basic site information (e.g., practice size, investigator specialty, site type) will be collected via a site qualification survey.

Eligible patients will be invited to provide informed consent to participate in the study at the time of presentation for a routine clinic visit. No specific clinic visits are required as part of participation in this study. All assessments are intended to be based on routine patient care or by referencing the medical records.

All patients presenting during the enrolment period will be assessed for eligibility according to the defined selection criteria and all eligible patients will be invited to participate in the study. A screening log will be 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, non-identifiable information will be recorded for all patients who are screened for study enrolment, but no patient-identifiable information should be recorded. To formally address the concern of selection bias for the retrospective patients, the reasons will be collected, if possible, for each patient who received brentuximab vedotin and was not enrolled.

4.2.4 Patient Withdrawal and Treatment Discontinuation

Patients may withdraw consent and discontinue participation in the study at any time, with no effect on their medical care or access to treatment. If a patient is withdrawn prior to completing the study follow-up period, any known reason for withdrawal should be documented in the database. All information already collected as part of the study will be retained for analysis; however, no further efforts will be made to obtain or record additional information regarding the patient. If the last assessment was more than three months prior to withdrawal from study and patient status has not been documented, if possible a final

assessment of treatment status and any SAEs and both serious and non-serious AESI (per Section 7.2 Procedures for Recording and Reporting SAEs and AESI) should be recorded at the time of withdrawal from study.

All patients who permanently discontinue brentuximab vedotin should continue to be followed according to the protocol's recommended recording of essential data.

4.3 Exposure Definition and Measures

This is an observational study of real-world treatment practices in this patient population. This protocol does not recommend the use of any specific treatments. No study medication is provided as part of participation.

Patients will be enrolled after the patient agrees to participate and signs the informed consent form. All exposure to brentuximab vedotin (including any exposure prior to enrolment) will be collected.

As an observational study to understand safety in patients treated in the post-marketing setting, no restrictions on concomitant treatments are associated with the study. All concomitant treatments (and subsequent treatments for lymphoma during follow-up) will be carefully recorded in order to evaluate their potential influence on the outcomes of interest.

4.4 Outcome Definition and Measures

4.4.1 Safety measures

The frequency, intensity and relationship to treatment will be evaluated for all reported serious adverse events (SAEs) (refer to Section 7.1 for the definition of SAEs).

In addition to SAEs overall, the frequency, intensity and relationship to treatment for the following adverse events of special interest (AESI), both serious and non-serious, will be evaluated:

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

These outcomes will be evaluated in the overall treated population and also specifically within the elderly subpopulation (age at enrolment $\geq$ 65 years) and the population of patients who receive brentuximab vedotin for more than 16 cycles.

4.4.2 Effectiveness measures

The focus of this study is safety; therefore no measures or analyses regarding treatment effectiveness are included in the study.

4.4.3 Other measures

All dose modifications including dose delays, temporary interruptions and permanent interruptions, and reported reason for change(s) will be summarised, and where possible the effect of modifications on safety will be explored.

4.5 Data Collection

4.5.1 Schedule of Recommended Recording of Essential Data

Essential data for the study are presented in the Schedule of Recommended Recording Essential Data provided in Table 1. For eligible patients who provide informed consent, data elements will be abstracted from information routinely recorded in the medical record. Follow-up data will be collected in conjunction with all routine care visits, typically occurring at approximately every three months. No study visits or examinations, laboratory tests or procedures are mandated as part of this study.

Table 1 Schedule of Recommended Recording of Essential Data

	Enrolment[a]	**On-Treatment Follow-up**[b]	**Post-Treatment Follow-up**[c] (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
SAE and AESI recording in eCRF (Refer to section 7.2)[d]	X	X	
Both SAEs and AESI considered related to brentuximab vedotin - recording in eCRF (Refer to Section 7.2)[d]			X
Date and reason for discontinuation (if applicable)		X[e]	X[e]

[a] Exposure to brentuximab vedotin may have started prior to enrolment. All brentuximab vedotin treatment and concomitant medication exposures, SAEs/AESI and relevant medical history since starting the current brentuximab vedotin regimen should be recorded at the time of enrolment.
[b] The On-Treatment period is defined as beginning at the time of enrolment and continuing through 30 days after the last dose of brentuximab vedotin.
[c] The Post-Treatment Follow-up period is defined as beginning 31 days after the last dose of brentuximab vedotin and continuing until study discontinuation.
[d] Refer to Section 7.2 for the procedures for recording and reporting SAEs and both serious and non-serious, AESIs.
[e] Refer to section 4.5.4 for a listing of data to be recorded at the time of study discontinuation.

