EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 July 2012
EMA/702390/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Adcetris

International non-proprietary name: **brentuximab vedotin**

Procedure No. **EMEA/H/C/002455**

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Product information

Name of the medicinal product:	Adcetris
Applicant:	Takeda Global Research and Development Centre (Europe) Ltd. 61 Aldwych London WC2B 4AE United Kingdom
Active substance:	brentuximab vedotin
International Nonproprietary Name/Common Name:	brentuximab vedotin
Pharmaco-therapeutic group (ATC Code):	Monoclonal antibodies (L01XC12)
Therapeutic indication(s):	ADCETRIS is indicated for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL): 1. following autologous stem cell transplant (ASCT) or 2. following at least two prior therapies when ASCT or multi-agent chemotherpay are not a treatment option ADCETRIS is indicated for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).
Pharmaceutical form(s):	Powder for concentrate for solution for infusion
Strength(s):	50 mg
Route(s) of administration:	Intravenous use
Packaging:	vial (glass)
Package size(s):	1 vial

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List of abbreviations

A280	Absorbance at 280 nm
ABVD	doxorubicin, bleomycin, vinblastine, dacarbazine
ADC	Antibody-Drug Conjugate
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
ALCL	anaplastic large cell lymphoma
ALT/SGTP	alanine transaminase
alloSCT	allogeneic stem cell transplant
ALK	anaplastic lymphoma kinase
ASCT	autologous stem cell transplant
ASM-free	Animal Source Material-Free
AST	Aspartate Aminotransferase
ATA	antitherapeutic antibodies
AUC	area under the concentration-versus-time curve
BDS	Bulk Drug Substance
BCNU	carmustine
BCRP	breast cancer resistance protein
BEACOPP	bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone
BSA	body surface area
BSC	best supportive care
cAC10	Anti-CD30 Antibody
CALGB	Cancer and Leukemia Group B
CD	Circular Dichroism
CDC	complement-dependent cytotoxicity
CE-SDS	Capillary Electrophoresis-SDS
CEX	Cation Exchange Chromatography
CFU	Colony Forming Unit
cGMP	Current Good Manufacturing Practice
CE-LIF	Capillary Electrophoresis with Laser-Induce Fluorescence
CHEF	Chinese Hamster Elongation Factor
CHO	Chinese Hamster Ovary
CHOP	cyclophosphamide, doxorubicin (hydroxydaunorubicin), vincristine (Oncovin®), prednisone
CI	confidence interval
CL	clearance
Cmax	maximum concentration
CMPI	2-Chloro-1-Methyl Pyridinium Iodide
CMV	cytomegalovirus
CNS	central nervous system
CR	complete remission
CRu	unconfirmed complete remission
CSR	clinical study report
CT	computed tomography
CTCAE	Common terminology criteria for adverse events
CTCL	cutaneous T cell lymphoma
CV	coefficient of variance
CYP	cytochrome P450
Da	Dalton
DCHA	Dicyclohexylamine
DDI	Drug drug interaction
DHAOx	dexamethasone, high-dose cytarabine, and oxaliplatin
DHFR	Dihydrofolate Reductase
DIPEA	N,N-Diisopropylethylamine
DLT	Dose limiting toxicity
DMSO	Dimethyl Sulphoxide
DO	Dissolved Oxygen

DoR	duration of response
DP	Drug Product
DS	drug substance
DSC	Differential Scanning Calorimetry
dSEC	Denaturing Size Exclusion Chromatography
DTNB	5,5"-dithiobis-(2-nitrobenzoic acid)
DTT	Dithiothreitol
EBV	Epstein-Barr virus
ECG	electrocardiogram
ECL	electro-chemiluminescent
ECOG	Eastern Cooperative Oncology Group
EdU	5-ethynyl-2′-deoxyuridine
EDTA	Ethylenediaminetetraacetic Acid
EFS	event free survival
ELISA	Enzyme Linked Immunoadsorbent Assay
EOT	end of treatment
EPOCH	etoposide, vincristine, and doxorubicin
ESHAP	etoposide, cisplatin, cytarabine, prednisone
ESMO	European Society for Medical Oncology
EtOAc	Ethyl Acetate
Et2O	Ethyl Ether Refined (Diethyl Ether)
EU	Endotoxin Units
Fab	antigen-binding fragment
Fc	heavy chain constant
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FIO	For Information Only
FMOC-MeVal-OH	Nα-(9-Fluorenylmethyloxycarbonyl)-N-Methyl-L-Valine
FTIR	Fourier Transform Infra Red Spectroscopy
GGT	Gamma Glutamyltransferase
GI	gastrointestinal
GLP	Good Laboratory Practice
GM-CSF	granulocyte macrophages colony stimulating factory
GMP	Good Manufacturing Practice
GMR	geometric mean ratio
GVD	gemcitabine, vinorelbine, and pegylated liposomal doxorubicin
HAP	Hamster Antibody Production
HC	Heavy Chain
HCl	Hydrochloric Acid
HDPE	High Density Polyethylene
HEK	human embryonic kidney
HEPA	High Efficiency Particulate Absorbing
hERG	human ether à-go-go related gene
HIC	Hydrophobic Interaction Chromotography
HL	Hodgkin lymphoma
HMW	High Molecular Weight
HNST / HNSTD	Highest Non-Severely Toxic Dose
HPLC	high-performance liquid chromatography
HR	hazard ratio
HRP	Horseradish Peroxidase
HRS	Hodgkin Reed-Stenberg
HPS	High Potency Substances
IAA	Iodoacetic Acid
IC50	concentration producing 50% inhibition
ICE	ifosfamide, carboplatin, etoposide
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEF	Isoelectric Focusing
IEX	Ion Exchange Chromatography
Ig	immunoglobulin

IGEV	ifosfamide, gemcitabine, vinorelbine
IP	intraperitoneal(ly)
IPC	In Process Control
IRF	independent review facility
IRR	infusion-related reaction
ISO	International Organisation for Standardisation
ITT	intention-to-treat
IU	International Units
IV	Intravenous
JP	Japanese Pharmacopoeia
kD	Kilo Dalton
KD	dissociation constant
kg	Kilogramme
KF	Karl Fischer
Ki	inhibition constant
Kinact	rate constant of irreversible inactivation
Km	Michaelis constant
kV	Kilovolt
Lamp-1	lysosome-associated membrane protein 1
LAL	Limulus Amebocyte Kinetic Quantitative Chromogenic Lysate
LC	Light Chain
LC/MS	Liquid Chromatography/Mass Spectrometry
LLOQ	lower limit of quantitation
LMW	Low Molecular Weight
LRF	Log Reduction Factor
LSC	liquid scintillation counting
Mab	Monoclonal Antibody
MAP	Mouse Antibody Production
MedDRA	Medical Dictionary for Regulatory Activities
MCB	Master Cell Bank
MIC	metabolite inhibitory complex
MMAE	Monomethyl Auristan E
MMV	Murine Minute Virus
mOsm	Milliosmole
MR	Molar Ratio
MRD	Drug to Antibody Molar Ratio
MRI	magnetic resonance imaging
MRP2	multidrug resistance protein 2
MS/MS	Tandem Mass Spectrometry
MTD	maximum tolerated dose
MTX	Methotrexate
MTBE	Methyl-t-Butyl Ether
MW	Molecular Weight
N/A	Not applicable
NADPH	nicotinamide adenine dinucleotide phosphate
NANA	N-Acetylneuraminic Acid
NCCN	National Comprehensive Cancer Network, Inc.
NCI CTCAE	National Cancer Institute Common Terminology Criteria for
AE	Adverse Events
NE	not estimable
NF	United States National Formulary
NG-H	Non-glycosylated Heavy Chain
NHL	non-Hodgkin lymphoma
NK	natural killer
NMR	Nuclear magnetic resonance
NOAEL	No Observable Adverse Effect Level
NT	Not Tested
NYHA	New York Heart Association
OATP	organic anion transporting polypeptide
OR	objective response
ORR	objective response rate

OS	overall survival
PABC	p-aminobenzylcarbamate
PAGE	Polyacrylamide Gel Electrophoresis
PAHA	primate antihuman antibodies
PBMC	peripheral blood mononuclear cell
PCR	Polymerase Chain Reaction
PD	progressive disease
PDCB	Process Development Cell Bank
PDCO	Paediatric Committee
PET	positron emission tomography
PETG	Polyethylene Terephthalate Copolyester Glycol
PFMP	Pierre Fabre Medicament Production
PFS	progression-free survival
P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopoeia
pI	Isoelectric Point
PIP	paediatric investigation plan
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PN	peripheral neuropathy
PPCB	Post Production Cell Bank
ppm	Parts per Million
PR	partial remission
PTCL	peripheral T-cell lymphoma
PTSA	p-Toluenesulphonic Acid Monohydrate
q4d	every 4 days
QC	Quality Control
QTc	corrected QT interval
QTcF	Fridericia's corrected QT interval
RAHA	rat antihuman antibodies
RBC	red blood cell
Reo-3	Reovirus Type 3
RH	Relative Humidity
RMP	Risk Management plan
RNA	ribonucleic acid
RP-HPLC	Reverse Phase-High Performance Liquid Chromatography
RT	Reverse Transcriptase
sALCL	systemic anaplastic large cell lymphoma
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SCT	stem cell transplant
SCID	severe combined immunodeficient
SDS-PAGE	Sodium Dodecyl Sulphate Polyacrylamide Gel Electrophoresis
SGEN	Seattle Genetics, Inc.
SEC	Size Exclusion Chromatography
SEC-LS	Size Exclusion Chromatography Light Scattering
SEM	standard error of the mean
SGD-1010	= MMAE
SGN-30	= cAC10
SGN-35	Immunoconjugate of cAC10 and the drug-linker SGD-1006
SMQ	Standardised MedDRA Query
SOC	system organ class
SPD	sum of products of diameters of up to 6 of the largest dominant nodes or nodal masses
t1/2	half-life
TAb	total antibody
TBTU	2-(1H-Benzotriazol-1-yl)-1,1,3,3-Tetramethyluronium Tetrafluoroborate□
TCEP	Tris(carboxyethyl)phosphine

TDAR	T cell-dependent antibody response
TEAE	treatment-emergent adverse event
TEM	Transmission Electron Microscopy
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIC	Total Ion Chromatogram
TK	toxicokinetic(s)
TLC	Thin-Layer Chromatography
TLS	tumor lysis syndrome
Tm	Thermal Transitions
Tmax	time to maximum concentration
TSE	Transmissable Spongiform Encephalopathy
TTP	time to progression
UF/DF	Ultrafiltration/Diafiltration
ULN	upper limit of normal
ULOQ	upper limit of quantitation
URTI	upper respiratory tract infection
USP	United States Pharmacopoeia
UV 280	Ultraviolet Absorbance Spectroscopy at 280 nm
V	volume of distribution
vc	valine-citrulline
Vd	Volume of Distribution
VH	Antibody Heavy Chain Variable Region
VL	Antibody Light Chain Variable Region
Vss	volume of distribution at steady-state
v/v	Volume per volume
w/v	Weight per volume
w/w	Weight per weight
WCB	Working Cell Bank
WFI	Water For Injection
X-MuLV	Xenotropic Murine Leukaemia Virus
Z-Val-OH	N-Carbobenzyloxy-L-Valine

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Takeda Global Research and Development Centre (Europe) Ltd. submitted on 31 May 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Adcetris, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the CHMP on 24 November 2010.

Adcetris was designated as an orphan medicinal product (EU/3/08/596 and EU/3/08/595) on 15 January 2009. Adcetris was designated as an orphan medicinal product in the following indications: Treatment of Hodgkin lymphoma (EU/3/08/596) and Treatment of Anaplastic Large Cell Lymphoma (EU/3/08/595).

The applicant applied for the following indications:

Adcetris is indicated for the treatment of patients with relapsed or refractory Hodgkin lymphoma (HL) and for the treatment of patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).

The legal basis for this application refers to:

A - Centralised / Article 8(3) / New active substance.

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/59/2011) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP (P/59/2011) was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance brentuximab vedotin, contained in the above medicinal product, to be considered as a new active substance in itself.

Protocol Assistance

The applicant received Protocol Assistance from the CHMP on 23 July 2009 and 20 May 2010. The Protocol Assistance pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

Adcetris has been given a Marketing Authorisation in the USA on 19 August 2011.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **Pieter de Graeff** Co-Rapporteur: **Jan Müller-Berghaus**

- The application was received by the EMA on 31 May 2011.
- The procedure started on 22 June 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 September 2011. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 12 September 2011.
- During the meeting on 20 October 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 21 October 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 11 January 2012.
- The summary report of the inspection carried out at the following sites Dr. Rosenblatt Miami Florida, USA), Dr. Bartlett (St. Louis, USA) and Seattle Genetics (Bothell, USA) between 26-28 September 2011, 19-21 October 2011, 24-28 October 2011 respectivelo was issued on 1 February 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 28 February 2012.
- During the CHMP meeting on 15 March 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 20 April 2012.
- During a meeting of a SAG-Oncology on 7 May 2012, experts were convened to address questions raised by the CHMP.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 12 May 2012.
- During the CHMP meeting on 22 May 2012, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the CHMP meeting on 24 May 2012, the CHMP agreed on a 2nd list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 18 June 2012.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the 2nd List of Outstanding Issues to all CHMP members on 3 July 2012.
- During the meeting on 19 July 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a conditional Marketing Authorisation to Adcetris on 19 July 2012.

2. Scientific discussion

2.1. Introduction

Hodgkin lymphoma (HL) is a neoplasm arising from germinal or post germinal B cells. In Europe there were 2.40 newly diagnosed cases of classical HL per 100,000 in 2000-2002 (Sant *et al*, 2010). HL is characterised histologically by malignant Hodgkin and Reed Sternberg cells that are surrounded by non-malignant inflammatory cells. HL is divided in two major subtypes, based on immunohistological features and microscopic appearance of the malignant cells. The nodular lymphocyte predominant subtype (NLPHL) makes up 5% of all HL and has a generally more indolent course than classical Hodgkin lymphoma (cHL). Most but not all NLPHL are CD30 negative, whereas CD30 expression is a standard feature of RS cells in cHL. NLPHL expresses CD45 and CD20, whereas cHL is typically CD45 negative and CD20 negative in 60-80% of cases.

Classical Hodgkin lymphoma has four subtypes. The most common subtype is the nodular sclerosis subtype: 40-70%. The mixed cellularity subtype makes up 30-50% of cHL and possibly has a less favourable clinical course. The lymphocyte depletion subtype is rare and can be associated with AIDS. The lymphocyte rich subtype has been distinguished from NLPHL since 1999. It differs from NLPHL in that it is CD30+, CD20- and it has a higher relapse rate.

HL is highly curable, with 80% of patients reaching complete remission. Prognosis is worse in patients who present with advanced disease, with 30-40% relapse after initial treatment or immediate treatment failure. Staging is according to the Ann Arbor criteria, which are based on localisation, the extent of nodal and extranodal involvement and the presence of the classical B symptoms.

Standard first line treatment for limited stage disease consists of the ABVD combination chemotherapy regimen, followed by involved field radiotherapy. There is no consensus on the optimum treatment for advanced stage disease, with different approaches in the U.S. and Europe. Different combination chemotherapy regimens such as ABVD, BEACOPP and Stanford V have been compared. The role of radiotherapy and intermediate staging by FDG-PET are also currently evaluated.

There is no standard treatment of relapsed or primary refractory disease. Salvage chemotherapy regimens such as DHAP/VIM/DHAP are usually followed by high dose chemotherapy and autologous stem cell transplantation. Patients, who are not cured with front-line or second-line therapy, including stem cell transplantation, have an estimated median survival of less than 3 years. Gains are limited to disease free survival, but usually no overall survival gains are achieved (Horning *et al*, 2008).

Anaplastic large cell lymphoma (ALCL) is an aggressive non-Hodgkin lymphoma of T-cell origin. There are two distinct forms, systemic ALCL and a primarily cutaneous form. ALCL accounts for 2-8% of all T-cell lymphomas. CD30 is invariably expressed on the surface of ALCL cells.

The clinical course is to a large extent dependent on ALK status. ALK positive patients are younger and have a better prognosis. Five year failure free survival after treatment was 60% in ALK positive compared to 36% in ALK negative ALCL and five year overall survival rate was 70% in ALK positive and 49% in ALK negative ALCL (Savage et al. Blood (2008) 111: 5496). Other independent prognostic factors include absence of marrow involvement and expression of CD56.

In adults treatment with doxorubicin based regimens results in complete response in 70% and a 60% five year survival rate. Comparison of ABVD and MACOP-B showed comparable efficacy for these two regimens. About half of the patients relapse within two years (Tilly *et al*, 1997; Savage *et al*, 2008).

There is no consensus on the treatment of relapsed or refractory disease. Some patients benefited from high dose chemotherapy and autologous stem cell transplant. There have been reports of a graft versus ALCL effect after allogeneic stem cell transplantation.

Adcetris contains brentuximab vedotin (also known as SGN-35), which is a CD30-directed antibody-drug conjugate (ADC) composed of the monoclonal antibody (cAC10) covalently linked, via an enzyme-cleavable linker, to the antimitotic small molecule monomethyl auristatin E (MMAE). It is produced via the chemical conjugation of cAC10 to the small molecule SGD-1006 intermediate (SGD-1006), which contains both the linker and the MMAE. Brentuximab vedotin and consists of on average four molecules of monomethyl auristatin E (MMAE) conjugated to the cAC10 monoclonal antibody. After binding to surface CD30 the conjugate undergoes endocytosis. MMAE becomes active after the linker between MMAE and the antibody is cleaved by the lysosome. MMAE interferes with tubulin polymerisation and thus disrupts formation of the mitotic spindle in dividing cells. The ensuing mitotic arrest eventually leads to cell death.

CD30 is a member of the tumour-necrosis factor receptor superfamily. It was originally identified on Reed-Sternberg cells of Hodgkin Lymphoma (CD30 positive Hodgkin or Reed Sternberg cells express 5,000 – 10,000 molecules of CD30) but is also expressed on subsets of non-Hodgkin-Lymphoma, including anaplastic large cell lymphoma and cutaneous T cell lymphoma as well as on rare solid tumours such as testicular carcinomas of the non-germinal type (embryonal carcinomas). In non-malignant cells, CD30 is expressed on activated but not resting lymphocytes (T, B and NK cells) and weakly on activated monocytes. After binding to its ligand CD153, CD30 can activate NF-κB, JNK and p38. Furthermore, CD30 is expressed in decidual cells in the pregnant uterus. However, information on the function of CD30 in the immune system or during pregnancy is lacking.

The applicant applied for the following indication: Adcetris is indicated for the treatment of patients with relapsed or refractory Hodgkin lymphoma (HL) and for the treatment of patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).

The finally approved indication is the following: Adcetris is indicated for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL): following autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option. Adcetris is indicated for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).

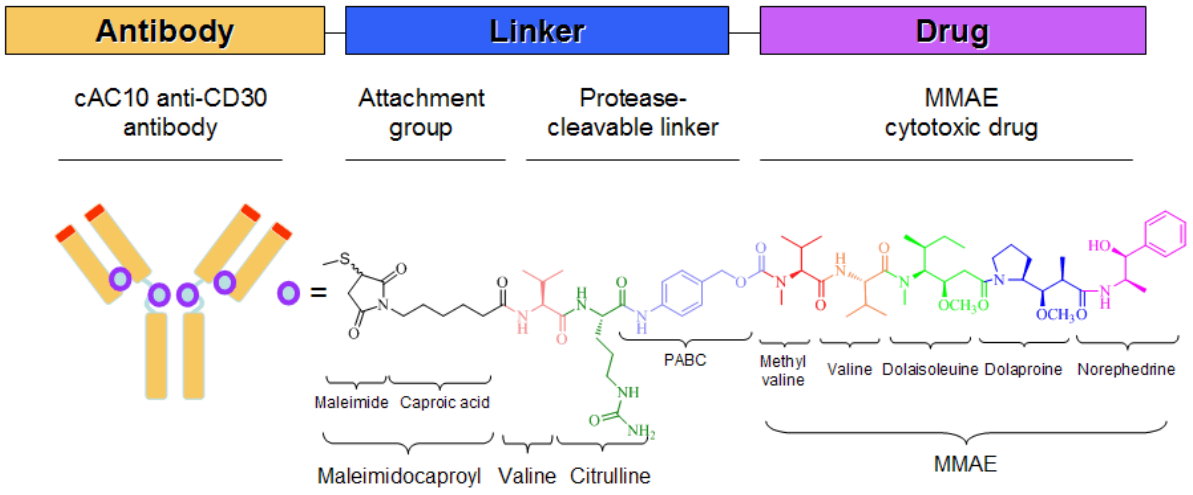
The recommended dose is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks.

2.2. Quality aspects

2.2.1. Introduction

Brentuximab vedotin (SGN-35) is an antibody-drug conjugate consisting of three components: A) the antibody cAC10, specific for human CD30, B) the highly potent antimicrotubule agent monomethylauristatin E (MMAE), and C) a protease cleavable linker that covalently attaches MMAE to cAC10.

Figure 1: Schematic Diagram of SGN-35



Binding of SGN-35 to CD30 on the cell surface initiates internalization of the SGN-35-CD30 complex, which then traffics to the lysosomal compartment. Within the cell, MMAE is released from the monoclonal antibody via proteolytic cleavage and degradation of the drug linker. Binding of MMAE to tubulin disrupts the microtubule network within the cell, induces mitotic cell cycle arrest, and results in apoptotic death of the CD30-expressing tumor cell.

SGN-35 was also tested for effector function activity. In vitro assays demonstrated no complement dependent cytotoxicity (CDC) and little antibody-dependent cell-mediated cytotoxicity (ADCC).

2.2.2. Active Substance

Brentuximab vedotin (SGN-35) is a CD30-directed antibody-drug conjugate (ADC) composed of the monoclonal antibody (cAC10) covalently linked, via an enzyme-cleavable linker, to the antimitotic small molecule monomethyl auristatin E (MMAE). It is produced via the chemical conjugation of the cAC10 Intermediate (cAC10) to the small molecule SGD-1006 Intermediate (SGD-1006), which contains both the linker and the MMAE.