4.5.2 Baseline/Enrolment

The following data will be recorded, where available, at baseline for all enrolled patients:

- Demographics [date of birth, sex, race/ethnicity (where allowed by local regulations)]
- Weight, height (calculated BMI)
- ECOG performance status
- Relevant medical history, including cardiovascular (e.g., congestive heart failure, rhythm abnormalities), diabetes, pulmonary (e.g., chronic obstructive pulmonary

disease), hepatic, renal, other malignancies, neurologic (e.g., neuropathies), autoimmune disease, infectious disease (e.g., HIV, Epstein Barr virus), abnormal blood counts (cytopenias and growth factor exposure), thyroid dysfunction

- Relevant laboratory testing [e.g., 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)
    - Date of initial diagnosis
    - Diagnostic testing performed
    - Disease stage
    - Presence of lymphoma-related symptoms (B symptoms)
    - Extent of disease determined by both physical examination and imaging
    - ALK status (positive, negative, unknown) (sALCL patients only)
    - ALCL variant: common, small cell, lymphohistiocytic, sarcomatoid, other, unknown (sALCL patients only)
    - HL subtype: nodular sclerosing, mixed cellularity, lymphocyte-rich, lymphocyte depleted, unspecified/unknown
    - Previous treatment
        - Previous lines of therapy, with number of cycles
        - Autologous stem cell transplant or allogeneic stem cell transplant
        - Radiation therapy
- Brentuximab vedotin treatment, 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 AESI (per Section 7.2 Procedures for Recording and Reporting SAEs and AESI) since start of current treatment regimen of brentuximab vedotin
- Concomitant medications

4.5.3 On-Treatment Follow-up

The following data will be recorded, where available, for all enrolled patients at each follow-up time point through 30 days after the last dose of brentuximab vedotin.:

- Visit date
- Current weight (kg)
- ECOG (if recorded)/Survival status
    - Date and cause of death, if applicable
- 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 treatment status
    - Brentuximab vedotin cycles
        - dose changes/discontinuations, change type, date (or duration) of change and reason for change
    - Any newly initiated lines of therapy
    - Radiation therapy

    - Stem cell transplant (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)
- Concomitant medications
- Relevant laboratory testing
- Occurrence of SAEs and both serious and non-serious AESI(per Section 7.2 Procedures for Recording and Reporting SAEs and AESI), since last follow-up

4.5.4 Post-Treatment Follow-up

The following data will be recorded, where available, in the post-treatment follow-up period:

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

4.5.5 Study Discontinuation

The following data will be recorded, where available, for all enrolled patients at the time of discontinuing the study:

- Date of discontinuation
- Reason for discontinuation
- Updated assessments as outlined in Table 1, which depend on whether the patient is in the On-Treatment Follow-up or Post-Treatment Follow-up period
- Survival status

5. STATISTICAL METHODS

5.1 Sample size

The sample size for this study was chosen to provide better evaluation of the both serious and non-serious AESI, given the size of the current safety database. Evaluation of the sample size for the study was performed based on the expected rate of AESI 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 2 shows the estimated 95% CIs for given frequencies of AESI from a study population of 500 patients which was calculated using an appropriate model for proportions, assuming a normal approximation to the binomial distribution. The targeted sample size of 500 (at least 50 of whom have a diagnosis of sALCL), provides an adequate level of precision to achieve the objectives of this study related to AESI, through estimating the proportion of patients with each individual AESI. The sample size of 500 includes the patients already being treated with brentuximab vedotin at the time of enrolment, the retrospective patients. It is assumed that approximately 15 to 20% (75 to 100 patients) of the study population will be retrospectively enrolled.

Table 2. Incidence Proportion and 95% Confidence Intervals for AESI

Proportion	Number of Events	95% Confidence Interval
0.00	0	(0.0%, 0.7%)
0.01	5	(0.0%, 2.0%)
0.02	10	(0.7%, 3.3%)
0.03	15	(1.4%, 4.6%)
0.04	20	(2.2%, 5.8%)
0.05	25	(3.0%, 7.0%)

5.2 Data Analyses

5.2.1 General Considerations

All SAEs and AESI (including both serious and non-serious AESI) verbatim terms will be recorded and coded using MedDRA. The severity of adverse events will be graded utilizing NCI CTCAE v4.03. All computations and generation of tables, listings and figures will be performed using SAS® version 9.2 or higher (SAS Institute, Cary, NC, USA). No formal hypothesis or statistical significance testing is planned. This approach follows the Guidelines for Good Pharmacoepidemiology Practices, Section D, point 10.

Details of the statistical analysis will be fully described in a written and approved statistical analysis plan (SAP). Descriptive analyses will be performed to gain an understanding of the qualitative and quantitative nature of the data collected and the characteristics of the sample studied. Descriptive statistics will be reported for all measured variables captured in this study. Summary statistics for continuous variables to be reported will include N, mean, median, standard deviation, 95% confidence interval (CI) and range. Skewed variables may be log-transformed or classed into quantiles of the distribution and analyzed as a categorical variable. Categorical variables will be reported using counts and proportions.

Analyses will be conducted on the entire enrolled population, including all patients exposed to brentuximab vedotin. In addition, analyses will be presented separately for patients prospectively and retrospectively enrolled to account for potential differences in the data reported, in particular the volume and nature of adverse events. Analyses by cohort will include disease history, ECOG performance status, and other background information to determine whether there are baseline differences between groups which could influence the safety results.
Because information collected is routinely recorded in medical records, it is expected that nearly all the data collected for the prospective cohort will also be available for the retrospective cohort. In addition, SAEs and the AESIs, in general, are events that should also be captured in patient records. However, to formally address the concern for completeness of

data for the retrospective cohort, where possible, the number and percentage of missing data items will also be tabulated and compared between the two cohorts.

Specific studies of brentuximab vedotin in elderly patients have not been conducted and clinical studies did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Therefore, where possible, relevant subgroup analyses will be performed by age group (i.e., < 65 years and ≥ 65 years). Where appropriate, subgroup analysis may also be performed according to the following variables of interest: sex, CD30+ lymphoma type, ALK positivity (sALCL patients), long term treatment (i.e., > 16 cycles) and post-ASCT status. Additional subgrouping may also be applied as described in the SAP.

5.2.2 Planned analyses

5.2.2.1 Primary analyses

Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESI)

SAEs and AESI (including both serious and non-serious AESI) will be summarized by MedDRA system organ class (SOC) and preferred term (PT). Frequency and incidence proportion for all SAEs and AESI (as defined in Section 4.4.1) will be reported for patients who received at least one dose of brentuximab vedotin while on study.

The incidence rate and the associated 95% CI will be reported for SAEs and AESI.

Time at risk of SAEs and AESI will correspond to current/recent treatment with brentuximab vedotin. Current/recent treatment will be defined as time between the dates of first and last dose plus 30 days. All other follow-up time accrued for the patient will be considered occurring during past treatment with brentuximab vedotin; events reported during the past treatment period will be presented separately.

In addition, select events will be displayed by timing in relation to treatment start (e.g., by number of completed cycles) or time-to-event analysis may be carried out using Kaplan-Meier plots for the occurrence of the first reported occurrence of the adverse event, as appropriate for the event.