The amino acid sequences of SGN-35 heavy and light chains as well as the post-translational modifications associated with each are the same as those described in cAC10. Each antibody molecule has, on average, two of its interchain disulfides reduced and the resulting cysteine residues alkylated with SGD-1006, leading to a molar ratio (MR_D) of four drugs per antibody. This leaves, on average, two interchain disulfides per molecule intact. One drug conjugation site is located in the light chain and three conjugation sites are located in the heavy chain, resulting in many active forms with up to eight possible conjugation sites per antibody.

cAC10 Monoclonal Antibody Active Substance Intermediate

Manufacture

cAC10 is a recombinant heterotetrameric chimeric IgG1 with two kappa light chains and two gamma 1 heavy chains. The expected average molar mass is 148,081 Da.

cAC10 is manufactured according to a conventional cell culture system using a Chinese Hamster Ovary (CHO) cell line. The chimeric antibody product cAC10 is expressed from the fusion of the heavy and light chain variable region genes (VH and VL, respectively) from the murine anti-CD30 monoclonal antibody (mAb) AC-10 to the human immunoglobulin gamma 1 (G1) and kappa (κ) constant region genes, respectively.

This recombinant antibody is encoded in expression plasmids and is expressed by CHO cells stably transfected with these plasmids. The description of generation of expression vectors is detailed and sufficient. Subsequent subcloning by limiting dilution produced a cell line with relatively high specific productivity, good growth characteristics, and desired product quality, and was used to produce the process development seed bank (PDSB), from which the cGMP master cell bank (MCB) and working cell bank (WCB) were derived. Testing and characterization of the Host Cell Bank (i.e. CHO cells) were performed in accordance with ICH Q5A, Q5B, and Q5D. The procedure for the generation and qualification of WCB has been provided.

The cAC10 Intermediate manufacturing process is separated into six stages: 1. inoculum expansion, 2. production, 3. primary recovery and capture, 4. fine purification, 5. final bottling, and 6. shipping.

The manufacturing for cAC10 is initiated by thawing a vial of the WCB containing CHO cells expressing the monoclonal antibody cAC10. After thaw, cells are serially expanded in vessels of increasing size until the production bioreactor where cells and cAC10 accumulate. After the production stage, cells and cell debris are removed from the harvest fluid. The product is purified via three chromatography steps. This is followed by a nanofiltration step to remove any potential adventitious viral agents. The pool is then concentrated and buffer exchanged into the formulation buffer via an ultrafiltration/diafiltration step. The purified and formulated cAC10 bulk is filtered, filled into bottles and stored frozen. Frozen cAC10 is shipped according to a validated process and stored frozen until further processing to brentuximab vedotin (SGN-35) bulk drug substance.

Three consecutive manufacturing batches were executed under process validation to demonstrate process consistency in cell culture, primary recovery and capture, and fine purification. During the cAC10 conformance manufacturing campaign, several other validation studies were also conducted in parallel to process validation. The capability of the downstream process steps to reduce process-related impurities was evaluated in an impurity clearance validation study, which sufficiently guarantees adequate removal and consistent low levels.

cAC10 is a recombinant heterotetrameric chimeric IgG1 with two kappa light chains and two gamma 1 heavy chains. The structure, physicochemical characteristics, and immunological and biological properties of cAC10 have been established using a comprehensive set of methods. The expected average molar mass (148,081 Da) was confirmed. The N-terminal residue of the heavy chain is encoded as a glutamine, but exists mainly in the pyroglutamic acid form. There is one N-glycosylation site on the heavy chain (Asn297), and it is predominantly occupied with a typical core fucosylated biantennary glycan with 0, 1 or 2 terminal galactose residues. Additionally, the encoded C-terminal lysine of the heavy chain is post-translationally removed in the most prevalent form of cAC10. These properties are as expected for a chimeric IgG1 produced via a CHO cell culture process.

Specification

The release specifications for cAC10 intermediate include tests for Identity, Purity, Potency, Content, Safety and Physical Characteristics, such as IEF, ELISA, peptide mapping, CE SDS, SEC, CE LIF, UV spec, bioburden, endotoxin, polysorbate 80, pH, osmolality and appearance. Satisfactory validation of the analytical procedures has been performed in accordance with current ICH guidelines. The specifications have been established based on principles outlined in ICH Q6B and overall cover the structural features of the molecule.

Batch analysis data from twelve GMP batches (eight development batches, three conformance batches and one post-conformance batch) are provided. The release results for batches manufactured using Process A&B, Process C and for the conformance batches demonstrate that the manufacturing process is well controlled. In addition, the data demonstrates that each of the manufacturing processes consistently produces cAC10 with similar quality attributes.

The commercial reference material, derived from a liquid fill of cAC10 lot manufactured using the commercial process, (Process C), was qualified by release testing using analytical procedures appropriate at the time of qualification and extensive characterization.

A sterile polyethylene terephthalate glycol (PETG) media bottle with white high density polyethylene (HDPE) screw closure is used as the container closure system for cAC10 Intermediate.

Stability

Overall, the stability data obtained from stability testing of 3 primary stability lots, 3 conformance lots, and 3 supporting stability lots support the cAC10 expiration dating of 60 months when stored at the designated storage condition in the commercial container closure system. The proposed cAC10 shelf-life of 60 months, when stored at the designated storage condition in the commercial container closure system, is acceptable.

Protease Cleavable Linker - MMAE (SGD-1006) Intermediate

Manufacture

SGD-1006 Intermediate (SGD-1006) is the drug-linker component of the SGN-35. The final SGD-1006 Intermediate is packaged in amber glass bottles, and stored frozen. Following release, it is shipped using validated procedures to storage facilities and/or other manufacturer for further processing into SGN-35 BDS.

In general, the chemistry, production, and quality control of SGD-1006 have been described in sufficient detail in the dossier. Process validation has demonstrated that the manufacturing process is consistent, reliable, and repeatable.

The characterisation of SGD-1006 has been established by state-of the-art analytical methods. Purity is the most important parameter of this intermediate as it influences the final product quality and potency.

Specification

The release specifications for SGD-1006 intermediate include tests for physical characteristics, Identity, Purity, Related substances, Assay, Water content, Residual solvent, and Impurities such as appearance, FTIR, HPLC, Specific rotation, Karl Fischer titration, GC and ICPMS. Satisfactory validation of the analytical procedures has been performed in accordance with current ICH guidelines.

Stability

The stability data obtained from testing of primary stability lots, demonstrate that SGD-1006 when stored at specified conditions shows no degradation and no changes in other quality attributes for at least 24 months. A labelled storage condition with a retest period of 24 months is accepted for SGD-1006 Intermediate.

Brentuximab vedotin (SGN-35) active substance

Manufacture

The SGN-35 BDS manufacturing process is initiated by thawing, pooling, and filtering cAC10 solution into the reaction vessel. cAC10 interchain disulfide bonds are reduced by addition of the reducing agent tris(carboxyethyl)phosphine hydrochloride (TCEP HCl). SGD-1006 is then added, in excess, to react with the cAC10 thiols and form the ADC. Removal of process-related impurities and a citrate buffer exchange is accomplished by the tangential flow filtration step. The formulated bulk is filtered and filled into bottles to obtain the SGN-35 BDS. The individual bottles of BDS are frozen and stored. The frozen BDS is subsequently shipped to a storage facility.

Incoming materials are cAC10 and SGD-1006 which are manufactured and released as stable intermediates. At the end of processing, these intermediates are referred to as “cAC10 Intermediate” and “SGD-1006 Intermediate”, respectively.

Control of critical steps and intermediate

The Applicant performed extensive process characterization studies, together with process validation. The studies serve to demonstrate that the process is robust provided that it is performed within well-defined ranges. cAC10 and SGD-1006 are critical intermediates in the manufacture of SGN-35 BDS. Due to the importance of these intermediates, complete active substance sections are provided for cAC10 and SGD-1006.

The Applicant has used some elements taken from ICH Q8, however, the dossier is not a Quality-by-Design submission, therefore it might be called an ‘improved traditional approach’, or a ‘partially enhanced approach’.
During the evaluation procedure a Major Objection was raised with regard to the control strategy for cAC10 and SGN-35, and in particular the way in which Critical Process Parameters (CPPs) and In-Process Controls (IPCs) were defined for the manufacturing process of cAC10 and SGN-35, based on process characterization and validation data was not deemed adequate. During the review, the Applicant provided clarification and justification for its approach, reclassified some Process Parameters (PPs) into CPPs, a number of Normal Operating Ranges (NORs) have been given new limits and additional justification for the IPCs was provided.

This approach sufficiently assures that the manufacturing process is under control, that deviations will be handled in an appropriate manner, and that the process is able to manufacture a consistent product which will meet its specifications. Reclassification of PPs and re-evaluation of NORs within the Acceptable Operation Ranges (AORs) may happen through periodic process data review along with increased process knowledge and additional manufacturing history.

In addition, CHMP recommends the applicant to re-evaluate, according to principles and concept of ICH Q8 and ICH Q11, the proposed control strategy for cAC10 and SGN-35 when additional guidance on implementation of these guidelines is available.

Process Validation

The results of the validation studies including 3 consecutive batches show that all parameters met the acceptance criteria, demonstrating process consistency, ability of the purification to reduce process-related impurities, confirmation that mixing parameters ensure production of a homogeneous formulated bulk, and confirmation of uniformity of the batch across multiple bottle of BDS.

Process development

SGN-35 BDS has been manufactured by three versions of the same process designated Process A, Process B, and Process C. It is noted that process A, B, and C also include changes to cAC10 manufacture. Process C BDS has been slightly optimized further after some batches were manufactured. The Applicant submitted extensive analytical comparability studies, especially in view of the limited extent of the changes and the large clinical data set obtained with process C material.

Results show comparable performance between Process A, B, and C BDS manufacturing processes, as well as from batch-to-batch within a process. In addition, evaluation of BDS release data and analytical comparability studies demonstrate all three processes produced comparable BDS with a high degree of consistency. These data also serve as additional characterization data, suggesting that e.g. glycosylation/afucosylation is indeed consistent.

Characterisation and impurities

SGN-35 has been characterised structurally by spectroscopic, electrophoretic and chromatographic assays, and characterised functionally by ELISA and Immunoassays. Most experiments were performed in a comparative manner, comparing cAC10 and SGN-35, and demonstrating that conjugation does not have significant effects on primary structure, three-dimensional structure, charge heterogeneity, glycosylation, and binding to epitope. Conjugation does have significant effects on three parameters: potency (as intended), drug load (as intended) and aggregation.
The expected average molar mass (153,352 Da) of SGN-35 was confirmed by LC/ESI-MS and primary structure by peptide mapping and amino acid analysis. Three peptides (Lys-C peptides L13, H15, and H16) were identified conjugated with drug linker. In addition, the conjugated peptide map is the most important proof that only a limited number of specific cysteine residues are reduced and targeted for conjugation. Only the interchain conjugated peptides can be detected.

The glycoform structure was detailed. Secondary and higher order structures were analyzed. Drug load variants were characterized and identified. The average drug-to antibody molar ratio (MRD) for the commercial reference material was calculated as 4.0. All drug-load variants showed similar binding activity and showed increasing cytotoxicity with increasing drug load.

SGN-35 Size variants were assessed. The most abundant high and low molecular weight forms were identified as dimeric SGN-35 and Fc+Fab fragment. Conjugation increased the abundance of dimer and low molecular weight species relative to cAC10.

SGN-35 charge variants were separated and characterized. The basic charge variants are composed primarily of heavy chain variants that differ in the degree of amino terminal cyclization and in the number of C-terminal lysine residues. Acidic variants showed evidence of deamidation, sialylation, and fragmentation.

Free sulfhydryl levels were comparable for cAC10 and SGN-35 indicating that cysteine residues, reduced during the BDS manufacturing process, are efficiently alkylated with drug-linker.

The binding affinity of SGN-35 was assessed by ELISAs and by Surface Plasmon Resonance (SPR). The binding affinity of SGN-35 for human CD30 was assessed. These experiments show that SGN-35 retains the immunological properties of cAC10.

The main biological activity of SGN-35 is believed to be cytotoxicity upon its binding to CD30-expressing tumor cells, internalisation of ADC, release of MMAE and apoptosis of tumor cells. SGN-35

presented strong cell killing activity in a dose dependent manner as opposed to the cAC10 antibody. In addition, as observed for cAC10, SGN-35 lacks effector functions such as Complement-Dependent Cytotoxicity (CDC) activity and displays only little Antibody-Dependent Cellular Cytotoxicity (ADCC) activity.

The data presented in characterisation section confirm that conjugation targets cysteine residues involved in inter-chain disulfide bond formation resulting in an ADC with, on average, two of its interchain disulfides reduced and the resulting cysteine residues alkylated with SGD-1006 Intermediate (SGD-1006), leading to an average molar ratio (MRD) of four drugs per antibody. This leaves, on average, two inter-chain disulfides per molecule intact. One drug conjugation site is located in the light chain and three conjugation sites are located in the heavy chain, resulting in many active forms with up to eight possible conjugation sites per antibody. Despite the reduced number of inter-chain disulfide bonds, SGN-35 exists primarily as a monomer composed of 2 heavy and 2 light chains. Post-translational modifications, such as intra-chain disulfide bonds and glycans, are not impacted by the BDS manufacturing process. No evidence was found that the BDS manufacturing process induces chemical changes such as oxidation or deamidation to the peptide backbone nor does significantly disrupt the higher order structure of the molecule. Additionally, the BDS manufacturing process does not alter the charge profile of SGN-35, relative to cAC10.

Products and process related impurities are in general sufficiently discussed and their impact on safety is assessed.

Specification

The release specifications for the SGN-35 active substance include tests for Identity, Purity, Potency, Strength, Safety and Physical Characteristics such as IEF, HPLC, SEC, ELISA, CE SDS, free drug related impurities, cytotoxicity, UV spec, bioburden, endotoxin, polysorbate 80, pH, osmolality and appearance. Satisfactory validation of the analytical procedures has been performed in accordance with current ICH guidelines. Upon request, the applicant has reviewed the acceptance criteria for a number of specific methods.

Overall, the specifications proposed for SGN-35 is considered appropriate to ensure sufficient quality with respect to purity and level of impurities.

The Applicant has committed to review all specifications and limits after an appropriate number of batches have been manufactured with the commercial and validated process C.

Three lots of brentuximab vedotin (SGN-35) reference material have been used for release and/or stability testing of SGN-35 bulk drug substance (BDS). The reference materials are controlled by annual assessment of stability at the storage temperature. Written procedures are in place for qualification, certification, and control of current and future product reference material. Extended characterization, in addition to the certification testing was performed to qualify the SGN-35 commercial reference material.

A sterile polyethylene terephthalate glycol (PETG) media bottle with white high density polyethylene (HDPE) screw closure is used as the container closure system for SGN-35 BDS.

Stability

Overall, the stability data obtained from stability testing of 3 primary stability lots, 3 conformance lots, and 6 supporting stability lots support the SGN-35 BDS expiration dating of 60 months when stored at the designated storage condition in the commercial container closure system. In accordance with EU

GMP guidelines[1], any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

2.2.3. Finished Medicinal Product

SGN-35 finished product is a sterile, preservative free, white to off-white lyophilized cake or powder supplied in a single use container. Prior to administration, SGN-35 finished product is reconstituted with 10.5 mL of sterile Water for Injection resulting in a clear to slightly opalescent, colorless solution containing 5 mg/mL SGN-35, 20 mM sodium citrate, 6.3% (w/v) trehalose, 0.2 mg/mL polysorbate 80, pH 6.6. For administration, the reconstituted solution is added to an intravenous infusion bag containing infusion solution.

All formulation steps are performed during BDS manufacturing. There are no further formulation steps performed during the finished product manufacturing process. Each vial contains an overfill, relative to the nominal content (50 mg per vial). There are no overages. Each vial is filled with SGN-35 BDS and subsequently lyophilized.

The quantitative composition of SGN-35 in each vial, along with the function and quality standard of each component, is provided in the table below.

Pharmaceutical Development

The final formulation was selected prior to the initiation of the toxicology studies for the Investigational New Drug application and there have been no changes to the formulation throughout the development history of SGN-35 DP. The SGN-35 formulation was further characterized to assess the impact of pH, temperature, multiple freeze/thaw cycles, and elevated temperatures on a variety of product quality attributes. Studies were also conducted to examine the stability of the reconstituted SGN-35 finished product, and the photostability of both the SGN-35 BDS and SGN-35 finished product. These studies showed that the potential stresses during manufacturing, storage, and handling of the formulated BDS and finished product had no discernable impact on product quality.

Finished product development: SGN-35 BDS and finished product have been manufactured by three versions of the same process designated Process A, Process B, and Process C, the latter of which is the validated, commercial process.

Process A was used to produce material for initial clinical trials. For Process B, no changes to the finished product process were implemented, whereas process C is the up scaled commercial process. Comparability between finished product process B and C is demonstrated. Furthermore, all 3 lots manufactured using Process C show similar size distributions indicating good process consistency.

The differentiation between finished product Process A and Process B is a result of the changes to the SGD-1006, therefore comparability is described in the BDS part. Since only initial clinical studies were performed with DP from process A, the omission of a comparability study for finished product Process A is acceptable.

Adventitious agents

Compliance with the TSE Guideline (EMEA/410/01-rev.3) has been sufficiently demonstrated. The cAC10 Intermediate is produced in a serum-free culture medium. No animal derived material is added

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union

during fermentation of cAC10. The MCB and WCB which have been established are free from TSE-risk substances. The virus safety of Adcetris has been sufficiently demonstrated. The cells used for production of cAC10 have been sufficiently screened for viruses. No viral contaminant was found in the MCB, WCBs and PPCBs of cAC10 with the exception of intracellular A-type retroviral particles which are well known to be present in CHO cells. However, this is acceptable since there is sufficient capacity within the manufacturing procedure of cAC10 for reduction of this type of viral particles. Therefore, there are no concerns for the use in the production process of cAC10. The purification process of cAC10 includes several steps for inactivation/removal of enveloped viruses. The effectiveness of these steps has been sufficiently demonstrated. The reduction of enveloped viruses is mainly through low pH inactivation and removal by virus filtration (nanofiltration). For the non-enveloped viruses most reduction occurs at the virus filtration step. More moderate virus reduction is observed with two of the chromatography steps. One chromatography step was very effective for removal of the model virus reovirus type 3. The use of re-used chromatographic resins has been investigated and shown not to result in a loss of virus reduction capacity.

Manufacture of the product

Batch release of finished product is performed by Takeda Italia Farmaceutici S.P.A., Cerano, Italy.

SGN-35 finished product manufacturing process involves thawing of SGN-35 BDS, pooling and mixing, sterile filtration, aseptic filling, lyophilization, capping, visual inspection, and packaging. The control strategy for SGN-35 finished product manufacturing process includes raw material and intermediate controls, procedural and environmental, process parameter controls, in-process controls, release testing, stability testing, and process validation. The critical process steps, control points, and impacted CQA for the finished product manufacturing process are provided. Validation of the manufacturing process for SGN-35 was successfully completed. Three consecutive full scale conformance runs were produced meeting all the requirements defined in the validation protocols. In addition, the shipping process was also successfully validated for the shipment of SGN-35 finished product.

Product specification

Specification and release criteria for brentuximab vedotin finished product have been established to ensure Identity, Purity, Potency, Strength, Safety and Quality with test methods such as IEF, HIC, SEC, CE SDS, free drug related impurities, cytotoxicity, UV spec, conjugate content, sterility, content uniformity, endotoxin, reconstitution time, pH of reconstituted solution, osmolality of reconstituted solution and appearance . Many of the analytical procedures used for testing the finished product are the same as the active substance. Following request from CHMP the applicant has reviewed the acceptance criteria fora number of specific test methods. Upon request, the acceptance limit for potency determination by cytotoxicity has been further justified by the applicant and is considered acceptable at this point in time, although data suggests that future tightening should be feasible. In addition, an orthogonal method has been implemented as a separate test for finished product to further support the data from the cell-based assay. The specification has been aligned for all three cAC10 intermediate, BDS, and finished product.

Overall, all the methods for release testing of the finished product have been adequately described justified and validated. The proposed limits are acceptable.

All excipients are of compendial grade quality. No novel, human or animal derived excipients or excipients prohibited for use in drugs are used at any stage of manufacture.

Stability of the product

Available stability data (both real time and accelerated) from process A, B and C batches, and the comparability of process A, B and C material support a finished product shelf life of 36 months at the designated storage condition of 2-8°C. In accordance with EU GMP guidelines[2], any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

During the evaluation procedure a major objection was raised with regard to the control strategy for cAC10 and SGN-35. In particular, the way in which CPPs and IPCs were defined for the manufacturing process of cAC10 and SGN-35, was not deemed adequate. During the review, the Applicant provided clarification and justification for its approach, reclassified some PPs into CPPs, a number of NORs have been given new limits and additional justification for the IPCs was provided.

This approach sufficiently assures that the manufacturing process is under control, that deviations will be handled in an appropriate manner, and that the process is able to manufacture a consistent product which will meet its specifications. Reclassification of PPs and re-evaluation of NORs within the AORs may happen through periodic process data review along with increased process knowledge and additional manufacturing history.

In addition, CHMP recommends the applicant to re-evaluate, according to principles and concept of ICH Q8 and ICH Q11, the proposed control strategy for cAC10 and SGN-35 when additional guidance on implementation of these guidelines is available.

In addition, there were several minor issues/other concerns/points for clarification, which were resolved before approval to further guarantee that SGN-35 is manufactured and controlled according to the current state of the art. Most of the identified other concerns related to specifications, i.e. release testing, analytical methods, validation, and stability.

In conclusion, with regards to the biological and pharmaceutical aspects of Adcetris, the CHMP considers that all issues have been resolved by the Applicant.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends certain points for investigation.

[2] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union

2.3. Non-clinical aspects

2.3.1. Introduction

Primary pharmacodynamic studies were conducted in immunocompromised mice. The single *in vivo* safety pharmacology study was conducted in cynomolgus monkeys and it was GLP compliant (and so was the only other safety pharmacology study conducted in hERG-transfected HEK cells). Single- and repeat-dose toxicology studies were conducted in rats and monkeys. The pivotal repeat-dose toxicity studies were GLP compliant.

The Applicant received Protocol Assistance from the CHMP. The non-clinical advice pertained to safety pharmacology, repeat-dose toxicity, genotoxicity, carcinogenicity and embryofoetal development studies.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Binding of brentuximab vedotin and unconjugated brentuximab to CD30 was evaluated by using flow cytometry and time-resolved fluorometry. Both brentuximab vedotin and unconjugated brentuximab bound with a Kd of 0.2 nM to human and cynomolgus CD30-positive primary lymphocytes, but not to rat or mouse CD30-positive cells or cells not expressing CD30. As a positive control, recombinant humanCD30L/murineCD8α fusion protein did bind to rat and mouse cells (data not shown).

By using immunofluorescence microscopy, it was shown that brentuximab vedotin was bound to the surface of CD30-positive L540cy cells and detected within the lysosomal compartment within 4 hours of treatment. Co-localisation within lysosomes increased over time of exposure to brentuximab vedotin. Unconjugated brentuximab was similarly internalised but with delayed kinetics compared to brentuximab vedotin. Neither agent was detected on the surface of CD30-negative cells (data not shown).