Identification and Description of Risk Factors for Peripheral Neuropathy

In addition, multivariable adjusted analysis will be performed to identify and describe risk factors for peripheral neuropathy (e.g., BMI, previous history of neuropathy, known toxic exposures) in the cohort. Risk factors for the first occurrence of new onset or worsening of peripheral neuropathy will be explored using a multivariable adjusted Cox regression model. Model assumptions concerning proportionality will be evaluated graphically in the usual manner. The inclusion of specific risk factors will be described in the SAP. A preliminary univariate analysis of the association of variables of interest with the outcome measure will be

performed. For the multivariable Cox regression, the number of variables included will be based on the number of outcome events. If any data reduction is required to reduce the pool of variables under consideration, an iterative process for variable selection will be conducted. Variables deemed of a priori importance for inclusion in multivariate models may be identified in discussion with clinical subject matter experts in order to compile a full set of potential covariates for selection in multivariate modeling.

Effect of Dose Modification

All brentuximab vedotin dose modifications including dose delays, temporary interruptions and permanent interruptions, and reported reason for change(s) from the start of brentuximab treatment will be summarised. The resolution of SAEs and AESI that require dose modification (e.g., dose decrease, discontinuation) will be explored. In addition, the occurrence of SAEs or AESI in patients for whom treatment is interrupted, modified or delayed will be explored.

5.2.2.2 Exploratory analyses

Additional relevant analyses may be identified during the conduct of the study. Any additional exploratory analyses will be outlined in the SAP prior to analysis.

5.2.3 Missing data

Full details on handling of all missing data, which are common in observational studies, will be described separately in the SAP. The proportion of missing data will be reported for each measured variable in the study. In general, missing data will not be imputed and the data will be analysed as they are recorded in the study eCRFs.

5.2.4 Limitations

As with all observational studies, one of the greatest concerns for external validity is selection bias. In order to minimise this source of bias, broad inclusion and exclusion criteria are to be applied and it is expected that most, if not all, patients indicated for treatment according to the product labeling (refer to SmPC in Appendix 2) will be eligible for enrolment in the study. In addition, sites will be instructed to invite consecutive eligible patients initially being prescribed who are planned to start or have already started treatment with single agent brentuximab vedotin as part of routine clinical care. Sites will be expected to complete a screening log which will collect a limited amount of data (e.g., age range, lymphoma type, disease stage, reason for not participating) for non-enrolled patients newly prescribed brentuximab vedotin in order to understand through descriptive analysis the representativeness of the enrolled population.

The risk of developing some of the AESI 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 will be 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 will be limited by the availability of relevant medical history and exposure data across all patients.

Finally, 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, will be limited by the actual use of brentuximab vedotin in routine clinical care.

5.3 Data Reporting

5.3.1 Progress reports

Annual progress reports will be submitted to relevant competent authorities, as required.

5.3.2 Interim analyses and reporting

An interim analysis including both study objectives will be performed approximately 2.5 years after the first patient is enrolled.

5.3.3 Final analyses and reporting

A final study report will be generated after all data collection is complete. The final report will encompass all planned analyses, including a description of the complete study population, as described above and in the SAP. All reporting will be consistent with the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) Initiative checklist for cohort studies (STROBE 2008).

6. STUDY MANAGEMENT

This study will be performed by Quintiles (CRO), with guidance, input, review and approval of the Millennium project team, including development of materials, recruitment, training and management of sites, electronic data capture and data management and analysis. To ensure the quality and integrity of research, this study will be conducted under the Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, the principles outlined in the Declaration of Helsinki, and any applicable national guidelines.

6.1 Data entry/Electronic data capture

All data will be collected and entered directly into the electronic data capture (EDC) system. All sites will be 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 will be able to access their account with a username and password. All eCRFs should be completed by designated, trained personnel or the study coordinator, as appropriate. In most cases, the eCRF should be reviewed, electronically signed, and dated by the investigator. All changes or corrections to eCRFs should be documented in an audit trail and an adequate explanation is required. All participating sites will have access to the data entered by the individual site on their own enrolled patients through the EDC system.

6.2 Source documents

In most cases, the source documents are contained in the patient's medical record and data collected on the eCRFs must match the data in the medical records. In some cases, the eCRF, or part of the eCRF, may also serve as source documents. In these cases, a document should be available at the investigator's site and clearly identifying those data that will be recorded in the eCRF, and for which the eCRF will stand as the source document. All original source documentation is expected to be stored at the site for the longest possible time required by local applicable regulations. The site will be instructed to notify the Sponsor before any destruction of medical records of study participants.

6.3 File retention and archiving

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the investigator agrees to keep records, including the identity of all participating patients, all original signed informed consent forms, copies of all eCRFs, SAE forms, source documents and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to local regulations, or as specified in the study contract, whichever is longer.

Each site will receive a study site file at study initiation which contains all documents necessary for the conduct of the study and is updated throughout the study. This file must be available for review in the event the site is selected for monitoring, audits, or inspections and must be safely archived for at least two years after completing participation in the study. Documents to be archived include the patient enrolment log and the signed ICFs. In the event that archiving of the file is no longer possible at the site, the site will be instructed to notify the Sponsor.

6.4 Quality assurance and monitoring

A study monitoring plan, including for-cause monitoring, that is appropriate for the study design will be developed and implemented.

During the site initiation visit, the monitor will provide 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 will be monitored. Site monitoring will be performed by clinical research associates (CRAs) 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 may perform source data verification by review of original patient records.

The monitor will close out each site after the last patient's final follow-up assessment is completed, all data have been entered and all outstanding monitoring issues and data queries have been resolved or addressed. All monitoring procedures and frequency of monitoring visits will be described in a Monitoring Plan. Monitor contact details for each participating site will be maintained in the Investigator Site File.

Representatives of the Sponsor's quality assurance unit/monitoring team and competent regulatory authorities must be permitted to inspect all study-related documents and other materials at the site, including the Investigator Site File, the completed eCRFs and the patients' original medical records. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data.

6.5 Data management

A data management plan will be created before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning and validation. The eCRFs will include programmable edits to obtain immediate feedback if data are missing, out of range, illogical or potentially erroneous. Concurrent manual data review will be performed based on parameters dictated by the plan. Ad hoc queries will be generated within the EDC system and followed up for resolution.

High data quality standards will be maintained and processes and procedures utilised to repeatedly ensure that the data are as clean and accurate as possible when presented for analysis. Data quality will be enhanced through a series of programmed data quality checks that automatically detect out-of-range or anomalous data.

6.6 Changes to the protocol

Changes to the protocol will be documented in written protocol amendments. Major (i.e., substantial, significant) amendments will be approved by the relevant regulatory authorities and will usually require submission or notification to the relevant IECs for approval or favorable opinion, if applicable. In such cases, the amendment will be implemented at the site only after approval or favorable opinion has been obtained.

Minor (non-substantial) protocol amendments, including administrative changes, will be filed at each participating site and will be submitted to the relevant IEC or regulatory authorities

where required by pertinent regulations. Any amendment that could have an impact on the patient's agreement to participate in the study requires the patient's informed consent prior to continued participation in the study.

6.7 Publication policy

Any publication of the results from this study must be consistent with the Sponsor's publication policy and guided by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication of the International Committee of Medical Journal Editors (ICMJE), updated April 2010. The rights of the Investigator and of the Sponsor with regard to publication of the results of this study are described in the Investigator contract. Any submissions for publication will be consistent with the STROBE Initiative checklist for cohort studies (STROBE 2008).

7. SAFETY REPORTING

7.1 Definitions

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 unfavorable 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 jeopardize 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 (e.g., prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

Adverse events of special interest (AESI)

For the purposes of this study, the following treatment-emergent AEs are 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)

Event intensity

Intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE (Version 4.03 effective date 14 June 2010, or higher). Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is 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 is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and are usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does 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 will be determined by the investigator responding yes or no to this question: Is there a reasonable possibility that the event is associated with brentuximab vedotin? This means that there are facts (evidence) or arguments to suggest a causal relationship.