Incubation of brentuximab vedotin with purified human lysosomal protease cathepsin B or lysosome-enriched fractions purified from the human ALCL Karpas 299 cell line released MMAE from brentuximab vedotin in a time-dependent manner as measured by Western blot analysis and liquid chromatography with tandem mass spectrometry. Addition of a cysteine protease inhibitor, E64d, blocked the catabolism of brentuximab vedotin and restored the drug-associated signal detected by Western blot analysis. Quantification of MMAE release by using LC-MS/MS revealed that 43-55% of MMAE was released after 2 hours of incubation.

To determine the fraction of total MMAE that is released from brentuximab vedotin, CD30-positive Hodgkin lymphoma L540cy and anaplastic large cell lymphoma Karpas 299 cells were incubated with brentuximab vedotin containing [^{14}C]MMAE. Results revealed that most of the drug was initially membrane-associated, but that intracellular drug levels increased over the course of the experiment. In addition, the majority of intracellular drug was free. Generation of free MMAE inside and outside of L540cy cells was greatly reduced when cells were treated with chloroquine, an agent that raises lysosomal pH and reduces the activity of lysosomal protease (data not shown).

In a cell-free system using bovine brain tubulin, MMAE was shown to inhibit microtubule polymerisation with an IC_{50} of approximately 1 µM. Treatment of Tera-2 carcinoma cells with MMAE (0.75 nM, 24 hours) led to disruption of the intracellular microtubule network (data not shown).

Anti-tumour activity of brentuximab vedotin was shown in proliferation assays *in vitro*. Cytotoxic activity of brentuximab vedotin against a panel of CD30+ Hodgkin Lymphoma and anaplastic large cell lymphoma cell lines was shown. The IC_{50} was approximately 0.01 – 0.1 nM, while it was > 6.7 nM for CD30-negative cell lines. In this in vitro cytotoxicity assay, the free drug MMAE was effective against both CD30-positive and –negative cell lines (IC_{50} 0.1 – 2.3 nM). In vivo anti-tumour activity of brentuximab vedotin was demonstrated in three xenograft transplant models derived from human HL and ALCL cell lines. In all 3 models, brentuximab vedotin treatment induced a dose-dependent anti-tumour activity (i.e. delay in tumour growth or durable complete remission, data not shown).

In addition to the cytotoxic activity, the immunological effector functions potentially mediated by brentuximab vedotin were evaluated *in vitro*. Brentuximab vedotin induced phagocytosis of CD30-positive WIL-2S cells by human monocyte-derived macrophages while it did not induce antibody-dependent or complement-dependent cytotoxicity. No studies addressing the potential interaction of brentuximab vedotin with F_C-gamma receptors were submitted (see discussion on non-clinical aspects).

The anti-tumour activity of SGN-35 was evaluated in vivo in xenograft models derived from human HL and ALCL cell lines.

The L428 HL cells form progressive tumours when injected subcutaneously in NOD SCID gamma mice. Dosing was initiated when the average tumour volume was 100 mm3 (day 10). In mice treated with SGN-35 (1 mg/kg IP every 4 days for 4 doses), L428 growth was delayed. In a second experiment, SGN-35 was dosed at 2 mg/kg every 4 days for 3 doses. In this study all tumours regressed and 4/5 mice had no detectable tumours at the end of the study on day 108. At this higher dose, a delayed tumor progression was observed also in mice treated with the control ADC (data not shown).

L540cy HL cells form progressive tumours when injected SC into SCID mice. Treatment was initiated when the average tumour volume in all mice was approximately 100 mm3. In mice treated with SGN-35 (1 mg/kg IP, q4dx4) tumour growth was delayed. When SGN-35 was dosed at 3 mg/kg q4dx4, all tumors regressed and 5/5 mice had no detectable tumours at the end of the study on day 102. At 3 mg/kg a delay in tumour growth was also observed for the control ADC, but the response was not durable (data not shown).

SCID mice bearing SC Karpas 299 tumours were treated via IV injection q4dx4. A dose-dependent delay in tumour growth was observed in the SGN-35 treated groups. At the higher dose of 0.5 mg/kg, 7/8 mice had no palpable tumour at the end of the study (day 96). cAC10, MMAE alone or in combination did not induce tumour growth inhibition. In mice bearing disseminated Karpas 299 tumours, a dose-dependent survival advantage was observed in mice treated with SGN-35. A mixture of cAC10 and MMAE prolonged survival but was less active than the equivalent 3 mg/kg dose of SGN-35 (data not shown).

Secondary pharmacodynamic studies

Biotin-conjugated brentuximab vedotin was applied to sections from 30 various tissues of humans and cynomolgus monkeys to evaluate the potential cross-reactivity of 2.5 and 12.5 µg/ml brentuximab vedotin (optimal concentration and 5 times the optimal concentration, respectively). No specific staining was observed when biotinylated brentuximab vedotin was applied to a panel of representative human tissues from 3 separate individuals at either of the 2 concentrations tested. With the exception of epithelial cells in the thyroid, no binding of biotinylated brentuximab vedotin was seen in any cynomolgus monkey tissue examined at either concentration. Low to moderately high positive staining of cells in the thyroid epithelium was observed in 2/3 cynomolgus monkey samples at 2.5 µg/ml biotinylated brentuximab vedotin. At 12.5 µg/ml, epithelial cells in all 3 samples of cynomolgus

monkey thyroid were low to moderately positive. No evidence of biotinylated brentuximab vedotin binding was observed in the adjacent parathyroid tissues at both concentrations (data not shown).

In an additional study, evaluating tissue cross-reactivity of 2.5 and 12.5 µg/ml brentuximab vedotin with human tissues and rat liver tissue, specific staining was observed with biotinylated brentuximab vedotin in several tissue elements of the human tissue panel: human mononuclear cells, hematopoietic precursor cells, spindloid cells, oviduct and bronchial epithelium (cilia), and keratin squames/debris. This intracellular staining was observed mostly at the highest concentration tested. There was also staining of extracellular material, notably intracolonic fecal material, pulmonary amorphous material, ovarian cystic fluid, contents of a dermal duct, endometrial luminal secretions, colloid, and lens protein. There was no biotinylated brentuximab vedotin-specific staining of rat liver tissues.

Safety pharmacology programme

Regarding safety pharmacology, the effect of the free drug MMAE on hERG K^+ channel activity was examined in vitro by whole cell voltage clamp analysis. In HEK 293 cells which expressed the human hERG K^+ channel, MMAE produced a fractional block of peak hERG tail current that was significantly different from the negative control at high MMAE concentration (100 µM) but not at the low concentration (10 µM, data not shown).

In a dedicated safety pharmacology study in cynomolgus monkeys a single IV infusion of 0.3, 1 and 3 mg/kg brentuximab vedotin to conscious, radio-telemetered cynomolgus monkeys did not affect cardiovascular parameters (heart rate, mean arterial blood pressure, ECG intervals including RR, QT and QTc), respiratory parameters (respiratory rate and blood gases), central nervous system parameters (behaviour, visual evaluation, reflex evaluation, motor/sensory, facial movement, pupils, visual field, vestubilocochlear, prehension and swallowing, proprioception and body temperature), body weight, hematology, plasma chemistry and coagulation parameters within 4 days after infusion (data not shown).

Pharmacodynamic drug interactions

No non-clinical pharmacodynamic interaction studies were submitted.

2.3.3. Pharmacokinetics

Pharmacokinetic and toxicokinetic studies of brentuximab vedotin were conducted in rats and monkeys using the clinically intended IV route. In order to characterise the pharmacokinetics of SGN-35, concentrations of three analytes were measured: 1. SGN-35, 2. total antibody (TAb) (SGN-35 plus unconjugated cAC10), and 3. SGD-1010.The immunogenicity of brentuximab vedotin in both rats and monkeys was also assessed by measuring rat and primate anti-human antibodies (RAHA and PAHA).

After IV application of SGN-35 to the rat, the primary moiety in circulation was SGN-35. The pharmacokinetic profile of SGN-35 was similar to other monoclonal antibody products with a limited volume of distribution, a low clearance and a long half-life of 8 to 15 days. SGN-35 exposures were approximately dose-proportional. TAb (cAC10 plus SGN-35) exposures were generally greater than exposures to SGN-35. The active moiety, SGD-1010, was present at a molar ratio of 0.001 or lower. Because of the very low levels of SGD-1010 in circulation, concentrations could only be measured for 10 days. For purposes of comparison, a truncated SGN-35 half-life was estimated over a time period of up to 7 days, comparable to the duration used for estimation of half-life of SGD-1010. The truncated SGN-35 half-life was 2 to 2.5 days, similar to that of SGD-1010. In a subsequent study in which rats received a single dose of un-conjugated SGD-1010 alone, the half-life for SGD-1010 was about 5.6

hours. These results suggest that the pharmacokinetic of SD-1010 is governed by the rate of SGD-1010 release from SGN-35 resulting in longer exposure to SGD-1010 from SGN-35 than when SGD-1010 was administered alone.

The incidence of RAHA (rat antihuman antibodies) was determined in the rat PK study. 50 % of rats (3/6) administered 5 mg/kg SGN-35 showed RAHA whereas in the lower dose group of 0.5 mg/kg no RAHA were detected.

The pharmacokinetics of SGN-35, TAb and SGD-1010 were evaluated after a single IV infusion of SGN-35 in two separate studies in the monkey. SGN-35 exposures were dose-proportional to greater than dose-proportional from 0.3 to 3 mg/kg SGN-35. The SGN-35 terminal elimination half-life ranged from 1.6 to 2.7 days. Clearance and distribution at steady state were similar across doses. Exposure to TAb (cAC10 plus SGN 35) increased with SGN-35 dose and was greater than exposure to SGN-35. The increase in mean serum Cmax was approximately dose-proportional. Circulating SGD-1010 concentrations were approximately 1000-fold lower than SGN-35 on the basis of molar ratios. Like in rats, SGD-1010 exhibited formation-limited kinetics depending on release from SGN-35.

PAHA (primate antihuman antibodies) were seen in all animals in the one study and in 5 of 6 of animals in the other study. The impact of PAHA on the pharmacokinetic parameters was not formally characterised. In general, the incidence of PAHA appeared to be higher than the incidence of RAHA.

Data on repeat-dose kinetics are available from the repeat-dose toxicology studies and are discussed in the section on toxicokinetics below. Interspecies comparison was only performed for SGN-35 exposure (AUC and Cmax) and is also presented in the same section.

The apparent terminal half-life of MMAE was 2.5 and 3.0 days in rats and monkeys, respectively, which is similar to the half-life of brentuximab vedotin when measured over the same time range. MMAE exposure was approximately dose-proportional in rats and monkeys after administration of brentuximab vedotin. Circulating MMAE concentrations were approximately 1000-fold lower than brentuximab vedotin. The pharmacokinetic parameters of MMAE after administration of brentuximab vedotin appeared to be governed by the rate of release of MMAE from brentuximab vedotin, resulting in a longer but much lower exposure to MMAE than when MMAE was administered. After a single IV dose of MMAE, V_{ss} was high, suggesting extended tissue distribution. This was confirmed in a study in rats, showing rapid and wide distribution to the tissues after intravenous administration of MMAE. MMAE was mainly distributed to pituitary gland, adrenal gland, thyroid, lung, kidney, liver and subsequently bile and intestine. The apparent half-life of MMAE after administration of brentuximab vedotin was considerably longer (2.5-3.0 days) than the half-life after administration of unconjugated MMAE (5.7-5.8 hours).

Binding of SGD-1010 to plasma protein from mouse, rat, monkey, and humans showed that the protein binding of SGD-1010 was species-dependent, with higher levels of binding (67.9% to 82.2%) in rats and humans than in mice and monkeys (17.1 % to 28.5 %). Moreover, in vitro experiments suggested that the mc-vcSGD-1010 drug linker is transferred to serum proteins. Serum albumin was identified as being the primary species to which mc-MMAF (monomethyl auristatin F) is transferred. Maleimide transfer was assessed in human samples and the extent of maleimide transfer was determined to be approximately 1.5 % of all conjugated SGD-1010. Finally, no studies on blood cell distribution of SGD-1010 were submitted (see discussion on non-clinical aspects).

Studies to assess the permeability of SGD-1010 across Caco-2 cell monolayers indicated that SGD-1010 is actively transported by P-gp through the Caco2 monolayers and, accordingly, is a substrate for P-gp. SGD-1010 was found to slightly inhibit the active transport of the P-gp substrate digoxin, with an IC50 greater than 50 µM. In conducting experiments with specific inhibitors for BCRP and MRP2, it could be shown that SGD-1010 is not a substrate for BCRP and MRP2.

No animal metabolism studies for the antibody component of brentuximab vedotin were submitted (see discussion on non-clinical aspects). However, to examine brentuximab vedotin cellular catabolism, unlabeled or ^{14}C-radiolabeled brentuximab vedotin was added to cultures of CD30-positive cells and CD30-negative cells. CD30-negative cells did not release detectable levels of MMAE through the entire 3-day course of the assay. In contrast, CD30-positive cell lines released MMAE from brentuximab vedotin, with high intracellular concentrations (>400 nM) reached within 24 hours of treatment. MMAE was identified as the only product of brentuximab vedotin catabolism. This finding was confirmed by the agreement of radiometric, mass spectrometry, and bioassay measurements of released drug concentration. Moreover, brentuximab vedotin was stable in rat, monkey, and human plasma. The rates of MMAE appearance in human and cynomolgus monkey plasma were barely discernible from the conversion rate measured in PBS. Approximately 2% of the MMAE was observed in rat plasma over the 3-week period.

SGD-1010 metabolism was evaluated using cultured rat, monkey, and human hepatocytes and human liver microsomes and in vitro model systems. Mass shifts and fragmentation patterns observed for the majority of metabolites detected were consistent with formation of metabolites by hydroxylation, demethylation, dehydrogenation, or hydrolysis. Metabolites formed in human hepatocytes were similar to those formed in rat and monkey hepatocytes. No human-unique metabolites were detected. Certain metabolites retained some of the cytotoxic activity of SGD-1010 (data not shown).

Recombinant human CYP3A4 was able to covert [^{3}H]-SGD-1010 to metabolites and formation of metabolites was blocked by the CYP3A4 inhibitor ketoconazole and by a monoclonal antibody against CYP3A4. CYP2D6 also converted [^{3}H]-SGD-1010. In addition, strong correlations were observed between CYP3A4 activity and the formation of the main metabolites in a bank of 16 individual human liver microsomes.

An *in vitro* study in cultured human hepatocytes assessed the potential of SGD-1010 to induce CYP1A2, 2B6, 2C8, 2C9, 2C19, and 3A4/5, On the basis of these findings, SGD-1010 was postulated not to be an inducer of CYP1A2, 2B6, 2C8, 2C9, 2C19, and 3A4/5 (data not shown).

An in vitro study was performed in human liver microsomes to evaluate the potential of SGD-1010 to inhibit the major CYP isozymes: CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5. SGD-1010 caused little or no direct inhibition of CYP1A2, 2B6, 2C8, 2C9, 2C19, and 2D6. SGD-1010 was found to be a weak reversible CYP3A inhibitor (with an IC50 of 10 µM) and a quasi-irreversible, time-dependent CYP3A4 inhibitor, as formation of a metabolite inhibitory complex prevents the catalytic hematoporphyrin from binding oxygen. Further characterisation of this time-dependent inhibition suggests that SGD-1010 has the potential to be a mechanism-based inhibitor of CYP3A4/5, with a Kintact (rate constant of irreversible inactivation) value of 0.10 minutes to 1 minute, and a Ki (inhibition constant) value of 1.12 µM, yielding a modest kintact-to-ki ratio of 90 minutes to $1mM^{-1}$.

The major route of elimination in animals dosed with cAC10-vc-[^{3}H]SGD-1010 or [^{3}H]SGD-1010 was biliary/fecal with approximately 106 % to 112 % recovery of radioactivity in male and female rats. The majority of the radioactivity was recovered in feces for both male and female rats (89.3 % to 101.8 %). The remainder of the radioactivity was recovered in urine (7.1 % to 15.1 %). The rate of [^{3}H]SGD-1010 excretion for animals dosed with cAC10-vc-[^{3}H]SGD-1010 was slower than for animals dosed with [^{3}H]SGD-1010, the active moiety alone, indicating that conjugation to the antibody lowers the rate of excretion. The primary species excreted in animals dosed with either test article was [^{3}H]SGD-1010, showing that cAC10-vc-[^{3}H]SGD-1010 is converted to [^{3}H]SGD-1010 and excreted intact. cAC10-vc-[^{3}H]SGD-1010 was not excreted. A second radiolabeled species was observed in faeces and 5 additional metabolites were observed in urine. However, 86 % to 100 % of the radioactivity excreted in urine was accounted for as [^{3}H]SGD-1010 and 75 % to 100 % of the dose administered was excreted as [^{3}H]SGD-1010 in faeces in rats administered either test article.

2.3.4. Toxicology

Single dose toxicity

A series of single-dose IV toxicity studies was conducted to evaluate the acute toxicity of MMAE and the antibody-drug-conjugate SGN-35. For selection of the lead candidate different antibody-drug conjugates, i.e. cAC10 conjugated to 4 or 8 vcMMAE molecules, were tested in rats and cynomolgus. In addition, data on acute toxicity were obtained after a single administration in cynomolgus repeat-dose studies. Single dose toxicity studies are summarised in the following Table 10.

Table 10: Single dose toxicity studies

Study ID	**Species/ Sex/Number/ Group**	**Dose/Route (mg/kg)**	**Observed max non-lethal dose (mg/kg)**
1019-001	Rat Sprague-Dawley 4/sex/gp	MMAE: 0.05, 0.25 cAC10-vcMMAE 8 pure**: 1.5, 7.5 cAC10-vcMMAE 4 pure*: 3, 15 cAC10-vcMMAE 4 mix* (=SGN-35): 3, 15 IV bolus	None of the administered doses was lethal
Major findings: bone marrow: atrophy/hypocellularity, **mesenteric lymph node**: lymphoid depletion, **thymus**: lymphoid depletion, atrophy, and lymphoid necrosis, **spleen**: lymphoid depletion, **liver**: single-cell hepatocellular necrosis, bile duct hyperplasia/hypertrophy, and inflammation, **intestine**: crypt epithelium single-cell necrosis, **pancreas**: acinar cell single-cell necrosis			
R-Toxicity-15, Amendment 1	Rat Sprague-Dawley 2-3/sex/gp	MMAE: 0.01, 0.1, 0.2 SGN-35: 0.5, 5.0, 10.0 IV bolus	MMAE: 0.1 SGN-35: 10.0
Major findings: bone marrow: hypocellularity, myeloid, erythroid hypoplasia **thymus**: lymphoid depletion, **liver**: single-cell necrosis, biliary hypertrophy/hyperplasia, **Hematology**: decreases in leukocytes, **Serum chemistry**: elevations in AST and ALT			
R-Toxicity-17, Amendment 2	Rat Sprague-Dawley 3F/gp	SGN-35: 10.0 IV bolus	ND
Major findings: Bone marrow: pancytopenia during the first week postdose with complete recovery within 2 weeks postdose			
R-Toxicity-33	Rat Sprague-Dawley 3F/gp	MMAE: 0.2-mg/kg	Mortality in 3 of 33 (10%) animals
Major findings: Bone marrow: progressive, severe, pancytopenia from 2 to 5 days postdose with a rapid regenerative recovery by 7 to 8 days postdose			
8213480	Cynomolgus monkey 6F/gp	SGN-35: 3.0 30 min IV infusion	SGN-35: 3.0 (*in this study single repeated dose were compared*)
Major findings: Non-toxic			

Study ID	Species/ Sex/Number/ Group	Dose/Route (mg/kg)	Observed max non-lethal dose (mg/kg)
1644-167	Cynomolgus monkey 1/sex/gp	cAC10-vcMMAE 4 mix: 1, 2, 3, 4, 6 cAC10-vcMMAE 8 pure: 1 cAC10-vcMMAE 4 pure: 4, 6 60 min IV infusion	cAC10-vcMMAE 4 mix: 6 cAC10-vcMMAE 8 pure: 1 cAC10-vcMMAE 4 pure: 4
Major findings: ≥ 1 mg/kg (4 mix): Reddened skin and decreased activity in a few animals; **≥2 mg/kg** (4 mix): Decreases in erythrocyte mass and leucocytes, especially neutrophils; Increase in globulin and decrease in albumin			
SNBL.163.19	Cynomolgus monkey 1/sex/gp	MMAE: 0.116	q3wx2 of MMAE at 0.058 mg/kg (*in this study single high and repeated low dose were compared*)
Major findings: Mortality: Male found dead on Day 28. Cause of death was pneumonia; **Clinical Observations:** inappetence, body weight decrease, hunched posture, and dry or hard feces; **Clinical Pathology:** decreased white cells (neutrophils, lymphocytes, and monocytes), erythrocytes, haemoglobin, haematocrit, and reticulocytes, decreased albumin and elevated AST			

* cAC10-vcMMAE is the parent conjugate and can be produced by various methods resulting in different versions, including cAC10-vcMMAE4M, cAC10-vcMMAE4P (pure) and cAC10-vcMMAE8 derivatives.
** The cAC10-vcMMAE8 derivative contains twice the concentration of cytotoxic agent (auristatin E) as the cAC10-vcMMAE4M

Repeat dose toxicity

Repeat dose toxicity studies are summarised in the following Table 11.