7.2 Procedures for Recording and Reporting SAEs and AESI

Table 3 Serious and Non-Serious Adverse Event Recording and Reporting

Time Point	Data Collected	Data Reported to Millennium PV&RM or designee
From first dose of brentuximab vedotin through 30 days after last dose of brentuximab vedotin	• SAEs • AESI	• SAEs • AESI considered related to brentuximab vedotin
From 31 days after last dose of brentuximab vedotin through the end of patient's participation in the study	• SAEs considered related to brentuximab vedotin • AESI considered related to brentuximab vedotin	• SAEs considered related to brentuximab vedotin • AESI considered related to brentuximab vedotin

7.2.1 Events to be recorded in the eCRF

All SAEs and both serious and non-serious AESI will be recorded in the eCRF, from the patient's first dose of brentuximab vedotin through 30 days after the patient's last dose of brentuximab vedotin. For retrospectively enrolled patients, this includes any SAEs or both serious and non-serious AESI identified in the medical record which occurred prior to study enrolment but after initiating the current regimen of brentuximab vedotin. From 31 days after the patient's last dose of brentuximab vedotin, only SAEs and both serious and non-serious AESI considered related to brentuximab vedotin will be recorded in the eCRF (see Table 3).

Documentation regarding an SAE or both serious and non-serious AESI, observed by the investigator or reported by the patient upon indirect questioning, should be 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 both serious and non-serious AESI , occur on several occasions in the same patient, then the event in question must be documented and assessed each time.

7.2.2 Events to be reported to Millennium Pharmacovigilance & Risk Management (PV&RM) or designee (in addition to being recorded in the eCRF)

All SAEs (regardless of relationship to brentuximab vedotin) and both serious and non-serious AESI considered related to brentuximab vedotin, occurring from the patient's first dose of brentuximab vedotin in the current regimen through 30 days after the patient's last dose of brentuximab vedotin, must also be reported to Millennium PV&RM or designee by faxing a completed SAE Form **within one business day after becoming aware of the event** (see Table 3). For retrospectively enrolled patients, this includes any SAEs (regardless of relationship to brentuximab vedotin) or AESI, both serious and non-serious, considered related to brentuximab vedotin identified in the medical record which occurred prior to study enrolment but after initiating the current regimen of brentuximab vedotin.

From 31 days after the administration of the patient's last dose of brentuximab vedotin and through the end of the patient's participation in the study, only SAEs considered related to brentuximab vedotin and AESI, both serious and non-serious, considered related to brentuximab vedotin should be reported to Millennium PV&RM or designee by faxing a completed SAE Form **within one business day after becoming aware of the event**.

The SAE Form, created specifically by Millennium, will be provided to each study site. SAEs reported to Millennium PV&RM or designee will be followed to resolution per standard SAE follow-up processes. Follow-up information on reported events may be requested by Millennium or designee. Information faxed to Millennium on a SAE Form must be consistent with the data recorded in the eCRF.

All completed SAE Forms should be faxed to:

For country-specific SAE Reporting Contact Information, please refer to Appendix 3

SAEs and both serious and non-serious AESI considered related to brentuximab vedotin a will be reported to local and regional health authorities by the sponsor, when appropriate, in accordance with applicable local and regional regulations. Compliance with any applicable site-specific requirements related to the reporting of SAEs or other safety information to the local IEC that approved the study will be maintained.

7.3 Procedures for Reporting Pregnancies

If a patient exposed to brentuximab vedotin becomes pregnant or suspects that she is pregnant while participating in this study, the investigator should be informed immediately. The sponsor must also be contacted immediately by faxing a completed Pregnancy Form to Millennium PV & RM or designee (for country-specific contact details, refer to Appendix 3). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient exposed to brentuximab vedotin becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately by faxing a completed Pregnancy Form to Millennium PV & RM or designee (for country-specific contact details, refer to Appendix 3). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

7.4 Procedures for Reporting Product Complaints and Medication Errors

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation associated with brentuximab vedotin should immediately contact MedComm Solutions (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium quality representative.

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. While overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error situation associated with brentuximab vedotin should immediately contact MedComm Solutions (see below) and report the event.

For Product Complaints or Medication Errors, call MedComm Solutions at 877-674-3784 (877 MPI DRUG)

Product complaints and medication errors in and of themselves are not AEs. If a product complaint or medication error is associated with an SAE or non-serious AE considered related to brentuximab vedotin identified during the patient's participation in the study, an SAE form should be completed and submitted, as described in Section 7.3.

8. ETHICAL AND REGULATORY CONSIDERATIONS

8.1 Guiding principles

The study will be conducted in compliance with all applicable legislation, and national regulations, directives and guidelines regarding the conduct of post-authorisation studies

(PASS), including Good Pharmacovigilance Practices (GVP) Module VIII – Post-marketing Authorisation Studies.

To ensure the quality and integrity of research, this study will be conducted under the Guidelines for Good Pharmacoepidemiology Practices (GPPs) issued by ISPE, the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, the Declaration of Helsinki and its amendments, and any applicable national guidelines. The final study protocol will be included in the ENCePP E-register of Studies prior to the start of data collection. The completed ENCePP Checklist for Study Protocols is included in Appendix 4.

8.2 Patient information and informed consent

An informed consent form (ICF) must be signed by the patient (or the patient's legally authorised representative) before his or her participation in the study. The medical file for each patient should document the informed consent process and that written informed consent was obtained prior to participation in the study. A copy of each signed ICF must be provided to the patient or the patient's legally authorised representative. If applicable, it will be provided in a certified translation of the local language. All signed and dated ICFs must remain in each patient's study file and must be available for verification by study monitors at any time.

The ICF should be revised whenever there are changes to procedures outlined in the informed consent or when new information becomes available that may affect the willingness of the patient to participate. For any updated or revised ICFs, the medical file for each patient should document the informed consent process and that written informed consent was obtained for the updated/revised ICF for continued participation in the study.

8.3 Patient confidentiality

In order to maintain patient confidentiality, each patient will be assigned a unique patient identifier upon study enrolment. This patient identifier will be used in place of patient name for the purpose of data analysis and reporting. Medical record number or other local reference identifiers are not collected as part of the database. All parties will ensure protection of patient personal data and will not include patient names on any study forms, reports, publications, or in any other disclosures, except where required by law. In accordance with local regulations in each of the included countries, patients will be informed about data handling procedures and asked for their consent. Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing patient data. Every effort will be made to protect participant confidentiality according to the Directive 95/46/EC on the protection of individuals, and in compliance with Safe Harbor privacy principles.

The database will be housed at Quintiles in a physically and logically secure computer system maintained by Quintiles in accordance with a written security policy. The system meets approved established standards for the security of health information and is validated. The system also meets the standards of the International Committee on Harmonisation (ICH) guideline E6R1 regarding electronic study data handling and is available for audit upon request. Patient confidentiality will be strictly maintained.

8.4 Ethics Committees

Consistent with local regulations and prior to enrolment of patients at a given site, the study protocol will be submitted together with its associated documents (e.g., ICF) to the responsible IEC for its review. Patient enrolment will not start at any site before the Sponsor has obtained written confirmation of a favorable opinion/approval from the relevant central or local IEC. The IEC will be asked to provide documentation of the date of the meeting at which the favorable opinion/approval was given that clearly identifies the study, the protocol version, and the ICF version reviewed.

Before implementation of any substantial changes to the protocol, protocol amendments will also be submitted to the relevant IEC in a manner consistent with local regulations. Pertinent safety information will be submitted to the relevant IECs during the course of the study in accordance with local regulations and requirements. It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents, if applicable, from their local IEC and provide documentation of approval to Quintiles . All correspondence with the IEC should be retained in the Investigator File.

Should the study be terminated early for any unanticipated reason, the investigator will be responsible for informing the IEC of the early termination.

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10. APPENDICES

Appendix 1 ECOG Performance Status

The ECOG Performance Status instrument is a widely accepted and used method based on a 5-point scale for assessing the functional status of patients with cancer and their ability to maintain self-care [Oken 1982, Buccheri 1996].

Grade	Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix 2 Brentuximab vedotin SmPC

The SmPC will be provided to sites for their reference.

Appendix 3 SAE, AESI considered related to brentuximab vedotin and Pregnancy Reporting Contact Information

To be provided to sites according to country.