Table 11: Repeat-dose toxicity studies

Study ID	Species/Sex/ Number/Group	Dose/Route (mg/kg)	Duration	NOEL/ NOAEL (mg/kg/day)
Supportive Studies				
R-Toxicity-13	**Rat**/Sprague-Dawley 2-5/sex/gp	**SGN-35**: 0.5, 5, 15 **MMAE**: 0.0097, 0.097, 0.29 IV bolus	3 weeks q1wk × 4	SGN-35: 0.5 MMAE: 0.0097
Major findings: MMAE ≥0.0097 mg/kg *Clinical observations:* piloerection; *Haematology:* WBC↓. **SGN-35 ≥5 mg/kg and MMAE 0.29 mg/kg** *Mortality*: 2 rats dosed with 15-mg/kg SGN-35 and all male rats dosed with 0.29-mg/kg MMAE. *Histopathology*: Target organs related to administration of SGN-35 and MMAE were similar and included bone marrow (depletion), liver (necrosis and biliary hypertrophy/hyperplasia), spleen (atypical mitosis). **With SGN-35 only**, target organs also included testes (tubular degeneration), lung (alveolar histiocytosis), and small intestine (crypt apoptosis). *Hematology*: reductions in red cell mass, leukocytes, and platelets; *Serum chemistry* elevations in AST, ALT, total bilirubin, GGT, ALP, total protein, and cholesterol, and decreased albumin; *Macroscopic pathology*: multiorgan paleness, splenic atrophy, lymphadenopathy, and small testes.				
SNBL.163.13	Cynomolgus **monkey** 2/sex/gp	SGN-35: 1,4,6 60 min IV infusion	q2wk × 4 (0, 1 and 4 mg/kg) q1wk × 4 (1 mg/kg) q3wk × 4 (6 mg/kg)	1 mg/kg q2wk x 4
Major findings: *Histopathology*: **4 mg/kg q2wk x 4** Bone marrow alterations in granulopoiesis and decrements in erythropoiesis; **1 and 4 mg/kg q2wk x 4; 1 mg/kg q1wk x 4** atrophy of splenic germinal centers. *Haematology*: **≥4 mg/kg and for some parameters 1 mg/kg q1wk x 4** Reductions in total leukocytes, neutrophils, erythrocytes, reticulocytes, hematocrit, and hemoglobin. Increased platelet counts.				
SNBL.163.12	Cynomolgus **monkey** 1/sex/gp	SGN-35: 1,4 60 min IV infusion	q3wk × 4	1 mg/kg q3wk x 4

Study ID	Species/Sex/ Number/Group	Dose/Route (mg/kg)	Duration	NOEL/ NOAEL (mg/kg/day)
Major findings: 4 mg/kg *Histopathology*: Slightly increased level of granulopoiesis in sternal bone marrow and brown pigment deposition in the liver and spleen. *Hematology*: Slightly decreased leukocytes with markedly decreased neutrophils and lymphocytes 1-2 weeks after each dose. Minimal, transient increases in platelet counts 1-2 weeks after each dose.				
SNBL.163.19	Cynomolgus **monkey** 1/sex/gp	MMAE: 0.058 60 min IV infusion	q3wk × 2[§]	ND
Major findings: *Clinical Observations:* hunched posture; *Haematology:* decreased white cells (neutrophils, lymphocytes, and monocytes), erythrocytes, hemoglobin, hematocrit, and reticulocyte; *Clinical chemistry*: Decreased albumin and elevated AST.				
8213480	Cynomolgus **monkey** 4F/gp	SGD-35: 2, 3	q1wk × 4[§]	ND
Major findings: Weekly administration of 2- and 3-mg/kg SGN-35 was not tolerated and, as a result of severe neutropenia, the majority of the animals failed to receive the full 4-dose schedule. *Clinical Observations*: Hunched posture, oily haircoat, body weight decrease, and low food consumption with 3 mg/kg. *Clinical Pathology*: Decreased total protein, red cell mass, and absolute neutrophil count and increased reticulocytes with repeated doses of 2 or 3 mg/kg				
Pivotal studies				
7646-118	**Rat**/Sprague-Dawley 15/sex/gp (Low dose 10/sex/gp)	**SGN-35**: 0,5, 5, 10 **cAC10**: 10 **MMAE**: 0.0097, 0.097, 0.194 IV bolus	4 weeks (q1wk × 4) 4 week recovery	SGN-35: 0.5 MMAE: 0.0097
Major findings: SGN-35 ≥0.5: *Haematology*: M: platelet↓ (d-r); **SGN-35 ≥5:** *Haematology:* M+F: Ery, Hb, Htc, ret, eos, APTT↓ (d-r), MCV, MCH, MCHC↑ (d-r); M: WBC, neu, lym, mono↓ (d-r); *Serum chemistry*: M: glu, chol, AST↑ (d-r); M+F: alb↓ (d-r); *Organ weight*: M+F: thymus↓ (d-r); M: testis↓ (d-r); *Histopathology*: M+F: sternum+femur marrow: hypocellularity; M: testis: vacuolisation Sertoli cells; spermatocytes↓ *Recovery:* Ery↓, MCV↑, MCH↑, epididymus and testis weight↓, small testis, testis: vacuolisation Sertoli cells, seminiferous tubili degeneration; epididymus aspermia **SGN-35 10:** *Haematology:* F: WBC, lym, mono↓, fibr↑; *Serum chemistry*: F: Glu, glob, chol, AST↑; M+F: AP, ALT, bil ; *Gross pathology*: Testis: small and soft; *Histopathology*: M+F: thymus: lymphocytic depletion and necrosis; Liver: multifocal coagulative necrosis; M: testis: syncytial cells, seminiferous tubili degeneration; epididymus aspermia **MMAE ≥0.097:** M: BW gain↓ (d-r, day 1-8); *Haematology*:; M+F: Ery, Hb, Htc, ret↓ (d-r); MCV, MCH↑ (d-r); M: eos↓ (d-r); *Serum chemistry*: M+F: alb, A/G ratio↓; M: chol↑ (d-r); F: phos↑ *Recovery: F:* ery↓; M+F: MCV, MCH↑; M: APTT↓, chol↑ **MMAE 0.194:** M: BW ↓; BW gain↓ (day 15-22); *Haematology*: F: platelet↑; M+F: WBC, neu, lym, eos, mono↓, APTT↓; *Serum chemistry*: M+F: glu↑, prot↓, ALP↓, GGT↑; F: chol↑; M: bil, AST↑; *Histopathology*: M+F: thymus: lymphocytic depletion, bone marrow hypocellularity; F: thymus: lymphocytic necrosis, M: Testis: tubules with decreased spermatocytes; Liver: minimal coagulative necrosis *Recovery:* M: epididymus and testis weight↓; seminiferous tubili degeneration, Sertoli cell vacuolation, epididymus aspermia				
SNBL.163.16	Cynomolgus **monkey** 6 (control), 3 (LD SGN-35), 5 (MD SGN-35 and MMAE) or 8 (HD SGN-35) /sex	SGN-35: 1, 3, 6[#] MMAE: 0.058[#] 60 min IV infusion	9 weeks (q3wk × 4) Recovery 5 weeks	SGN-35: 1
Major findings: SGN-35 ≥1: *Organ weights:* Thymus↓ (non-d-r); *Histopathology*: F: Bone marrow: hypercellularity, **SGN-35 ≥3:** *Haematology:* F: ery↓, ret var. ↑ or ↓, RCDW↑; M+F: eos↓ *Histopathology*: M: Bone marrow: hypercellularity; M+F: bone marrow: necrosis, cellular debris **SGN-35 6:** *Mortality* 3/16; *Clinical observat.*: M: Hunched posture, anorexic condition, febrile, unresponsive, Petechial hemorrhage; *Haematology:* M+F: WBC↓; F: Hb↓, Htc↓, MCV↑, MCH↑, platelet↑, neu↓; *Histopathology*: M+F: Bone marrow: hypocellularity; Thymus: lymphocytic hypocellularity **MMAE 0.058:** *Haematology:* M+F: WBC↓, eos↓; F: neu↓; *Histopathology*: M+F: Bone marrow: hypocellularity; Spleen: lymphocytic hypocellularity				
8216375	Cynomolgus **monkey** 5 (control) or 10 (treated) /sex/gp	SGN-35: 1, 3 30 min IV infusion	24 weeks (q3wk × 9) recovery 6 weeks	1 mg/kg
Major findings: ≥1 mg/kg *Haematology:* F: WBC↓, neu↓, large unstained cells↓; M+F: eos↓ **3 mg/kg** *Haematology:* F: ery↓, M: Hb↓, WBC↓, neu↓; M+F: ret↑				

Study ID	Species/Sex/ Number/Group	Dose/Route (mg/kg)	Duration	NOEL/ NOAEL (mg/kg/day)
1151-167	Cynomolgus **monkey** 3-5/sex/gp	cAC10: 10, 50, 100 60 min IV infusion	5 weeks (q1wk × 6) recovery 4 weeks	100 mg/kg
Major findings: 100 mg/kg *Haematology:* M+F: polysegmented neu↓				

The SGN-35 6 mg/kg animals and the MMAE animals were additionally treated profylactically with the antibiotic Cefazolin or Cefazolin + Baytril while animals were neutropenic.
§ These data represent the repeat dose arm of a single- and repeat-dose study. See Table 16 on single dose studies for the results from the single-dose arms

Genotoxicity

The genotoxic potential of MMAE was evaluated in 2 in vitro assays (bacterial reverse mutation, and L5178Y TK+/- mouse lymphoma forward mutation assay) and in vivo in a rat bone marrow micronucleus assay. The potential genotoxicity of the linker molecule was assessed based on public available data and in silico analysis (data not shown).

Table 12: Overview of genotoxicity studies with MMAE

Type of test/study ID/GLP	Test system	Concentrations/ Concentration range/ Metabolising system	Results Positive/negative/equivocal
Gene mutations in bacteria/AA66EH.503.BTL/GLP	*S. typhimurium* strains TA98, TA100, TA1535, TA1537, and E. coli strain WP2 uvrA	0.25 – 5000 µg/plate/ +/- S9	negative
Gene mutations in mammalian cells/ 8204155/GLP	Mouse lymphoma L5178Y $TK^{+/-}$	1.5-100 ng/mL +S9 0.005-15 ng/mL (-S9)	negative (cytotoxic >2.5 ng/mL (-S9) and >30 ng/mL (+S9))
Chromosomal aberrations in vivo/ 8204151/GLP	Rat, micronuclei in bone marrow	0.01, 0.1, 0.2 mg/Kg (24 hours) 0.2 mg/Kg (48 hours) IV injection	Positive: Increase in micronucleated PCEs at 0.1 and 0.2 mg/kg. Induced micronuclei were predominately centromere+ (aneugenic mode of action)

Carcinogenicity

Carcinogenicity studies were not submitted (see discussion on non-clinical aspects).

Reproduction Toxicity

No studies on fertility and early embryonic development were submitted (see discussion on non-clinical aspects).

Studies of the effects of brentuximab vedotin and MME on embryo-foetal development are summarised in the following Table 13.

Table 13: Embryo-fetal developmental studies with brentuximab vedotin and MMAE

Study type/ Study ID / GLP	Species; Number Female/ group	Route & dose (mg/Kg)	Dosing period	NOAEL (mg/kg &AUC)
Embryo-fœtal development/	SD Rat/	SGD-35: IV bolus/	GD6-13 (q7d ×2)	F0: 1 mg/Kg q7d ×2

R-Toxicity-34, Amendment 2/ non-GLP	3F (q7d × 2)/gp 6F (q3d × 5)/gp	1, 3, 10 (q7d × 2); 0, 0.4, 1.2, 4.0 (q3d × 5)	GD6-18 (q3d ×5)	F1: 1 mg/Kg q7d ×2
Major findings: embryo-fetal lethality characterised by reductions in viable fetuses and increased resorptions				
Embryo-fœtal development/ 8204397/ GLP	SD Rat/25F/gp	SGD-35: 0.3, 1.0, 3.0, 10; MMAE: 0.2	GD6-13 (q7d ×2)	F0: 1 mg/Kg q7d ×2 F1: 1 mg/Kg q7d ×2
Major findings: F0: SGN-35 ≥3.0, MMAE 0.2: BW↓; haematological decrements; Thymus lymphocytic depletion. **SGN-35 ≥3.0** Abortion/resorption 22/24 and 25/25; Spleen: extramedullary haematopoiesis↓ **MMAE 0.2** Abortion/resorption 1/24; Bone marrow: hypercellularity **F1: SGN-35 ≥3.0, MMAE 0.2:** B **SGN-35 ≥3.0** live fetuses↓↓↓; **MMAE 0.2** Live fetuses↓ low incidence of external variations and malformations				

Toxicokinetic data

Toxicokinetic parameters were obtained concurrently with repeat-dose toxicity studies in monkeys and rats and an embryotoxicity study in rats.

An overview of the relative exposures to SGN-35 by species is provided in Table 14. Exposures associated with the highest non-severely toxic dose (HNSTD) in rats and at the no observed adverse effect level (NOAEL) in monkeys are shown. The human exposures reflect the data collected for the proposed marketed dose of 1.8 mg/kg. The serum exposure to SGN-35 in rats at the HNSTD was approximately 3 to 4 times that in humans. The serum exposure to SGN-35 in monkeys at the NOAEL was approximately 2 to 3 times that in humans.

Table 14: Comparative Systemic Exposure to SGN-35 after Intravenous Administration of SGN-35 to Rats, Monkeys, and Humans

Species	Dose Association	Dose (mg/kg)	Cmax [a] (µg/mL)	$AUC_{0-\infty}$ [b] (day*µg/mL)
Rat	HNSTD	5	103 – 138	253
Monkey	NOAEL	3	55.4 – 83.8	140 – 210 [c]
Human	proposed dose	1.8	33.18	82.61

HNSTD: highest non severely toxic dose; NOAEL: no observed adverse effect level; a: observed Cmax data are presented from subchronic repeat-dose toxicity studies in rats (Report 7646-118) and monkeys (Report 8216375) and from cycles 1 to 9 of phase 1 clinical study SG035-00001; b: AUC0-∞ data are presented from the single-dose pharmacokinetic studies in rats (Report R-PK-08) and monkeys (Report 8213480) and from cycles 1 to 9 of phase I clinical study SG035-0001; c: The range represents the values from primate antihuman antibodies (PAHA)-positive and –negative animals

Local Tolerance

Dedicated studies evaluating local tolerance of brentuximab vedotin were not submitted. Microscopic examination of the injections sites as part of the repeat-dose toxicology studies in both rats and monkeys identified no test article-related effects at the injection sites.

Other toxicity studies

With regard to immunogenicity, the presence of PAHA or RAHA was assessed in toxicology studies to determine the immunogenicity of brentuximab vedotin and to assist in interpretation of the toxicokinetic data. The impact of PAHA on the toxicokinetics of brentuximab vedotin was not formally determined. Toxicokinetic parameters were estimated and reported separately for animals with and without PAHA. In some studies, particularly when brentuximab vedotin was administered weekly, a

more rapid decline in brentuximab vedotin concentrations was apparent in monkeys that were positive for PAHA. In the chronic toxicology study, the toxicokinetics of brentuximab vedotin in PAHA positive monkeys appeared to be altered in some and not in others. Monkeys with high PAHA titers (greater than 10,000) were associated with increases in MMAE exposure (AUC and Cmax). However, the increased MMAE exposures in monkeys in the chronic toxicology study were not associated with increased microscopic findings.

2.3.5. Ecotoxicity / environmental risk assessment

Table 15: Summary of main study results

Substance (INN / Invented Name): brentuximab vedotin			
CAS-number (if available): n/a			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	e.g. OECD107	No study available	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	No study available	
	BCF	No study available	
Persistence	DT50 or ready biodegradability	No study available	
Toxicity	NOEC or CMR	No study available	
PBT-statement :	A PBT assessment has not been completed. Because of the nature of the active ingredient it is not amenable to the determination of log K_{ow} according to standard guidelines. For the MMAE part of the active ingredient it would be possible to determine a log Kow. This has not been done. However, the resulting log K_{ow} is not to be expected to be above 4.5 as the log octanol-water partitioning coefficient of the building blocks of MMAE Methylvaline, Valine, Dolaisoleucine, Dolaproline, and Norephedrine are each below 4.5 (Platts *et al*, 2000, Pliska *et al*, 1981). Brentuximab vedotin is not PBT nor vPvB.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.0005	µg/L	< 0.01 threshold (N)

The PECsurfacewater value for brentuximab vedotin is below the action limit of 0.01 µg/L and brentuximab vedotin is not considered a PBT substance due to the size of the molecule. Therefore brentuximab vedotin is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

The following effector mechanism was proposed by the applicant: upon binding of brentuximab vedotin to cell surface CD30, the antibody-drug-conjugate is internalised, traffics to lysosomes and MMAE is released. This leads to dissolution of intracellular microtubule networks finally resulting in cell cycle arrest at the G2/M phase and ultimately cellular apoptosis. Each individual step of the proposed effector mechanism was experimentally demonstrated. Brentuximab vedotin was shown to traffic to lysosomes within 4 hours of treatment by co-localisation with the lysosomal antigen LAMP-1 using immunofluorescence microscopy. By subcellular fractionation using brentuximab vedotin conjugated to 14C-labelled MMAE, it was shown that the drug is released intracellularly. This release occurred at 37°C and was dependent on lysosomal activity. By mass spectrometry, released drug was identified as MMAE.

After intracellular release, free MMAE appeared extracellularly over time. By this mechanism, free toxin may get into the circulation of treated patients and may cause toxicity in bystander cells. Such effect has indeed been demonstrated experimentally (Okeley *et al*, 2010). In co-cultures of CD30-positive and CD30-negative tumour cells treated with brentuximab vedotin, cytotoxic activity was also observed for CD30-negative cells. In cultures of CD30-negative cells alone, brentuximab vedotin did not mediate cytotoxicity. Of note, this study (Okeley *et al*, 2010) was not presented by the applicant in the MAA dossier.

Taken together, the anti-tumour effector mechanism mediated by brentuximab vedotin as proposed by the applicant was sufficiently demonstrated. However, the presence of free MMAE in rats which are CD30-negative, and the appearance of free (unconjugated) brentuximab indicate that CD30-independent release of MMAE may occur as well. It remains unclear if the linker may be cleaved as a result from proteolytic cleavage via non-lysosomal pathways following the cellular uptake of brentuximab vedotin via pinocytosis or binding to the FC-receptor, or as a consequence of maleimide transfer of the linker.

With regard to the immunological effector functions potentially mediated by brentuximab vedotin, it was shown that brentuximab vedotin induced phagocytosis, while it did not induce antibody-dependent or complement-dependent cytotoxicity. No studies addressing the potential interaction of brentuximab vedotin with FC-gamma receptors were submitted. However, this is acceptable given the lack of immunological effector functions induced by brentuximab vedotin.

In a cynomolgus monkey tissue cross-reactivity study, positive staining of thyroid samples of 3 animals suggests that the thyroid might be a potential target organ for brentuximab vedotin in patients. However, in the repeated-dose toxicity studies in cynomolgus monkeys no effect on thyroid tissue was observed. Furthermore, in human thyroid no tissue cross-reactivity was observed. Therefore, the finding in cynomolgus monkey thyroid tissue appears to be of limited or no toxicological significance. In a second tissue cross-reactivity study against human and rat tissues, staining of mononuclear and hematopoietic cells was in accordance with the expression pattern of CD30, while staining of spindloid cells, epithelia and extracellular material was unexpected but, nevertheless, no secondary pharmacodynalic effects have been identified to date. No other secondary pharmacodynamic studies were submitted which is considered acceptable, as secondary pharmacodynamic effects of SGN-35 have not been identified to date.

With regard to safety pharmacology, MMAE produced a fractional block of peak hERG tail current that was significantly different from the negative control at high MMAE concentration (100 µM) but not at the low concentration (10 µM).The 10 µM concentration of MMAE is approximately 1000x higher than the mean plasma Cmax of MMAE (approx. 7 nM) in patients treated with the clinical dose of

brentuximab vedotin. Therefore, it is considered unlikely that MMAE derived from brentuximab vedotin would block hERG K+ channels in vivo.

In a dedicated safety pharmacology study in cynomolgus monkeys a single IV infusion of brentuximab vedotin up to 3 mg/kg had no effect on the cardiovascular, respiratory or central nervous systems.

In addition to these studies, overall safety was based on the outcome of repeated-dose toxicity studies in which animals were treated with doses that achieved exposure levels that were 2- to 3-fold higher than the exposure level associated with the proposed marketed dose of 1.8 mg/kg for human patients.

No pharmacodynamic drug interaction studies were submitted (see discussion on clinical pharmacology).

The pharmacokinetic properties of SGN-35 were evaluated in Sprague-Dawley rats and cynomolgus monkeys. Since SGN-35 has been developed for intravenous (IV) administration all non-clinical studies were conducted using the IV route of administration. In addition, to support the interpretation of exposure-response relationships in the toxicology studies, kinetic parameters after administration of MMAE (the active drug released from brentuximab vedotin) and unconjugated brentuximab (monoclonal antibody) was investigated in both rats and monkeys. For the purposes of interspecies comparison of the nonclinical findings in animals with those in humans, protein binding, metabolism, and excretion of MMAE was specifically addressed. The immunogenicity of SGN-35 was evaluated by measuring rat and primate anti-human antibodies (RAHA and PAHA) to determine whether anti-human antibodies affected exposure to SGN-35 in animals. Since cAC10 binds to monkey CD30 with a similar affinity as human CD30, the toxicity study in cynomolgus monkey allowed for assessment of antigen-dependent toxicity of SGN-35.

Brentuximab vedotin, unconjugated brentuximab, total antibody (TAb) and MMAE were measured using validated methods. Yet, interference of brentuximab vedotin in the rat anti-human antibody (RAHA) and primate anti-human antibody (PAHA) assays may have led to erroneous interpretation of samples as being RAHA or PAHA negative.

Brentuximab vedotin showed a low clearance in rats and monkeys. The volume of distribution of brentuximab vedotin at steady state is low in both species, which suggests limited tissue distribution. The half-life for brentuximab vedotin was 8.5 to 14.6 days in rats and 1.6 to 2.7 days in monkeys compared to 4 to 6 days in patients. The exposure of brentuximab vedotin was approximately dose-proportional in rats and approximately or greater than dose-proportional in monkeys. Exposures to brentuximab vedotin in humans were also approximately dose-proportional, similar to those in animals. The Cmax and Tmax of TAb after administration of brentuximab vedotin to rats were similar to those of brentuximab vedotin, while the exposure (AUC) was almost 2-fold higher. These results indicate deconjugation independent of CD30 may occur. As brentuximab vedotin is stable in plasma, deconjugation is possibly the result of intracellular cleavage of the linker by as yet unidentified pathways.

Binding of MMAE to plasma proteins was low to moderate, suggesting that variation in the binding capacity of plasma proteins does not have a major impact on the concentration of free drug in plasma. Protein binding was concentration-dependent in mouse and human plasma and was shown to be higher in rats and humans than in mice and monkeys. Brentuximab vedotin, TAb and MMAE were measurable in fetal compartments on day 18 of gestation after administration of brentuximab vedotin on day 6 and 13 of gestation, which demonstrates that brentuximab vedotin and unconjugated brentuximab and/or MMAE are transferred across the placenta following brentuximab vedotin treatment in rats.

A blood-to-plasma ratio of 2 was observed after application of [3H]MMAE showing quick distribution of [3H]MMAE to erythrocytes, but after application of [3H]brentuximab vedotin, low blood-to-plasma

ratios suggest only minor distribution of [3H]brentuximab vedotin or of [3H]MMAE released from [3H]brentuximab vedotin to erythrocytes.

Since brentuximab vedotin was expected to be catabolised into individual amino acids in vivo, traditional metabolism studies were not performed for the antibody component. However, MMAE was the only product released from cells incubated with 14C-radiolabelled brentuximab vedotin. Moreover, brentuximab vedotin was stable in plasma. Yet, several signals, e.g. higher total antibody exposure values as compared to brentuximab vedotin exposure values and off-target toxicity and toxicity in rats, shown to have no binding sites for brentuximab vedotin, suggest that there might be CD30 independent mechanisms of MMAE release. Moreover, MMAE exposure in cynomolgus monkeys after brentuximab vedotin administration is initially much lower than in humans treated with brentuximab vedotin. However, when cynomolgus monkeys develop a high anti-brentuximab antibody titer, MMAE exposure greatly increases, resulting in plasma Cmax values similar to those in humans, although AUC is still lower than in humans. The mechanism behind this interaction remains unclear.

Metabolism of the active drug MMAE was studied. Twelve metabolites were identified in in vitro metabolism studies of MMAE in rat and monkey hepatocytes. The metabolism of MMAE is similar in rat, monkey, and human hepatocytes. Metabolites formed in human liver microsomes were similar to those formed in rat and monkey hepatocytes. Metabolite C8 was found to be approximately as cytotoxic and metabolites C4 and C7 less cytotoxic than MMAE in CD30-positive cell lines. MMAE was found to be a quasi-irreversible, mechanism-based CYP3A inhibitor and the primary in vitro metabolites are formed by CYP3A4. No human-unique metabolites were found in vitro, while an additional human metabolite was found in vivo. This metabolite is a product of 2 previously identified metabolic pathways. Yet, considering the relatively low plasma levels of metabolites and their 'off-target' formation, the contribution to the efficacy or side effects of brentuximab vedotin may be considered negligible.

The predominant route of elimination of MMAE in rats was via faeces, suggesting that biliary excretion has occurred. One major metabolite was found in faeces (dolaproine O-demethyl-MMAE) and 5 metabolites were found in urine, although the concentrations were low. Studies of excretion into milk were not submitted. A risk to the newborn/infant cannot be excluded. A decision should be made whether to discontinue breast-feeding or to discontinue/abstain from this therapy, taking into account a potential risk of breast-feeding for the child and the benefit of therapy for the woman.

MMAE did not induce any CYP isozymes in vitro. MMAE had a weak inhibitory effect on CYP3A4, but it is unlikely to have any clinical relevance. MMAE was not a substrate of BCRP or MRP2, but it was a substrate of P-gp. MMAE inhibits P-gp, however, not at clinically relevant concentrations. Therefore, interactions via P-gp inhibition are not expected. In addition, MMAE was shown not to be a substrate for OATP1B1, OATP1B3, OCT2, OAT1, OAT3 uptake transporters. However, inhibition of these uptake transporters by MMAE has not been studied. Placental transfer of brentuximab vedotin, MMAE and TAb was shown in the rat.

Myelotoxicity was the primary test article-related toxicity associated with single-dose IV administration of brentuximab vedotin and MMAE across both species. In rats, the test article-related target organs were bone marrow (atrophy/hypocellularity), mesenteric lymph node (lymphoid depletion), thymus (lymphoid depletion, atrophy, and lymphoid necrosis), spleen (lymphoid depletion), liver (single-cell hepatocellular necrosis, bile duct hyperplasia/hypertrophy, and inflammation), intestine (crypt epithelium single-cell necrosis), and pancreas (acinar cell single-cell necrosis). The findings in the spleen and intestine were observed only at a dose of 15 mg/kg brentuximab vedotin and not at doses of 10 mg/kg or less. Single-cell necrosis in the pancreas and in the intestine was not noted in the GLP compliant 4-week repeat-dose toxicology study in rats and the toxicologic significance of this effect in humans is unknown. After a dose-free recovery period of up to 6 weeks, all findings were reversible.

The single-dose NOAEL for brentuximab vedotin and MMAE in rats was 0.5 and 0.01 mg/kg, respectively.

In monkeys, microscopic pathology was not assessed after single-dose administration of brentuximab vedotin. Single-dose administration of brentuximab vedotin to monkeys was tolerated at doses up to 6 mg/kg; however the molar equivalent MMAE dose of 0.116 mg/kg was not tolerated.

With repeat-dose administration of brentuximab vedotin, unconjugated brentuximab, and MMAE in rats and monkeys the principal test article-related effects of brentuximab vedotin and MMAE in both species included changes in the bone marrow and lymphoid tissues; in rats, but not monkeys, effects on the testis and liver were seen. The administration of unconjugated brentuximab at all doses was well tolerated, with no apparent target organ toxicity or clinically significant adverse effects.

Myelotoxicity was the primary test article-related toxicity associated with administration of brentuximab vedotin and MMAE and was dose-dependent in both species. In monkeys, at 1 mg/kg slight bone marrow hypocellularity and very slight to moderate granulocytic/megakaryocytic hypercellularity was observed. The findings increased in severity with increasing doses. At 6 mg/kg brentuximab vedotin, slight to marked bone marrow hypocellularity and slight to marked megakaryocytic hypercellularity were observed. Similarly in rats, myelotoxicity was moderate to severe at 15 mg/kg brentuximab vedotin, minimal to marked at 5 and 10 mg/kg and absent at 0.5 mg/kg. Bone marrow findings were generally reversible.

In rats, lymphoid depletion was observed in spleen only at 15 mg/kg brentuximab vedotin (single dose). Lymphoid depletion and reduced thymus weights were observed at 10 mg/kg, while at 5 mg/kg a reduction in thymus weight was detected, however, without microscopic correlates. In monkeys, lymphoid depletion was observed in spleen and thymus at 6 mg/kg brentuximab vedotin, accompanied by reductions in thymic weight in males.

Consistent with the microscopic findings, decreases in peripheral haematology parameters were observed in both species. In cynomolgus, in the 11-week repeat-dose toxicology study, the predominant effect on haematology was a dose-dependent decrease in neutrophils. At 6 mg/kg brentuximab vedotin (lethal dose), neutrophils were markedly decreased 1 and 2 weeks post-dose, with a nadir a 2 weeks and reversibility by 3 weeks. At 3 mg/kg (HNSTD), a similar, but less severe cyclic decrease in neutrophil counts was observed, while at 1 mg/kg (NOAEL) no biologically relevant effects on neutrophil counts was observed. In addition, in this study other leukocyte, RBC and reticulocyte counts were variably decreased. The haematologic changes observed in the 26-week repeat-dose toxicity study were similar to those of the 11-week study.

In the 4-week repeat-dose toxicity study in rats treated with brentuximab vedotin at 5 and 10 mg/kg, significantly reduced erythropoiesis was observed, resulting in non-regenerative anaemia. This is consistent with the findings of the single-dose study evaluating the kinetics of bone marrow toxicity in the rat, were pancytopenia (erythroid, myeloid and megakaryocytic) was evident. Within the myeloid lineage, neutrophils were most severely affected (up to 85% reduction in neutrophil counts). These data are supported by bone marrow cytology and microscopic data, demonstrating hypocellularity from day 1 to 5 post dose, a compensatory hyperplasia from day 5 to 12 and a return to normal by day 13. In this study, complete recovery of all cell lineages was evident in peripheral haematology endpoints and in bone marrow findings.

Following treatment with the toxin moiety MMAE at molar equivalent doses, the myelotoxicity was qualitatively similar but quantitatively more severe than the toxicity observed with brentuximab vedotin. MMAE at 0.2 mg/kg in rats (molar equivalent of 10 mg/kg brentuximab vedotin) and at 0.116 mg/kg (molar equivalent of 6 mg/kg brentuximab vedotin) induced mortality. Also, the microscopic findings in monkeys given 0.058 mg/kg MMAE were more severe than upon treatment with the

equivalent dose of brentuximab vedotin (3 mg/kg). Thus, on an equimolar basis, MMAE appears to be more myelotoxic than brentuximab vedotin. This is consistent with a high peak concentration of MMAE following IV administration of the toxin, compared to a slower release and lower absolute peak concentrations of MMAE when given as antibody-drug-conjugate. Consequently, toxic effects appear to be more persistent in animals treated with the ADC compared to those treated with the toxin alone.

Neutropenia and associated mortality was the clinically most significant toxicity observed in non-clinical studies in monkeys. Neutropenia was a relatively common treatment-emergent adverse event in patients. Furthermore, two treatment-related deaths in patients were associated with neutropenia and severe infection.

Brentuximab vedotin and MMAE resulted in reversible, dose-dependent hepatic toxicity in rats but not in monkeys. Focal hepatocellular coagulative necrosis and increases in serum hepatobiliary enzymes were observed in rats administered 10-mg/kg brentuximab vedotin q1wk × 4 and the molar equivalent dose of MMAE (0.194 mg/kg). The hepatotoxicity noted in repeat-dose toxicology studies in rats seems to pose minimal risk for the intended population of patients with relapsed or refractory HL and sALCL, since hepatotoxicity was not noted in monkeys. However, it should be considered that MMAE plasma levels in patients are two orders of magnitude higher than those observed in monkeys. Therefore, hepatotoxicity might still be of concern. Yet, the hepatobiliary enzyme elevations were reversible and can be easily monitored in patients. Thus far only very few patients have shown moderately elevated liver enzymes.

Brentuximab vedotin and MMAE resulted in partially reversible dose-dependent testicular toxicity in rats. Degenerative changes in the seminiferous tubules were observed in rats dosed with 5- and 10-mg/kg brentuximab vedotin q1wk × 4 (at 5 mg/kg, approximately 3 times the exposure associated with the proposed marketed dose of 1.8 mg/kg). Testicular toxicity was also observed with MMAE, but with lower potency when doses are compared on a molar basis. Although pharmacological *in vitro* studies indicate that brentuximab vedotin does not have affinity for rat CD30, the Applicant suggests that besides a possible interaction of brentuximab vedotin with testicular CD30, the longer apparent half-life of MMAE after administration of brentuximab vedotin also may have contributed to the observed differential testicular toxicity of brentuximab vedotin and free MMAE. A trend toward reversibility of testicular toxicity was demonstrated after a 16-week recovery phase. But even after almost two cycles of spermatogenesis some rats still had severely affected testes. In two out of four male cynomolgus monkeys administered 3 mg/kg brentuximab vedotin, minimal to slight hypospermatogenesis was observed. However, given the sexual immaturity of most of the monkeys used in the toxicological assessment of brentuximab vedotin, definitive conclusions regarding the potential for testicular toxicity in this species cannot be drawn. As appropriate, due warnings and advice are included in the SmPC.

Although peripheral neuropathy was the most common treatment-emergent adverse effect in the clinic, no microscopic evidence of peripheral neuropathy was observed after 4 doses in monkeys or rats at systemic exposures (AUC) up to 6-fold that in humans. The Applicant reviews sporadic findings in the non-clinical studies that might point to neuropathy in these animals. However, as these findings were sporadic and no microscopic correlates were found, the Applicant concludes that in the non-clinical species no peripheral neuropathy occurred. The reason for these species differences is not clear, but higher MMAE plasma levels obtained in humans may have contributed to these differences. As neuropathy was not identifiable as such in animals, these models do not provide a means to study the underlying mechanism for peripheral neuropathy as observed in humans. Nevertheless, peripheral neuropathy is frequently observed in humans with compounds that interact with tubulin and microtubules. It is assumed that with MMAE as with other compounds acting by this mechanism, the mode of action is interaction with tubulin.

Toxicokinetic parameters of brentuximab vedotin, TAb and MMAE after repeat-dose administration was generally consistent with the single-dose kinetics in animals without antihuman antibodies. Kinetic parameters after repeated doses in monkeys were variable, likely due to the formation of antihuman antibodies. Accumulation was not observed following multiple weekly doses of brentuximab vedotin in monkeys. This is in line with the finding in humans where minimal to no accumulation was observed following repeated doses every 3 weeks. Exposure ratios at the NOAEL, respectively HNSTD, of the repeat-dose toxicity studies were calculated in comparison to the human exposure. Exposure was found to be greater in animals. Basis for calculation of exposure ratios were non-clinical studies with a different dosing scheme than the clinical one (for Cmax data from rat study) or single dose studies instead of repeat-dose studies (for AUC data from rat and monkey studies). In light of the similarity of single and multiple dose kinetics and the life-threatening indication, calculation of exposure ratios can, however be accepted.

No genotoxic potential could be demonstrated in standard genotoxicity assays. While MMAE was not directly mutagenic, it was associated with an increase in micronuclei formation. MMAE induced predominantly the formation of centromere-positive micronuclei, consistent with aneugenic (chromosome lagging) micronuclear formation. This finding is not unexpected with compounds such as MMAE that bind tubulin, disrupt the microtubular network, and interfere with mitosis by arresting cells in the G2/M phase of the cell cycle.

No carcinogenicity studies, fertility and early embryonic development studies and prenatal or postnatal studies (including maternal function) or studies in which the offspring (juvenile animals) are further dosed and evaluated were submitted, which is acceptable as brentuximab vedotin is intended for the treatment of patients with relapsed or refractory HL and sALCL. With regard to fertility, the discussion on the effects of brentuximab vedotin and MMAE on rat testis is of relevance. The testicular toxicity observed is consistent with the pharmacologic disruption of microtubules by MMAE. Overall, it seems reasonable to assume brentuximab vedotin may have an adverse effect on spermatogenesis in man. As the testicular toxicity observed in rats was only partially reversible after 16 weeks recovery, this potential risk has been reflected in the SmPC. Men being treated with this medicine are advised to have sperm samples frozen and stored before treatment. Men being treated with this medicine are advised not to father a child during treatment and for up to 6 months following the last dose.

In rats, brentuximab vedotin was clearly embryo-foetal toxic, causing loss of almost all embryos at 3 mg/kg and above. This toxicity is greater than the one observed with equimolar doses of MMAE. Considering that CD30 is strongly expressed in decidual tissue, this tissue might be the actual target causing embryo-foetal lethality, but a more prolonged exposure (albeit at much lower levels) to MMAE after administration of brentuximab vedotin as compared to exposure after administration of the free toxin MMAE may have contributed to the differential embryo/foetal toxicity as well. Brentuximab vedotin should not be used during pregnancy unless the benefit to the mother outweighs the potential risks to the foetus. If a pregnant woman needs to be treated she should be clearly advised on the potential risk to the foetus. Moreover, w omen of childbearing potential should be using two methods of effective contraception during treatment with brentuximab vedotin and until 30 days after treatment.

With regard to immunogenicity, the lack of RAHA was unexpected. However, as discussed under analytical methods, it seems probable that the presence of brentuximab vedotin in the samples may have led to negative results for measurement of RAHA due to interference in the assay. The positive immunogenic responses in monkeys appeared to reduce the concentrations of brentuximab vedotin and TAb after multiple doses, and conversely increased the concentrations of MMAE after multiple doses in of the animals with high anti-brentuximab antibody (PAHA) levels. In these animals the Tmax for MMAE was also decreased. The precise mechanism behind this phenomenon is unclear, but since

even the higher apparent MMAE plasma levels did not cause toxicity in the monkeys and a similar sharp antibody-dependent increase of MMAE plasma levels was not observed in humans, this finding is possibly of little relevance for humans.

2.3.7. Conclusion on the non-clinical aspects

Toxicity of brentuximab vedotin and MMAE observed in rats and cynomolgus monkeys is consistent with the expected toxicity of a tubulin-binding agent, causing arrest of the cell cycle and apoptosis especially in rapidly dividing tissues. Although results from in vitro studies indicate that brentuximab does not bind to rat CD30, results from repeat-dose toxicology studies in rats suggest that antibody-mediated delivery of the toxicant to target tissues – i.e. testis and decidual tissue – cannot be excluded. As CD30 is expressed in decidual tissue and possibly spermatogonia/early spermatocytes (although human testis samples did not show cross-reactivity with brentuximab), the treatment with brentuximab vedotin is not compatible with pregnancy and possibly may bear a risk for infertility in males.

Peripheral neuropathy is a predominant side effect in humans, but not observable in animals. It is assumed that with MMAE as with similar compounds, the mode of action is interaction with tubulin.

2.4. Clinical aspects

2.4.1. Introduction

GCP

Compliance with GCP and applicable regulations was verified by a GCP inspection for studies SG035-003 and SG035-004 at 2 investigator sites in the USA as well as at the sponsor site, in particular where it could have had an impact on the validity of the data or the ethical conduct of the study. The inspection focused on the verification of selected efficacy and safety data reported in the MAA for a sample of patients that was determined by the inspectors. Based on the documentation seen during the inspections, there has not been any indication that the study has not been conducted in accordance with established quality standards and regulations. In addition, the inspectors did not find any major inconsistency and did not find any indication of fraud or manipulation of documents. In summary, the inspection team concluded that the data presented in the clinical study reports are accurately described and hence the data can be considered for the evaluation of the MAA.

The clinical trials were performed in accordance with GCP as claimed by the applicant. Moreover, the applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular listing of clinical studies**

Table 16: Overview of clinical studies with brentuximab vedotin (SGN-35)

Study Number Phase	Design	Study Objective	Diagnosis	SGN-35 Dosage Frequency Duration[a]	Primary Endpoint	Planned/ Treated/ Analyzed[b]
Clinical Pharmacology Studies						
SGN35-007 Phase 1	Open-label, single-arm	Clinical pharmacology	CD30+ hematologic malignancies	1.8 mg/kg IV q3 wk 16 cycles	Duration of ventricular repolarization	48/ 52/ 46
SGN35-008A Phase 1	Open-label, non-randomized, 3-arm, drug-drug interaction, excretion	Clinical pharmacology	CD30+ hematologic malignancies	1.2 or 1.8 mg/kg IV q3 wk 2 cycles	PK parameters	36/ 56/ 45
Efficacy and Safety Studies						
SG035-0001 Phase 1	Open-label, single-arm, dose-escalation	Safety	CD30+ hematologic malignancies	0.1-3.6 mg/kg IV q3 wk NA	AEs; laboratory abnormalities	51/ 45/ 45
SG035-0002[d] Phase 1	Open-label, single-arm, dose-escalation	Safety	CD30+ hematologic malignancies	0.4-1.4 mg/kg IV q1 wk 12 cycles	AEs; laboratory abnormalities	72/ 44/ 44
SG035-0003 Phase 2	Open-label, single-arm	Efficacy and safety	HL	1.8 mg/kg IV q3 wk 16 cycles	ORR	100/ 102/ 102
SG035-0004 Phase 2	Open-label, single-arm	Efficacy and safety	Systemic ALCL	1.8 mg/kg IV q3 wk 16 cycles	ORR	55/ 58/ 58

Abbreviations: AE = adverse event; ALCL = anaplastic large cell lymphoma; HL = Hodgkin lymphoma; IV = intravenous(ly); NA = not applicable; ORR = overall objective response rate; PK = pharmacokinetic(s); q = once every; US = United State; wk = week(s); W. = Western.

a Maximum treatment duration represented as treatment cycles (1 cycle = q3 wk, 1 dose/21-day cycle; or q1 wk, 3 doses/28-day cycle).

b Contributed to evaluation of the primary endpoint.

c First patient visit to date of last assessment for submission.

d Designed as two-part dose escalation study of monotherapy followed by combination therapy (with gemcitabine); study was terminated prior to initiating combination therapy cohorts.

In addition, the applicant supplied data specifically for brentuximab vedotin-treated HL patients who had not received prior ASCT due to insufficient therapeutic response to prior therapy, comorbidities, age, or other reasons. Fifty-nine individual patient cases have been assembled from the following 6 sources: SG035-0001 phase 1 dose-escalating study (every 3 week dosing), n= 10; SG035-0002 phase 1 dose-escalating study (weekly dosing), n=10; SGN35-007 phase 1 QTc study (every 3 week dosing at 1.8 mg/kg), n=7; Study TB-BC010088 phase 1/2 Japan-only study (every 3 week dosing at 1.8 mg/kg), n=6; Named Patient Program Case Series 1 (every 3 week dosing at 1.8 mg/kg), n=14; and Named Patient Program Case Series 2 (every 3 week dosing at 1.8 mg/kg), n=12

Efficacy data were provided from two Phase I dose escalation trials in patients with CD30 positive haematological malignancies and two pivotal Phase II trials, one in patients with CD30+ relapsed or refractory Hodgkin lymphoma after autologous stem cell transplantation and the other in patients with refractory or relapsed anaplastic large cell lymphoma (ALCL).

2.4.2. Pharmacokinetics

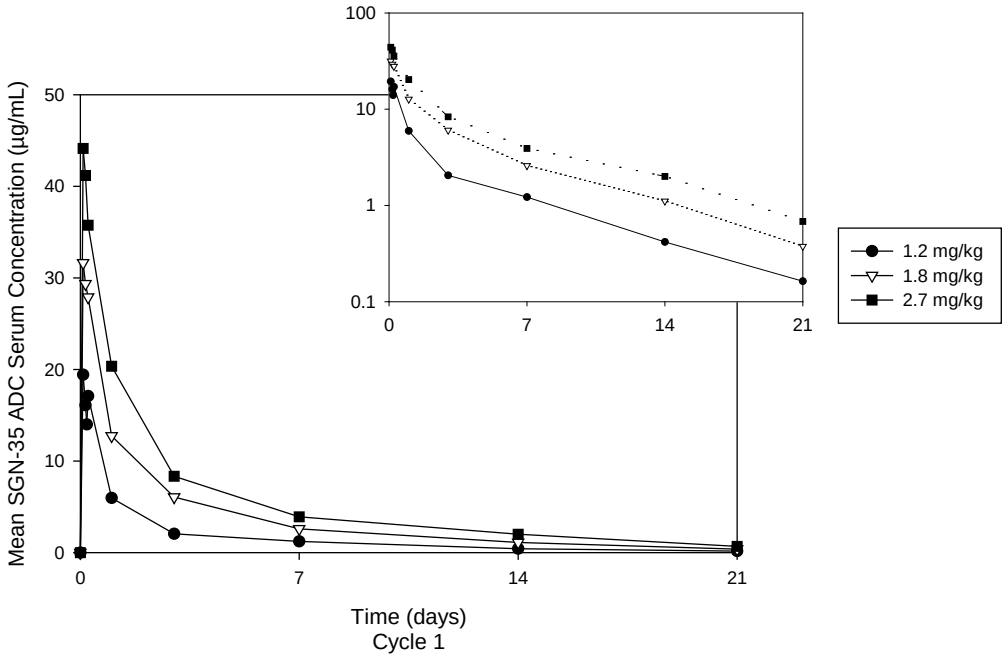
Five clinical studies conducted in patients with HL and sALCL (with CD30-expressing tumour cells) provided the primary clinical pharmacology data; phase 1 studies (SG035-0001 and SG035-0002) investigating safety, PK, and antitumor response to SGN-35; a study to assess the effects of SGN-35 on cardiac ventricular repolarisation (SGN35-007); and a study to determine the DDIs between SGN-35 and midazolam or modulators of CYP3A4 function, as well as the routes of excretion of MMAE (SGN35-008A). Study SGN35-008B to assess the PK of SGN-35 in patients with hepatic or renal impairment is still on going.

Sparse PK data from the (pivotal) phase 2 studies (SG035-0003 and SG035-0004) were also included in a population PK analysis. In this, a three-compartment model was used to describe the PK of ADC with zero order input and first-order elimination. The elimination of ADC was linked to the formation of MMAE through 2 pathways: direct conversion of ADC to MMAE and conversion of ADC to MMAE following binding to a target site. The PK of MMAE was described by a two-compartment model with first-order elimination and formation of MMAE both directly from ADC and through binding of ADC to a hypothetical target.

Distribution

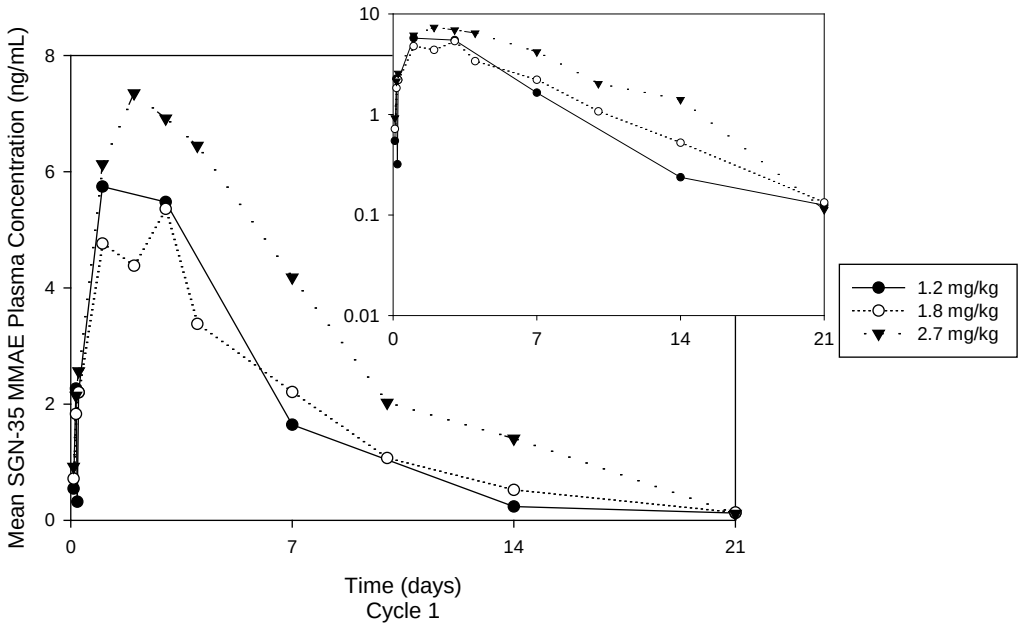
A multi-exponential decline in SGN-35 (ADC: Antibody Drug Conjugate) serum concentrations was observed with a terminal half-life of approximately 4-6 days at the 1.8 mg/kg dose level (Figure 3). Exposures were approximately dose proportional. No accumulation was observed with multiple doses at the q3wk schedule. Volume of distribution of SGN-35 was approximately 6–10 l, indicating that SGN-35 was primarily limited to the vascular space.

Figure 3: ADC serum concentration-time profile of SGN-35, study SG035-0001



The plasma pharmacokinetics of MMAE following an intravenous dose of SGN-35 in patients with CD30-positive hematologic malignancies appeared to be formation-limited (Figure 4). Maximum concentrations (5.0 ng/ml first dose) were typically observed 2 days post-dose and MMAE declined with an apparent terminal half-life of approximately 3-4 days at the 1.8 mg/kg dose level. Exposures were approximately dose proportional over the range of 0.1 – 2.7 mg/kg. MMAE AUC0-21d and Cmax decreased 20-50% after cycle 1 and achieved steady state thereafter. A decrease in MMAE exposure was not observed when SGN-35 was administered once weekly (study SG035-0002). The cause of the lower systemic exposure to MMAE after multiple dosing compared to single dosing for a q3wk schedule is not known.

Figure 4: MMAE plasma concentration-time profile of SGN-35, study SG035-0001



As with ADC, maximum concentrations of Tab were typically observed at the end of infusion or the sampling time point closest to the end of infusion. Exposures were approximately dose proportional and higher than those associated with ADC. The proportion of TAb to ADC increased with time. Based on the proposed mechanism of action, the increase in unconjugated antibody is expected to be a result of drug-linker cleavage.

The extent of SGD-1006 (the drug-linker and MMAE portion of SGN-35) transfer from SGN-35 to plasma proteins in humans administered SGN-35 was determined. The extent of drug linker transfer from SGN-35 to plasma proteins (albumin) was minimal with transferred drug linker being approximately 1.5% of the circulating conjugated and unconjugated MMAE in plasma.

Elimination

In study SGN35-008A, metabolism and excretion of MMAE was investigated in 12 subjects of whom 8 subjects had adequate urine and faeces sampling following SGN-35 administration cycle 1. Excretion of MMAE was followed for 7 days after administration of SGN-35. Approximately 23.5% of the MMAE received was recovered in both urine and faeces over a 1-week period. Of the MMAE recovered, the median percentage of MMAE excreted in feces was 72% (range, 59% to 77%), with the remainder excreted in urine. In the same study, metabolites of MMAE were analysed in urine and faeces. MMAE was the only observed species in unconcentrated urine and feces bulk pools. In urine and feces bulk pools concentrated ten-fold, 8 human metabolites of MMAE were observed.

Dose proportionality and time dependencies

Two dose escalating studies were conducted in patients with relapsed/refractory CD30-positive hematologic malignancies:

Study SG035-0001: 0.1 mg/kg -3.6 mg/kg SGN-35 iv, every 3 weeks. The pharmacokinetics of SGN-35 were best characterized at the 1.8 and 2.7 mg/kg dose levels, with 12 patients at each of those dose levels for the first cycle of dosing.

Increases in SGN-35 ADC exposure were approximately dose proportional. First dose geometric mean terminal half-life was between 4 and 6 days for the 1.8 and 2.7 mg/kg dose levels. Median time to maximum concentration (T_{max}) typically occurred immediately after the end of the infusion (approximately 0.089 to 0.094 days for the 1.8 and 2.7 mg/kg dose levels).

Increases in MMAE were approximately dose proportional. First dose apparent terminal half-life was between 3 and 4 days for the 1.8 and 2.7 mg/kg dose levels, and median T_{max} occurred approximately 2 days postdose for the 1.8 mg/kg dose and approximately 3 days postdose for the 2.7 mg/kg dose.

No accumulation was detected for ADC at the 1.8 mg/kg dose consistent with the half-life estimate. The observed Cycle 2/Cycle 1 and Cycle 3/Cycle 1 geometric mean ratio (GMR) for AUC_{0-21d} ranged from 0.93 to 1.24, and the observed C_{max} GMR ranged from 0.73 to 1.11.

MMAE AUC_{0-21d} and C_{max} decreased following multiple doses (data not shown).

Study SG035-002: 0.4 mg/kg – 1.4 mg/kg SGN-35 (IV, weekly, first 3 weeks of every 4-week cycle). Pharmacokinetics were best characterised at the 1.0 and 1.2 mg/kg dose levels, with 12 patients at each of those dose levels.

ADC exposure was approximately dose-proportional over the range 0.4 -1.4 mg/kg SGN-35 (IV, weekly, first 3 weeks of every 4-week cycle) by visual inspection. For MMAE, variability was rather high making the dose proportionality less clear.

Following a weekly administration (first 3 weeks of every 4-week cycle), the accumulation of ADC and MMAE was moderate. The intra- and inter-cycle accumulation ratio for ADC was approximately 1.72 at 1.0 mg/kg and 1.28 at 1.2 mg/kg. For MMAE, accumulation was modest; the intra- and intercycle accumulation ratio was approximately 1.09 at 1.0 mg/kg and 1.17 at 1.2 mg/kg.

Special populations

Evaluation of pharmacokinetics of ADC and MMAE in special populations has been based on population PK analysis. The effects of gender, age, race, weight, body surface area, and disease (HL, sALCL, or other) on the PK of SGN-35 and MMAE were evaluated using a population PK approach. A three-compartment model was used to describe the PK of ADC with zero order input and first-order elimination. The elimination of ADC was linked to the formation of MMAE through 2 pathways: direct conversion of ADC to MMAE and conversion of ADC to MMAE following binding to a target site. The PK of MMAE was described by a two-compartment model with first-order elimination and formation of MMAE both directly from ADC and through binding of ADC to a hypothetical target. A conventional phase 1 study is ongoing to examine the effect of renal and hepatic impairment on the pharmacokinetics of ADC and MMAE.

Weight was a clinically meaningful covariate for ADC and MMAE pharmacokinetics. For the range of weights in the current analysis (41 to 168 kg), this would result in a 32% lower to 87% higher clearance for the range of weights compared to a 70-kg individual. The recommended dose is weight-based (1.8 mg/kg) but with a maximum of 180 mg.

Age was not a significant covariate in the ADC and MMAE population PK model. No dose adjustment is recommended based on age for adults.

Pharmacokinetic interaction studies

In vitro assays indicated that MMAE is metabolised by CYP3A4 and that MMAE has the potential to be a mechanism-based inhibitor of CYP3A4/5 (see non-clinical pharmacokinetics section). Based on this information, study SGN35-008A was designed to determine the potential for CYP3A4-mediated DDIs

between SGN-35 and various drugs known to be metabolized by CYP3A4 or to affect CYP3A4 activity. Drug-drug interactions with rifampicin and ketoconazole decreased MMAE exposure with 31% and increased MMAE exposure with 73%, respectively. These data are consistent with a slow turnover of MMAE by CYP3A4. Rifampicin and ketoconazole did not affect the pharmacokinetics of SGN-35. Co-administration of midazolam with SGN-35 had no effect on the pharmacokinetics of midazolam, indicating that SGN-35 and MMAE do not inhibit CYP3A4 in vivo. The incidence of neutropenia grade 3 or higher was increased in the presence of ketoconazole. The wording in SmPC in section 4.5 warns appropriately for potential increase in neutropenia due to increased concentrations of MMAE in the presence of strong CYP3A4 inhibitors.

Pharmacokinetics using human biomaterials

Please refer to the non-clinical pharmacokinetics section.

2.4.3. Pharmacodynamics

Mechanism of action

No clinical studies addressing the mechanism of action were submitted.

Primary and Secondary pharmacology

A QT/QTc prolongation study indicated that there was no clinically significant change from baseline in the duration of ventricular repolarisation as measured by QTcF in patients treated with SGN-35, and that there was no significant relationship between plasma MMAE concentrations and changes in QTcF from baseline to Cycle 1 and Cycle 3, Days 1, 2, 3, or 4.

2.4.4. Discussion on clinical pharmacology

Five clinical studies conducted in patients with HL and sALCL (with CD30-expressing tumour cells) provided the primary clinical pharmacology data. Pharmacokinetics of SGN-35 was consistent with other monoclonal antibody products. In agreement with the effect of weight on the pharmacokinetics of SGN-35, the recommended dosing is 1.8 mg/kg. However, a maximal dose of 180 mg is recommended. Due to capping of the SGN-35 dose, exposure to ADC did not continue to increase in patients > 100 kg but decreased to level <70 kg. In contrast, MMAE AUC continued to increase in patients >100 kg. This results is a different ADC/MMAE ratio in patients >100 kg. Adcetris dosing was capped at 100 kg in clinical trials. This was not based on PK data but based on experience with other mAbs that as an obese individual is less vascularised per kg body weight than a lean individual, this may lead to over-compensation for increasing body weight. Efficacy parameters did not show statistically significant differences by patients' weight. The incidence of diarrhoea and fatigue appear increased in patients weighing >100 kg, but these adverse events have not been shown to correlate well with MMAE plasma concentrations in the dose finding studies. The incidence of neutropenia, which is correlated with SGN-35 and MMAE concentrations was not increased in patients >100 kg. Although there are no strong signals that the benefit risk balance is different in patients > 100 kg, the number of patients >100 kg was low and an updated efficacy and safety analysis from study SG035-0003 and SG035-0004 should be submitted when finalised.

Pharmacokinetics of MMAE appeared to be formation limited. Upon multiple dosing, exposure to MMAE was lower compared to the first dose. Population PK analysis showed that baseline serum albumin concentration was a significant covariate of MMAE clearance. The analysis indicated that MMAE clearance was 2-fold lower in patients with low serum albumin concentrations <3.0 g/dl compared with

patients with serum albumin concentrations within the normal range. As binding of MMAE to plasma proteins is moderate, the large impact of albumin on the pharmacokinetics of MMAE was unexpected. The incidence of neutropenia was slightly higher in subjects with albumin concentration <3.0 g/dl. However, as SGN-35 pharmacokinetics is not affected by albumin concentration, a priori dose modification based on albumin concentration is not justified as this would lower the SGN-35 exposure and may affect the efficacy.

MMAE is slowly metabolised by CYP3A4 but is mainly excreted unchanged. The fate of MMAE is not clear. Recovery of MMAE in the mass balance study (23.5%) was much lower than expected from the PK of MMAE. This may be due to the fact that only unchanged MMAE was measured. Furthermore, exposure to MMAE was lower in the second cycle compared to the first cycle but the cause for this is not known. The role of active metabolites is unclear. Given the importance of MMAE (and potentially some of its metabolites) for the toxicity of brentuximan vedotin, the applicant will further investigate MMAE metabolism in a phase 1 study which has been included as an additional pharmacovigilance activity in the RMP. Similarly, hepatic and renal impairment may affect the elimination of MMAE. This is currently under investigation in study SGN35-0008b. The report should be submitted as soon as the study is finalised.

Co-administration of brentuximab vedotin with ketoconazole, a strong CYP3A4 and P-gp inhibitor, increased the exposure to the antimicrotubule agent MMAE by approximately 73%, and did not alter the plasma exposure to brentuximab vedotin. Therefore, co-administration of brentuximab vedotin with strong CYP3A4 and P-gp inhibitors may increase the incidence of neutropenia. If neutropenia develops, the dose of brentuximab vedotin should be adjusted as described in section 4.2 of the SmPC. Co-administration of brentuximab vedotin with rifampicin, a strong CYP3A4 inducer, did not alter the plasma exposure to brentuximab vedotin; however it reduced exposure to MMAE by approximately 31%. Co-administration of midazolam, a CYP3A4 substrate, with brentuximab vedotin did not alter the metabolism of midazolam; therefore brentuximab vedotin is not expected to alter the exposure to medicines that are metabolized by CYP3A4 enzymes.

In terms of pharmacodynamic drug interactions, it is known from clinical studies outside the claimed indication that combined use of bleomycin and brentuximab vedotin causes pulmonary toxicity (data not shown) and the concurrent use of the two is contraindicated.

2.4.5. Conclusions on clinical pharmacology

Pharmacology of SGN-35, including pharmacokinetics and pharmacodynamics of ADC and MMAE has been sufficiently characterised but additional efficacy data in patients >100 kg are awaited which will inform the recommendation for dose capping in these patients. The fate of MMAE and the importance of active metabolites need further investigation and the applicant will submit the results of a phase 1 study to explore the levels of some of the metabolites in the patients' blood and urine samples. Hepatic and renal impairment may also affect the elimination of MMAE. This is currently under investigation in study SGN35-0008b. The results should be submitted when available (see also Pharmacovigilance section).

2.5. Clinical efficacy

2.5.1. Dose response studies

Study SG035-0001 was a phase I dose-escalation study of SGN-35 in ptients with relapsed/refractory CD30-positive haematologic malignancies. Repeated doses of SGN-35 administered every 3 weeks were generally well-tolerated up to 1.8 mg/kg, the dose determined to be the MTD in the study based

on protocol-defined DLTs. Both the 1.8 mg/kg and the 2.7 mg/kg cohorts were expanded to 12 patients based on the occurrence of 1 DLT in the initial 6 patients enrolled to each cohort and subsequent to the enrolment of a single patient at 3.6 mg/kg who experienced a Grade 5 (fatal) febrile neutropenia and septic shock (presumed, all cultures negative for microbial findings) and died 14 days after receiving the dose. No additional DLT occurred in the expanded 1.8 mg/kg cohort and 3 DLTs occurred in 2 patients in the expanded 2.7 mg/kg cohort. Additionally, events of peripheral neuropathy and neutropenia generally occurred less frequently and were less severe in patients receiving 1.8 mg/kg compared with those receiving 2.7 mg/kg. Fewer treatment discontinuations or modifications due to neutropenia occurred in patients receiving 1.8 mg/kg compared with those receiving 2.7 mg/kg. Pharmacokinetics was best defined at the 1.8 mg/kg and 2.7 mg/kg doses (all other dose cohorts had 3 or 4 patients each). No accumulation of SGN-35 was detected at 1.8 mg/kg and slight accumulation was observed at 2.7 mg/kg. Objective response rate in HL patients in the 1.8 mg/kg cohort was 50% (6 of 12 patients) and in the 2.7 mg/kg cohort was 55% (6 of 11 patients).

Study SG035-0002 was a phase I dose-escalation study of weekly SGN-35 alone and in combination with gemcitabine in patients with relapsed/refractory CD30-positive haematologic malignancies. This study employed a more frequent dosing schedule. In this Study, SGN-35 was administered weekly for 3 out of 4 weeks (Days 1, 8, and 15 every 28 days). At this schedule, the MTD was determined to be 1.2 mg/kg based on dose limiting toxicities as defined by the protocol. After the monotherapy cohorts in the study were enrolled, the emergence of Grade 3 peripheral neuropathy (sensory with some motor) in 14% of patients with continued dosing (median time to onset, 25.9 weeks) resulted in a protocol amendment to reduce dose frequency specific to time on study treatment. Moderate accumulation was observed for SGN-35 and MMAE. The objective response rate in the 1.2 mg/kg cohort was 58% (7 of 12 patients).

2.5.2. Main studies

SG035-003

This was a single-arm, open-label, multicentre, pivotal clinical trial to evaluate the efficacy and safety of brentuximab vedotin as a single agent in patients with relapsed or refractory HL.

Methods

Study Participants

Eligible patients had relapsed or refractory HL, had previously received an autologous stem cell transplant (ASCT), and had histologically-documented CD30-positive disease by central review. Patients were required to have fluorodeoxyglucose (FDG)-avid disease by PET and measurable disease of at least 1.5 cm by spiral CT. At US sites, patients were to be age 12 years or older. At non-US sites, patients were to be age 18 years or older. Amongst other exclusion criteria, patients could not previously have been treated with brentuximab vedotin or received an allogeneic transplant. Patients with congestive heart failure or known cerebral/meningeal disease were also excluded.

Treatments

Brentuximab vedotin 1.8 mg/kg was to be administered via outpatient intravenous (IV) infusion on Day 1 of each 21-day cycle. Dose delays (up to 3 weeks each) and a one-level dose reduction to 1.2 mg/kg were allowed for toxicities. Patients could continue on study treatment until disease progression or unacceptable toxicity. Patients who achieved stable disease or better were to receive a minimum of 8, but no more than 16 cycles of study treatment.

Objectives

The primary objective was to determine the antitumor efficacy of single-agent brentuximab vedotin (1.8 mg/kg administered intravenously every 3 weeks) as measured by the overall objective response rate in patients with relapsed or refractory Hodgkin lymphoma following autologous stem cell transplant.

Secondary Objectives were to assess duration of tumour control, including duration of response and progression-free survival, to assess survival, to assess the safety and tolerability of brentuximab vedotin and to assess the pharmacokinetics of brentuximab vedotin.

Additional objectives were to assess disease-related symptoms as well as to explore the correlation of potential biomarkers with clinical outcomes.

Outcomes/endpoints

The primary efficacy variable was the overall objective response rate (ORR) per an independent review facility (IRF). Treatment response was assessed by spiral CT of the chest, neck, abdomen, and pelvis and PET scans. Determination of antitumour efficacy was based on objective response assessments made according to the Revised Response Criteria for Malignant Lymphoma (Cheson *et al*, 2007), which includes radiographic disease assessment by computed tomography (CT) and/or positron emission tomography (PET) scans and oncology review of clinical data. Clinical response of progressive disease (PD), stable disease (SD), partial remission (PR), or complete remission (CR) was to be determined at each assessment. Treatment decisions were based on investigator assessment of response.

For the secondary efficacy endpoints, progression-free survival (PFS) was defined as the time from start of study treatment to first documentation of objective tumour progression or to death due to any cause. Overall Survival (OS) was defined as the time from the start of study treatment to the date of death due to any cause.

Other efficacy parameters included Maximum Tumour Reduction for which descriptive statistics were generated based on the sum of the product diameters of target lesions at baseline, the minimum post-baseline SPD, and maximum percent observed reduction from baseline. The percentage of patients with any reduction from baseline was also generated. Regarding duration of response, this was defined as the time from start of the first documentation of objective tumour response (CR or PR) to the first subsequent documentation of objective tumor progression or to death due to any cause. B-symptom resolution was defined as the proportion of patients with lymphoma-related B symptom(s) at baseline who achieve resolution of all B symptoms at any time during the treatment period. B symptoms were defined as fever, night sweats, or weight loss >10%. PFS by best clinical response and EFS (with disease progression based on investigator's assessment) was defined as the time from start of study treatment to any treatment failure including treatment discontinuation due to toxicity or patient decision, initiation of a new treatment other than stem cell transplant without documented progression, disease progression, or death.

Sample size

It was planned to enrol 100 patients in the study. If the true objective response rate would be at least 35% with a sample size of 100 subjects a 2-sided binomial test for $\alpha = 0.05$ would have about 90% power to exclude an ORR less than 20%.

Randomisation

Not applicable

Blinding (masking)

Not applicable

Statistical methods

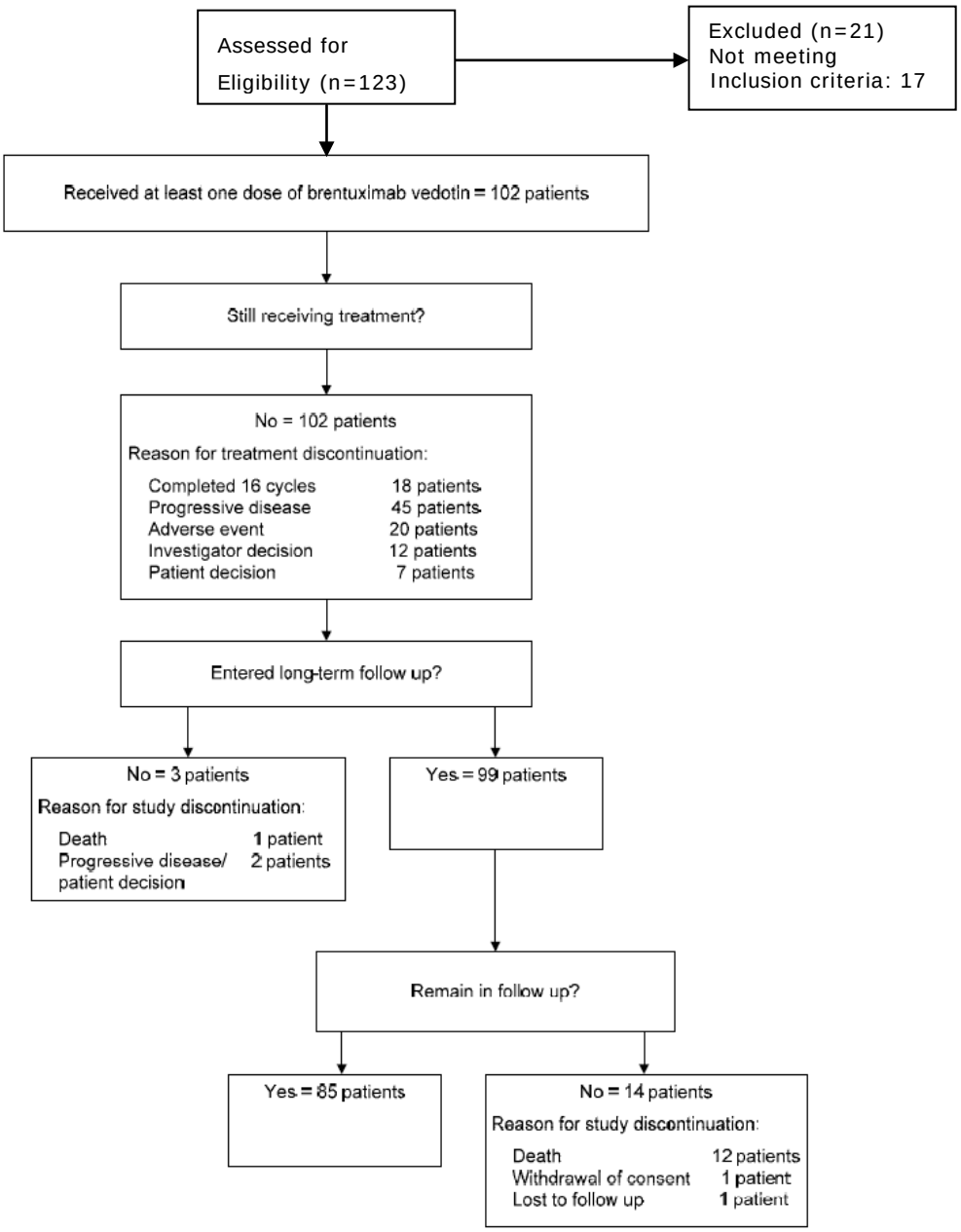
An exact 95% confidence interval was used to test the null-hypothesis that ORR according IRF for SGN035 was <20% vs. the alternative that ORR was ≥20%.

Categorical data were described by (absolute and relative) frequencies including the corresponding 95%confidence intervals. Kaplan-Meier plots and estimates were used to assess time to event data. Continuous data were described by statistical characteristics (mean, sd, median, min, max).

An independent data monitoring committee only reviewed the data for safety. No interim analysis to stop the study was planned.

Results

Participant flow



Recruitment

The first patient was enrolled on 18 February 2009 and the date of last patient last visit was 04 August 2010.

Conduct of the study

The original version of the protocol was dated 02 September 2008. The protocol was amended twice; both amendments were made prior to enrolment of any patients. A summary of the key changes made during Amendments 1 and 2 is provided below.

Two IDMC meetings were convened during the study as planned; however the actual timing of these meetings was different from that prespecified in the protocol and IDMC charter. Per the IDMC charter, the first IDMC meeting was to be scheduled approximately 1 month after the 30th patient had completed Cycle 2. Based on projected enrollment, the first meeting was scheduled for 27 August 2009. Because of more rapid than anticipated patient accrual, at the time of data-cut for the IDMC report (10 August 2009), 95 patients had been enrolled and Cycle 2 restage data were available for 49 patients. At the time of the first IDMC meeting, all 102 patients had been enrolled and the study was closed to enrollment. The second IDMC meeting was held on 28 March 2010. With agreement from the IDMC members, this date was selected to facilitate review of data from both the current study and study SG035-0004.

The definition of a protocol deviation/major protocol deviation as specified in the SAP was revised. For the purposes of this study, 2 categories of protocol variance were defined and used:

- Protocol deviation - defined as an incident involving non-compliance with the clinical protocol that does not have a significant effect on the subject's rights, safety, or welfare, or on the integrity of the resultant data.
- Protocol violation (major protocol deviation) - defined as a divergence from the protocol that has a significant effect on the subject's rights, safety, or welfare, or on the integrity of the resultant data.

40% of the patients had protocol violations. Amongst the protocol violations, drug administration violation was reported in 7 patients:

- 3 patients received a 10-13% lower dose (for 1 cycle: n=2; for 6 cycle: n=1)

- 4 patients received a higher dose (+32% for 2 cycle; +18% for 2/14 cycles; +17% for 1/13 cycles; +50% for 1/4 cycles)

Study conduct violations related to the conduct of restage assessments were reported for 26 patients. PET and /or CT assessments were not done or were performed out of window for 18 patients. Some assessments for the remaining 8 patients lacked diagnostic quality.

The following changes were made to the Planned Efficacy Analyses:

Additional subgroups that were analyzed included: relapsed versus refractory disease, primary refractory disease versus non primary refractory disease, bone marrow involvement at baseline, baseline SPD, patients who received a stem cell transplant after treatment with brentuximab vedotin (allogeneic or autologous)

The age subgroup was adjusted to reflect the definition of the geriatric population provided in ICH guidance documents. The revised age categories are: 12-17 years, 18-64 years, and ≥65 years.

A kappa coefficient was calculated to characteriSe the difference in objective response and best response assessments between IRF and investigator.

Pearson's correlation was used to assess the association of the maximum percent reduction from baseline in SPD by IRF with that by investigator.

A comparison of intrapatient PFS (prior vs. current study) was preplanned before any patients were enrolled. The methodology of this preplanned analysis was subsequently clarified to use a correlated survival analysis (Lin 1989).

Baseline data

Patient demographics and ECOG performance status at baseline for patients are summarised in the following Table 17.

Table 17: Baseline demographic characteristics, study SG035-0003

	All Patients (N=102)
Age (yr)	
N	102
Mean (SD)	34.1 (12.2)
Median	31.0
Min, Max	15, 77
Gender, n (%)	
Male	48 (47)
Female	54 (53)
Race, n (%)	
American Indian or Alaska Native	0
Asian	7 (7)
Black or African American	5 (5)
Native Hawaiian or Other Pacific Islander	0
White	89 (87)
Other	1 (1)
ECOG Performance Status, n (%)	
0	42 (41)
1	60 (59)

Baseline disease characteristics are summarised in the following Table 18.

Table 18: Baseline disease characteristics, study SG035-0003

	All Patients (N=102)
Pathological diagnosis[a], n (%)	
Hodgkin Lymphoma	102 (100)
Median time from initial HL diagnosis to first dose in months (min, max)	39.90 (11.8, 219.7)
Stage at initial diagnosis, n (%)	
Stage I	4 (4)
Stage II	47 (46)
Stage III	27 (26)
Stage IV	20 (20)
Unknown	4 (4)
Disease status relative to most recent prior therapy[b], n (%)	
Relapse	59 (58)
Refractory	43 (42)
Patients with primary refractory disease[c], n (%)	72 (71)
Median time from most recent relapse to first dose in months[d] (min, max)	2.1 (0.2, 28.5)
Baseline B symptoms[e], n (%)	35 (34)
Baseline bone marrow lymphoma involvement, n (%)	8 (8)

a By central pathology review
b Relapse=Best response of CR or PR to most recent prior therapy, Refractory=Best response of SD or PD to most recent prior therapy
c No CR or relapse within 3 months of front-line therapy
d For those with relapsed disease status to most recent prior therapy
e B symptoms present at the time of Cycle 1 Day 1

Prior cancer therapies are summarised in the following Table 19.

Table 19: Prior cancer therapies, study SG035-0003

	All Patients (N=102)
Any prior cancer-related radiotherapy, n (%)	67 (66)
Median number of prior cancer-related systemic therapy regimens[a] (min, max)	3.5 (1, 13)
Best response achieved with most recent regimen[b], n (%)	
Complete Response	12 (12)
Partial Response	35 (34)
Stable Disease	23 (23)
Progressive Disease	26 (25)
Unknown/Other	6 (6)
Median PFS (weeks) for most recent regimen (95% C.I.[b, c])	26.6 (19.0, 31.3)
Number of prior autologous stem cell transplants, n (%)	
1	91 (89)
2	11 (11)
Median time in months from initial HL diagnosis to most recent ASCT (min, max)	17.9 (5, 115)
Median time in months from most recent ASCT to relapse post-ASCT (min, max)	6.7 (0, 131)
Median time in months from most recent ASCT to first dose (min, max)	19.0 (3, 166)

a Includes chemotherapy given for stem cell mobilization
b Most recent cancer-related treatment systemic therapy regimen, excluding stem cell mobilizations, pre- or post-ASCT.
c Computed using the method of Brookmeyer and Crowley

Numbers analysed

The intent-to-treat (ITT) analysis set included all 102 patients enrolled in the study. The ITT analysis set was to be used for the primary efficacy analysis. Secondary and additional efficacy endpoints were also to be analysed using this analysis set.

The per-protocol analysis set was defined as those patients who satisfied the following criteria:

- received at least 1 dose of brentuximab vedotin
- had measurable disease at baseline
- had the correct histological cancer type per central pathology review
- had no other major protocol deviations that could potentially affect tumor response

The per-protocol analysis set was to be used for secondary analyses of all efficacy endpoints. In this study, the per-protocol analysis set comprises 99 patients; 3 patients were excluded from this analysis set because they did not have measurable disease at baseline per IRF assessment.

Outcomes and estimation

Based on the most updated efficacy results with an 1 August 2011 (2 April 2012 for OS) cut off date, the following results were reported:

- the ORR was 75% (76/102), with a CR rate of 33% (34/102), by IRF analysis

- the estimated median duration of response per IRF by Kaplan-Meier analysis was 6.7 months [95% CI (3.6, 14.8)] (range 1.2 to 26.1 months).

- the median duration of response in patients with CR has not been reached [95% CI (10.8, -)]; the current duration of response ranges from 1.4 to 26.1 months.

- the estimated median PFS per IRF by Kaplan-Meier analysis was 5.6 months [95% CI (5.0, 9.0 months)] (range, 1.2 to 27.3 months).

- at the time of the last analysis (2 April 2012), 40 of 102 patients were known to have died. The median overall survival (OS) by Kaplan-Meier analysis has not been reached [95% CI (27, – months)].

Ancillary analyses

PFS and estimated OS per IRF were analysed per type of response. Both PFS and OS correlated positively with response to brentuximab-vedotin as defined by CR, PR, SD and PD (data not shown).

The applicant also compared investigator-based PFS after brentuximab vedotin to PFS after last chemotherapy depending on whether ASCT had been one of the prior therapies (but not the latest one). The applicant also compared PFS after brentuximab depending on whether the latest prior therapy was ASCT or systemic chemotherapy. No meaningful differences were noted (data not shown).

A difference was shown in terms of IRF-based PFS between patients who received brentuximab vedotin as first line of therapy post-ASCT showing a CR compared to patients who received brentuximab vedotin after one or more systemic chemotherapies post-ASCT showing a CR (data not shown).

Furthermore, the applicant provided an intra-individual comparison of investigator-based PFS after brentuximab-vedotin with investigator-based PFS after the most recent prior therapy. An equal to longer PFS as compared to the last chemotherapy was seen in 59% (60/102) of the HL patients (data not shown).

Finally, the applicant submitted a meta-analysis of the literature as an external control to compare the efficacy of SGN-35 to that of gemcitabine and its combination regimens in the relapsed/refractory HL setting. CR rate was used as the endpoint for analysis. Separate analyses were submitted for studies/case series that included at least a third of enrolled patients with a prior transplant and those that included transplant-naïve patients. The overall CR rate for gemcitabine in the studies where patients were included who had received prior ASCT was 15%, compared to 34% after Adcetris. In the studies where patients had not received prior transplant the CR rate was 35%, but the median number of prior treatments was 1, compared with 3.5 in the Adcetris study (data not shown).

SG035-0004

This was a single-arm, open-label, multicentre, phase 2 study to evaluate the efficacy and safety of brentuximab vedotin as a single agent in patients with relapsed or refractory systemic ALCL.

Methods

Study Participants

Eligible patients had relapsed or refractory systemic ALCL, had received front-line chemotherapy with curative intent, and had histologically-documented CD30-positive disease. Patients were required to have fluorodeoxyglucose (FDG)-avid disease by PET and measurable disease of at least 1.5 cm by spiral computed tomography (CT). At US and Canadian sites, patients were to be age 12 years or older. At European sites, patients were to be age 18 years or older. Documented anaplastic lymphoma kinase (ALK) status was required.

Amongst other exclusion criteria, patients could not previously have been treated with brentuximab vedotin or received an allogeneic stem cell transplant (SCT). Patients with current diagnosis of primary cutaneous ALCL were also excluded; however patients who have transformed to systemic ALCL were eligible.

Treatments

Brentuximab vedotin 1.8 mg/kg was administered via outpatient intravenous (IV) infusion on Day 1 of each 21-day cycle. Dose delays (up to 3 weeks each) and a one-level dose reduction to 1.2 mg/kg were allowed for toxicities. Patients could continue on study treatment until disease progression or unacceptable toxicity. Patients who achieved stable disease or better were to receive a minimum of 8, but no more than 16 cycles of study treatment.

Objectives

The primary objective was to determine the antitumour efficacy of single-agent brentuximab vedotin (1.8 mg/kg administered intravenously every 3 weeks) as measured by the overall objective response rate in patients with relapsed or refractory systemic anaplastic large cell lymphoma following front line chemotherapy (CHOP or equivalent).

Secondary objectives were to assess duration of tumour control, including duration of response and progression-free survival, to assess survival, to assess the safety and tolerability of brentuximab vedotin and to assess the pharmacokinetics of brentuximab vedotin.

Additional objectives were to assess disease-related symptoms as well as to explore the correlation of potential biomarkers with clinical outcomes.

Outcomes / endpoints

The primary efficacy variable was the overall ORR per IRF. Treatment response was assessed by spiral CT of chest, neck, abdomen, pelvis and PET scans. Determination of antitumour efficacy was based on objective response assessments made according to the Revised Response Criteria for Malignant Lymphoma (Cheson *et al*, 2007). Clinical response of progressive disease (PD), stable disease (SD), partial remission (PR), or complete remission (CR) was to be determined at each assessment. Responses were determined by an independent review facility (IRF) and treatment decisions were made based on investigator assessment of response. Enrolled patients who were later determined to have the incorrect histological cancer type upon review were to be scored as non-responders for calculating the ORR.

Secondary endpoints were Duration of Response (DoR) per IRF, Complete Remission (CR) Rate per IRF, Progression-Free Survival (PFS) per IRF and OS.

Sample size

It was planned to enrol 55 patients in the study. If the true objective response rate would be at least 50%, with a sample size of 55 patients a 2-sided binomial test for $\alpha = 0.05$ would have more than 95% power to exclude an ORR less than 20%.

Randomisation

Not applicable

Blinding (masking)

Not applicable

Statistical methods

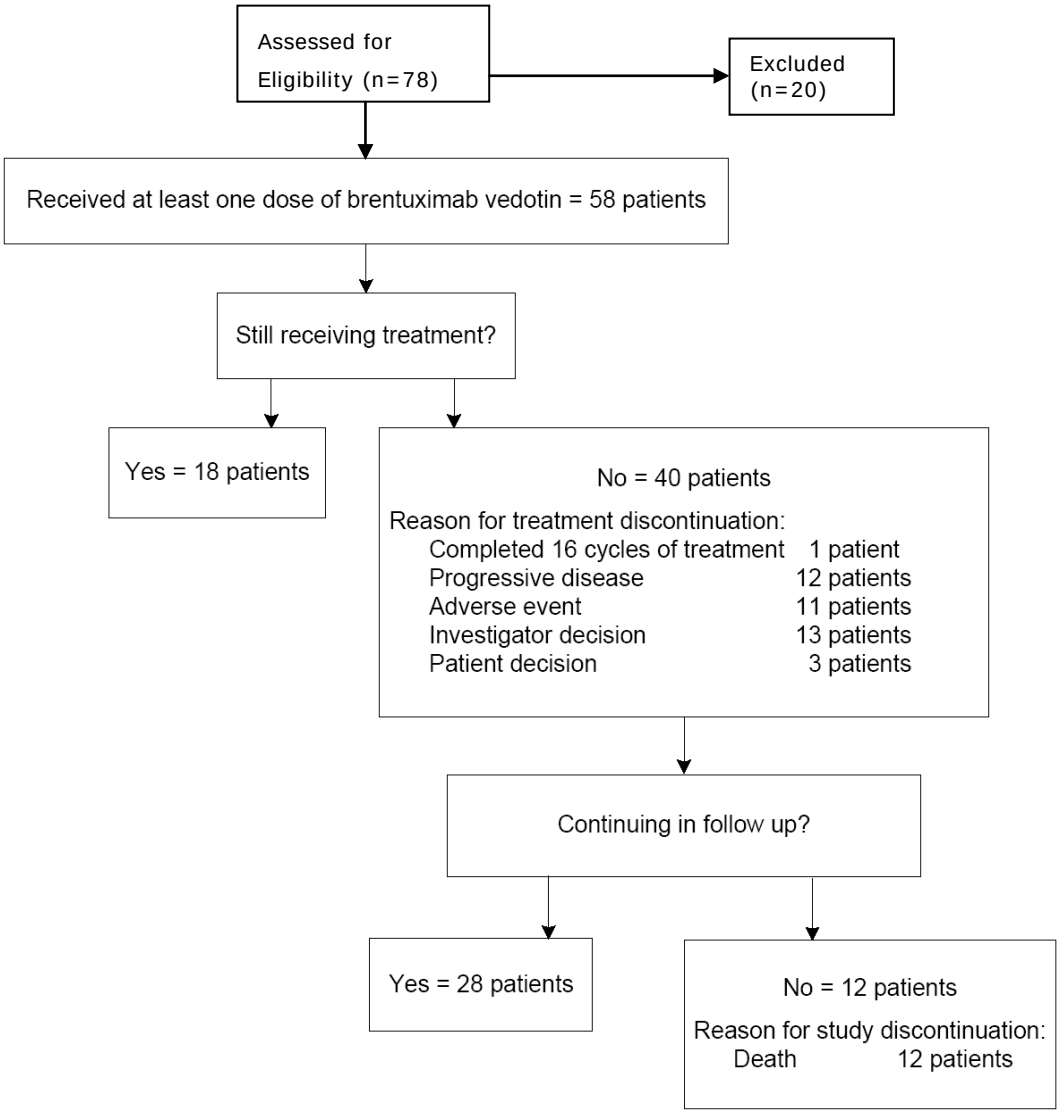
An exact 95% confidence interval was used to test the null-hypothesis that ORR according IRF for SGN035 was < 20% vs. the alternative that ORR is ≥ 20%.

Categorical data were described by (absolute and relative) frequencies including the corresponding 95% confidence intervals. Kaplan-Meier plots and estimates were used to assess time to event data. Continuous data were described by statistical characteristics (mean, sd, median, min, max).

An independent data monitoring committee only reviewed to the data for safety. No interim analysis to stop the study was planned.

Results

Participant flow



Recruitment

The first patient was enrolled on 17 June 2009 and the date of last patient last visit was 11 August 2010.

Conduct of the study

The original version of the protocol was approved 2 September 2008. The protocol was amended 3 times through the course of the study (see Table 23).

Table 23: Protocol amendments, study SG035-0004

SG035-0004	Date	Number of patients enrolled	Key Driver(s) for Amendment
Original	2 September 2008	0	–
Amendment 1	1 December 2008	4	• Increased sample size from 30 to 55 patients • CD30 assessment was to be centrally confirmed • Explained why no formal interim efficacy and/or futility analyses were planned • Specified how patients who do not have the correct histological cancer type will be handled in the analysis
Amendment 2	13 February 2009	31	• Allowed patients aged 12 years or older to enroll at sites in Canada • Refined entry criteria to ensure that all patients have active relapsed or refractory systemic ALCL at study entry • Increased the time since immunotherapy before study entry to ensure any therapeutic benefit is realized • Added descriptions of interim analyses that may be conducted for scientific meetings and/or regulatory submissions
Amendment 3	16 November 2009	23	• Allowed patients who have previously received treatment with non-anthracycline or anthracendione-based multi-agent chemotherapy regimens to enroll in the study provided they had received a frontline multi-agent chemotherapy regimen with curative intent • Removed the requirement for central pathology review to confirm CD30-positivity at the time of enrollment. Slides were to be submitted for central review prior to initiation of treatment with brentuximab vedotin • Clarified that prior treatments must have been completed in the protocol-specified timeframe unless patient was progressing on therapy. • Updated baseline platelet and bilirubin requirements for patients with bone marrow and hepatic lymphoma involvement • Clarified that patients with active infections Grade 3 or higher are not eligible for the study

The definition of a protocol deviation/major protocol deviation as specified in the SAP was revised. For the purposes of this study, 2 categories of protocol variance were defined and used:

- Protocol deviation: Defined as an incident involving non-compliance with the clinical protocol that does not have a significant effect on the subject's rights, safety, or welfare, or on the integrity of the resultant data.
- Major protocol deviation (protocol violation): Defined as a divergence from the protocol that has a significant effect on the subject's rights, safety, or welfare, or on the integrity of the resultant data.

Baseline data

Patient demographics and ECOG performance status at baseline for patients are summarised in the following Table 24.

Table 24: Baseline demographic characteristics, study SG035-0004

	N=58
Age (yr)	
N	58
Mean (SD)	47.7 (16.8)
Median	52.0
Min, Max	14, 76
Gender, n (%)	
Male	33 (57)
Female	25 (43)
Race, n (%)	
American Indian or Alaska Native	0
Asian	1 (2)
Black or African American	7 (12)
Native Hawaiian or Other Pacific Islander	0
White	48 (83)
Other	2 (3)
ECOG Performance Status, n (%)	
0	19 (33)
1	38 (66)
2[a]	1 (2)

[a] Baseline ECOG performance status of 2 was prohibited by protocol

Baseline disease characteristics are summarised in the following Table 25.

Table 25: Baseline disease characteristics, study SG035-0004

	N=58
Pathological diagnosis [a], n (%)	
Systemic anaplastic large-cell lymphoma (sALCL)	56 (97)
Other	2 (3)
ALK status, n (%)	
Positive	16 (28)
Negative	42 (72)
CD30-positive, n (%)	57 (98)
Median time from initial ALCL diagnosis to first dose in months (min, max)	16.8 (3.7, 186.5)
Stage at initial diagnosis, n (%)	
Stage I	11 (19)
Stage II	13 (22)
Stage III	8 (14)
Stage IV	21 (36)
Unknown	5 (9)
Disease status relative to most recent prior therapy[b], n (%)	
Relapse	29 (50)
Refractory	29 (50)
Subjects with primary refractory disease[c], n (%)	36 (62)
Patients who did not achieve an objective response with any prior therapy, n (%)	13 (22)
Median time from most recent relapse to first dose in months (min, max)	1.7 (0.4, 2.9)
Baseline B symptoms[e], n (%)	17 (29)
Baseline bone marrow lymphoma involvement, n (%)	7 (12)
Baseline malignant cutaneous lesions, n (%)	15 (26)

a By central pathology review
b Relapse=Best response of CR if a patient only had one prior therapy, or best response of CR or PR to most recent prior therapy if a patient had more than one prior therapy; Refractory=Best response of PR, SD or PD if a patient only had one prior therapy, or best response of SD or PD to most recent prior therapy if a patient had more than one prior therapy
c No CR or relapse within 3 months of frontline therapy
d For those with relapsed disease status to most recent prior therapy
e B symptoms present at the time of Cycle 1 Day 1

Primary cancer therapies are summarised in the following Table 26.

Table 26: Prior cancer therapies, study SG035-0004

	N=58
Any prior cancer-related radiotherapy, n (%)	26 (45)
Median number of prior cancer-related systemic therapy regimens[a] (min, max)	2 (1, 6)
Best response achieved with frontline multi-agent chemotherapy, n (%)	
Complete Remission (CR)	28 (48)
Partial Remission (PR)	14 (24)
Stable Disease (SD)	3 (5)
Progressive Disease (PD)	9 (16)
Unknown/Other	4 (7)
Best response achieved with most recent regimen[b], n (%)	
Complete Remission (CR)	21 (36)
Partial Remission (PR)	9 (16)
Stable Disease (SD)	5 (9)
Progressive Disease (PD)	17 (29)
Unknown/Other	6 (10)
Number of prior autologous stem cell transplants, n (%)	
1	15 (26)
2 or more	0
Most recent therapy was autologous SCT or multi-agent chemotherapy, n (%)	53 (91)

a Includes chemotherapy given for stem cell mobilization
b Most recent cancer-related treatment systemic therapy regimen, pre- or post-autologous SCT

Numbers analysed

The intent-to-treat (ITT) analysis set included all 58 patients enrolled in the study and it was used for the primary efficacy analysis. Secondary and additional efficacy endpoints were also analysed using this analysis set.

The per-protocol analysis set was defined as those patients who satisfied the following criteria:

- received at least 1 dose of brentuximab vedotin
- had measurable disease at baseline
- had the correct histological cancer type per central pathology review
- had no other major protocol deviations that could potentially affect tumor response

The per-protocol analysis set was used for secondary analyses of all efficacy endpoints.

The per-protocol set comprised 55 patients; 2 patients did not have the correct histological cancer type per central pathology review. The last patient not included in the per-protocol set was deemed to have protocol deviations that potentially affected tumour response (ECOG PS 2 at baseline).

Outcomes and estimation

Based on the most updated efficacy results with a 13 July 2011 (2 April 2012 for OS) cut off date, the following results were reported:

- the ORR was 86% (50/58) with a CR rate of 59% (34/58)

- the estimated median duration of response per IRF by Kaplan-Meier analysis was 13.2 months [95% CI (5.7,-)] (range, 0.1 to 21.7 months). Of the 50 patients who had an objective response, 27 have had disease progression or have died.

- among patients who achieved a best response of CR, the estimated median duration of response per IRF by Kaplan-Meier analysis was not reached [95% CI (13.0 months, -)] (range, 0.7 to 21.7 months). Of the 34 patients who had a CR, 13 have had disease progression or have died.

- the estimated median PFS per IRF by Kaplan-Meier analysis was 14.3 months [95% CI (6.9,-)] (range, 0.8 to 23.6 months).

- at the time of the last analysis (2 April 2012), 21 of 58 patients were known to have died. The median overall survival by Kaplan-Meier analysis was not reached [95% CI (21.3 , -)]. The estimated overall survival rate at 12 months was 71% [95% CI (57, 80)].

Ancillary analyses

PFS per IRF and the estimated OS per IRF, respectively, correlated positively with response to brentuximab-vedotin as defined by CR, PR, SD and PD (data not shown).

Furthermore, the intra-individual comparison of investigator-based PFS after brentuximab-vedotin to investigator-based PFS after the most recent prior therapy showed plot shows that brentuximab-vedotin induced an equal to longer PFS as compared to the last chemotherapy in 60% (35/58) of the sALCL patients (data not shown).

The applicant also submitted a meta-analysis of studies in relapsed or refractory non-Hodgkin lymphoma (NHL) that included sALCL patients. However, only a small proportion of all patients had ALCL, ranging from 1.6% to 20.8%, and in most reports the results were not specified by histological tumour type. Only a few of the publications indicated the specific outcome, mainly response, of sALCL patients (data not shown).

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 27: Summary of Efficacy for trial SG035-003

Title: A pivotal study of SGN-35 in treatment of patients with relapsed or refractory Hodgkin lymphoma (HL)		
Study identifier	SG035-003	
Design	Phase II, single arm, open-label, multicenter study designed to evaluate efficacy and safety of brentuximab vedotin as a single drug in patients with relapsed or refractory Hodgkin lymphoma	
	Duration of main phase:	Minimum 8 cycles of 21 days, up to 16 cycles
	Duration of Run-in phase:	not applicable

	Duration of Extension phase:		not applicable
Hypothesis	Exploratory: ORR ≥ 20%		
Treatments groups	Brentuximab vedotin		IV brentuximab vedotin 1.8 mg/kg as a single drug, administered on Day 1 of a 21-cycle, minimum 8 cycles of 21 days, up to 16 cycles. 102 patients received at least one dose
Endpoints and definitions	Primary endpoint	ORR	Objective Response Rate per Independent Review Facility (IRF)
	Secondary endpoint	DoR	Duration of Response per IRF
	Secondary endpoint	CR	Complete Remission per IRF
	Secondary endpoint	PFS	Progression Free Survival per IRF
	Secondary endpoint	OS	Overall Survival
Database lock	11 August 2010		

Results and Analysis

Analysis description	**Primary Analysis**	
Analysis population and time point description	Intent to treat End of treatment assessment (30 days +/- 7 days after last dose)	
Descriptive statistics and estimate variability	Treatment group	Brentuximab vedotin
	Number of subjects	102
	ORR (percentage)	75%
	(95% CI)	(64.9, 82.6)
	Estimated DoR by IRF (median)	6.7 months
	(95% CI)	(3.6, 14.8)
	Estimated PFS by IRF (median)	5.6 months
	(95% CI)	(5.0, 9.0)
	Estimated OS (median)	27.0 months
	(95% CI)	(23.9, -)

Table 28: Summary of Efficacy for trial SG035-004

Title: A Phase 2 study of SGN-35 in treatment of patients with relapsed or refractory systemic anaplastic large cell lymphoma (ALCL)		
Study identifier	SG035-004	
Design	Phase II, single-arm, open-label, multicenter study to evaluate the efficacy and safety of brentuximab vedotin as a single agent in patients with relapsed or refractory systemic ALCL.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Minimum 8 cycles of 21 days, up to 16 cycles not applicable not applicable
Hypothesis	Exploratory: ORR ≥ 20%	

Treatments groups	Brentuximab vedotin		IV brentuximab vedotin 1.8 mg/kg as a single drug, administered on Day 1 of a 21-cycle, minimum 8 cycles of 21 days, up to 16 cycles. 58 patients received at least one dose
Endpoints and definitions	Primary endpoint	ORR	Objective Response Rate per Independent Review Facility (IRF)
	Secondary endpoint	DoR	Duration of Response per IRF
	Secondary endpoint	CR	Complete Remission per IRF
	Secondary endpoint	PFS	Progression Free Survival per IRF
Database lock	11 August 2010		

Results and Analysis

Analysis description	**Primary Analysis**	
Analysis population and time point description	Intent to treat	
Descriptive statistics and estimate variability	Treatment group	Brentuximab vedotin
	Number of subjects	58
	ORR (percentage)	86%
	(95% CI)	(74.6, 93.9)
	Estimated DoR by IRF (Median)	13.2
	(95% CI)	(5.7, -)
	Estimated PFS by IRF (Median)	14.3
	(95% CI)	(6.9, -)
	Estimated OS (median)	Not Reached
	(95% CI)	--
	Estimated OS rate at 12 months	71%
	(95% CI)	(59, 82)

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

Clinical studies in special populations

Not applicable

Supportive studies

Supportive efficacy data were derived from the phase I studies SG035-0001 and SG035-0002 described previously under dose-response studies.

With regard to the efficacy of brentuximab vedotin in patients without prior ASCT, the applicant presented data derived from 59 patients who had not undergone ASCT and received 1 or more doses of brentuximab vedotin. These patients came the phase I/II studies, a Japanese-only study (TB-BC010088) and Named Patient Programmes (NPPs). Of these 59 patients, 41 received 1.8 mg/kg brentuximab vedotin every 3 weeks, the dose and regimen used in pivotal HL Study SG035-0003 and proposed for marketing authorisation. 3 patients received only 1 therapy prior to administration of brentuximab, hence the total number of patients fitting the proposed indication was 56, 40 of which were treated according to the applied for schedule of 1.8 mg/kg brentuximab vedotin every three weeks.

Baseline demographic and disease characteristics for these 59 patients are summarised in the following Tables 20 and 21. The exclusion of the 3 above mentioned patients on the reported data led to small adjustments of the reported data.

Table 20: Basic demographic characteristics for the 59-patient population with relapsed or refractory HL without prior ASCT

	All Patients (N = 59)
Age (years)	
Mean	27
Median	35
Min, Max	12, 88
Gender, n (%)	
Male	37 (62.7)
Female	22 (37.3)
ECOG Performance Status, n (%)	
0	22 (37.3)
1	23 (39.0)
2	10 (16.9)
3	4 (6.8)

Table 21: Disease characteristics of prognostic importance for the 59-patient population with relapsed or refractory HL without prior ASCT

	All Patients (N = 59)
Pathological diagnosis	
CD30+ Hodgkin lymphoma	59 (100%)
Stage at Initial Diagnosis, n (%)	
Stage I	1 (1.7)
Stage II	16 (27.1)
Stage III	14 (23.7)
Stage IV	21 (35.6)
unknown	7 (11.9)
Baseline B symptoms	
yes	23 (39.0)
no	35 (59.3)
unknown	1 (1.7)
Baseline bone marrow involvement of HL	
yes	6 (10.2)
no	32 (54.2)
unknown	21 (35.6)

Patients' most common first line of prior therapy was doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). Of the 56 no-prior-ASCT patients, 64% of the patients (was 66% with n=59) received the same first line of therapy, i.e. ABVD. The next most common frontline treatment was a BEACOPP-based regimen (6 patients, 11% (was 10% with n=59)). The most common second-line therapy among no-prior-ASCT patients was etoposide, methylprednisolone, high-dose cytarabine, and cisplatinum (ESHAP) as received by 11 of the 56 patients (20%; was 19% with n=59); 10 of 56 patients (18%; was 17% with n=59) received radiotherapy as second-line therapy; and 8 of 56 patients 14% received ICE (was 13.5% with n=59).

Response data among the 59 patients without prior ASCT are summarised in the following Table 22.

Table 22: Response data for HL patients with relapsed or refractory HL without prior ASCT

	All Patients (N = 59)	1.8 mg/kg Every 3 Weekly Set (n = 41)
Overall Response Rate	27 (46%)	22 (54%)
Complete Remission Rate	10 (17%)	9 (22%)
Partial Remission Rate	17 (29%)	13 (32%)
Patients going on to SCT after brentuximab vedotin	10 (17%)	8 (19%)

SCT = stem cell transplant

The applicant provided very limited PFS and/or OS data in the case reports, i.e. from 18/56 patients fitting the proposed indication (or 20 of all patients (n=59)). These data were derived from the phase I studies, meaning that from these 20 patients, 2 patients received brentuximab vedotin according to the schedule as proposed in this MAA. From another 12 patients, PFS and/or OS could be calculated on

the basis of the date of start of therapy, date of relapse or date of patient death. Together, these data are not sufficient to be used for assessment at this time.

2.5.3. Discussion on clinical efficacy

Data from two supportive studies and two pivotal studies –one for each proposed indication- have been submitted to support the efficacy of Adcetris in the two indications applied for. From the dose-escalation studies, 1.8 mg/kg administered every 3 weeks was selected as the recommended Phase 2 dose and this dose was supported by the DLT data, adverse event profile and PK data.

Design and conduct of clinical studies

The pivotal studies were phase II uncontrolled single arm trials. Patients with relapsed or refractory CD30+ HL who had received autologous stem cell transplantation and patients with relapsed or refractory ALCL who had received front-line chemotherapy with curative intent, respectively, were to receive 1.8 mg/kg of the drug administered intravenously every 3 weeks. Patients could continue on study treatment until disease progression or unacceptable toxicity occurred. Patients who achieved stable disease or better were to receive a minimum of 8, but no more than 16 cycles of study treatment. Primary endpoint was overall response rate, defined as rates of complete remission and partial remission combined. Secondary endpoints included duration of response, progression-free survival, overall survival, event-free survival.

Efficacy data and additional analyses

The Applicant has claimed that there is efficacy in terms of ORR, the median PFS and estimated OS in view of the limited treatment options for the stages of diseases HL and sALCL in which brentuximab-vedotin is studied. However, additional study of literature has shown that these results may also be achieved with conventional non-CD30 directed chemotherapy, in particular concerning the OS results in the sALCL population as studied. Since no comparative study has been pursued, uncertainty remains concerning the interpretation of the reported efficacy data and the validity of historical comparisons.

The median overall survival (OS) in the Hodgkin lymphoma population and in the sALCL population has not been reached. However, an OS plateau was observed in the sALCL study population and possibly as well in the HL study population (cut of date 2 April 2012). This suggests maturity of the OS results at least in the sALCL study population, although definitive conclusions can not be drawn yet.

When optimal treatment is given to patients, any next line therapy usually results in lower efficacy, both in relapsed or refractory HL or sALCL. In contrast, the comparison of the PFS results as obtained with brentuximab vedotin to those after the previous line of treatment suggested an important clinical benefit despite the fact that analysis of these data was investigator-based and not IRF-based. This benefit may be explained by the alternative working mechanism: a CD30-guided anti-tubulin cytotoxic compound. This working mechanism may provide an alternative approach to stabilise these malignancies, or even to reach a condition that allows ASCT, when this was not possible at an earlier stage.

Thus, the anti-tumour effect (in terms of ORR) and the efficacy (PFS and OS) of brentuximab-vedotin have been shown in the HL and sALCL pivotal study populations. However, the comparative benefit of brentuximab-vedotin has not been clearly established based on the uncontrolled trial and historical comparisons presented.

From the provided information in the detailed case reports of 56 patients fulfilling the proposed indication for the no-ASCT/no multi-drug chemotherapy HL patient group, it is not clear which methods

were used to asses therapy responses and AEs. This is in particular relevant for the data of the patients participating in the NNPs as the results from the other included studies have been obtained according to GCP standards. In view of this and together with the fact that the Japan-only study (TB-BC010088) has only recently started with all 6 patients still on brentuximab vedotin treatment, the data from the phase I/II studies (i.e. SG035-0001/0002) and from the SGN35-007 study (i.e. a phase I QTc study) acted as the basis for the assessment. The results from Japan-only studies and the NPPs are considered to be supportive, in particular the latter as these are more mature and illustrate the day-to-day clinical applicability of brentuximab vedotin. In addition, the applicant provided very limited PFS/OS data in the case reports, i.e. from 18 out of the 56 patients that fulfil the proposed indication. From another 12 patients, PFS and/or OS could be estimated on the basis of the date of start of therapy, date of relapse or date of patient death. Together, this illustrates that the data are obtained from a very heterogeneous set of patients, were in several aspects immature and limited, but still contained useful information.

The results showed that the overall response rate, the extent of the response and the percentage of patients that become eligible for transplantation are currently the most important read-outs for the anti-tumour activity of brentuximab-vedotin in this no-ASCT patient population. Regarding the overall response, this seemed lower as compared to the results as observed in the study SG035-0003, regardless of dose and schedule (46% ORR for all no-prior-ASCT patients, 55% ORR for proposed dose and schedule no-prior-ASCT patients versus 75% ORR for study SG035-0003 patients). This was true for CR rates as well (18% CR for all no-prior-ASCT patients, 23% CR for proposed dose and schedule no-prior-ASCT patients versus 33% CR for study SG035-0003 patients).

The applicant explained the generally lower response rate by, amongst others, referring to the lower exposure of the no-ASCT patient population. However, it may also be explained by intrinsic, biological variances not based on CD30 antigen expression (as this is similar and not subject to change upon therapy), but on absolute or relative differences in the involved intracellular signalling pathways downstream of CD30 internalisation.

Furthermore, non-eligibility for ASCT may have various reasons including poor response to previous chemotherapy, co-morbidity or age. Therefore, an ORR of 55% and a CR of 23% for the proposed dose and schedule in this patient group not suitable for ASCT may be considered clinically relevant in itself. In the NPP population only, that is considered to reflect day-to-day clinical practice, these response rates are similar. However, the percentage of patients that have become eligible for stem cell transplantation, i.e. 20% for the proposed dose and schedule patient group (n=40) and 27% when including only NPPs patients (n=26), is even more important, especially considering the absence of the possibility to apply this potentially curative therapy at an earlier stage in the treatment of this particular patient group. Finally, the provided PFS/OS data in these patients are considered too limited at this time to be evaluated.

Additional expert consultations

A Scientific Advisory Groupo (SAG)-Oncology was convened by the CHMP to address questions related to the Adcetris Marketing Authorisation application. The questions and the SAG-O responses were as follows:

1. Regarding the submitted clinical trial data:

a. Is it possible to interpret the observed effects with brentuximab-vedotin in CR, ORR, PFS and DoR in HL and sALCL on the basis of the submitted studies in the absence of a controlled trial where the effect of brentuximab-vedotin is compared to historical data obtained with established treatment?

The response rate in both HL and sALCL in the respective study populations (limited to patients after failure of ASCT in HL) is impressive. In relapsing refractory HL, this response rate suggests a high probability of clinical benefit, but there is no definitive proof of such benefit. It could also open the possibility for follow-up ASCT, but there is uncertainty as to how Adcetris might perform compared to other agents towards this end. In sALCL, the response rate is also high, but it is noted that only 20% of included patients had received ASCT prior to enrolment, this being likely so far the most potent therapy strategy. On the other hand, the targeted population (majority of older age and ALK negative patients) is expected to have more aggressive disease which increases confidence on the observed effects.

b. Can valid conclusions be drawn from the submitted comparison with results obtained by previous treatment in the same patients and treatment obtained with other products in other studies?

No definitive conclusions can be drawn about the value of Adcetris as a therapeutic option in the sought indications on the basis of historical comparisons, as these always entail a high risk for introducing bias. Especially for the historical comparison in the sALCL indication, the historical comparison was limited to a single population-based study that had recruited generally older patients and with a worse performance status.

Intra-patient comparisons in terms of PFS compared to prior treatment are more convincing. However, no definitive conclusions can be drawn due to the known limitations of this type of analysis, similar to historical comparisons. In addition, it is difficult to assess if the determination of the start of therapy and of progression was unbiased. Concerning the choice of prior treatment, ideally, comparison should have been made against the best previous therapy in relapsed disease (e.g. in HL against ASCT).

c. In light of the above does the SAG consider the observed efficacy convincing and clinically relevant?

Despite limited data, the observed antitumour activity of Adcetris is considered clinically relevant, as the high response rate and duration of response were associated with reduction of B symptoms (fever, night sweats, weight loss). Moreover, the high complete response rate and duration of response in HL may constitute a clinical benefit in allowing a relevant percentage of patients to undergo a subsequent ASCT, however definitive data are lacking. In sALCL, the long duration of PFS and high response rate (in light of potential future ASCT) are considered clinically relevant.

2. Do the proposed indications constitute an unmet medical need?

In relapsing refractory HL, there is an unmet medical need for patients who have relapsed after or are refractory to ASCT, but not necessarily for patients after at least two prior therapies when ASCT is not a treatment option.

In ALCL, an unmet medical need is uncertain with the possible exception of patients refractory to previous therapy or those unfit for ASCT.

3. Does the SAG consider a confirmatory (randomised, controlled) study in the HL population as studied on SG035-003 feasible in the EU after a marketing authorisation for brentuximab-vedotin in the EU and what would be the design of such study?

A randomised, controlled confirmatory study in the HL population as studied in SG035-003 would be difficult to conduct after approval; the feasible and preferred option would have been to conduct a randomised, controlled trial prior to approval.

4. **Does the SAG agree with the Applicant that patients with cutaneous TCL (e.g. pcALCL and mycosis fungoides eligible for treatment with bexarotene and MTX) represent an adequate population to study safety and efficacy of brentuximab-vedotin to support the currently proposed indication in the MAA for relapsed, refractory sALCL? Does the SAG have alternative suggestions?**

The proposed study in patients with cutaneous TCL could only provide confirmation in terms of safety, but it would not support the efficacy in the relapsed/refractory sALCL, as it refers to a different patient population. With regard to alternative confirmatory studies, a randomised study against other second line treatments would be desirable but it is not considered feasible; a further single-arm study looking at response rate, duration of response, rate of second ASCT and data in subpopulations (including but not necessarily restricted to ALK status and age) may serve this purpose instead.

Additional efficacy data needed in the context of a conditional MA

The median overall survival (OS) in the Hodgkin lymphoma population and in the sALCL population has not been reached, but an OS