Appendix 4 ENCePP Checklist for Study Protocols

ENCePP Checklist for Study Protocols (Revision 1)

Adopted by the ENCePP Steering Group on 19/08/2011

Section 1: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the formulation of the research question clearly explain:				
1.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	14
1.1.2 The objectives of the study?	☒	☐	☐	14
1.2 Does the formulation of the research question specify:				
1.2.1 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	15,16
1.2.2 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
1.2.3 if applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 2: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Is the source population described?	☒	☐	☐	15,16
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	☒	☐	☐	15
2.2.2 Age and sex?	☒	☐	☐	15-16
2.2.3 Country of origin?	☒	☐	☐	15-16
2.2.4 Disease/indication?	☒	☐	☐	15-16
2.2.5 Co-morbidity?	☐	☐	☒	
2.2.6 Seasonality?	☐	☐	☒	
2.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	16

Comments:

Due to the rareness of the condition, the study population is based on the expected size and availability of the total source population following approval.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	17,18

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.2 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	15,16
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	22,23
3.4 Is sample size considered?	☒	☐	☐	21,22
3.5 Is statistical power calculated?	☐	☐	☒	See comment

Comments:

Formal statistical power calculations were not performed; sample size considerations were based on the precision around the point estimates for relevant safety outcomes, consistent with the study design.

Section 4: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
4.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc)	☒	☐	☐	17
4.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self report, patient interview including scales and questionnaires, vital statistics, etc)	☒	☐	☐	18-20
4.1.3 Covariates?	☒	☐	☐	18-20
4.2 Does the protocol describe the information available from the data source(s) on:				
4.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	17-20
4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	17-20
4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	17-20
4.3 Is the coding system described for:				
4.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	☒	
4.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	☒	☐	☐	21
4.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☒	
4.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	See comment

Comments:

No linkage of data sources is planned.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	17
5.2 Does the protocol discuss the validity of exposure measurement?				

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
(e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	17
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	18,22
5.4 Is exposure classified based on biological mechanism of action?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☒	☐	☐	17,22

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	28-32
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	

Comments:

Section 7: Biases and Effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address:				
7.1.1 Selection biases?	☒	☐	☐	23
7.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	23
7.2 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	22, 23
7.3 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	
7.4 Does the protocol address other limitations?	☒	☐	☐	23

Comments:

Section 8: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the plan include measurement of absolute effects?	☒	☐	☐	22, 23
8.2 Is the choice of statistical techniques described?	☒	☐	☐	22, 23
8.3 Are descriptive analyses included?	☒	☐	☐	22, 23
8.4 Are stratified analyses included?	☒	☐	☐	22, 23
8.5 Does the plan describe the methods for identifying:				

Section 8: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
8.5.1 Confounders?	☒	☐	☐	22
8.5.2 Effect modifiers?	☐	☐	☒	
8.6 Does the plan describe how the analysis will address:				
8.6.1 Confounding?	☒	☐	☐	22
8.6.2 Effect modification?	☐	☐	☒	

Comments:

Section 9: Quality assurance, feasibility and reporting	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	24
9.2 Are methods of quality assurance described?	☒	☐	☐	25
9.3 Does the protocol describe quality issues related to the data source(s)?	☒	☐	☐	24, 25
9.4 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	15, 16
9.5 Does the protocol specify timelines for				
9.5.1 Study start?	☒	☐	☐	10
9.5.2 Study progress? (e.g. end of data collection, other milestones)	☒	☐	☐	10
9.5.3 Study completion?	☒	☐	☐	10
9.5.4 Reporting? (i.e. interim reports, final study report)	☒	☐	☐	10
9.6 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	9, 26
9.7 Are communication methods to disseminate results described?	☒	☐	☐	26, 27
9.8 Is there a system in place for independent review of study results?	☒	☐	☐	See comment

Comments:

As a post-authorisation safety study (PASS), the study is intended for submission to regulatory authorities, who will independently review the study results.

Section 10: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	31-33
10.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	33
10.3 Have data protection requirements been described?	☒	☐	☐	32

Comments:
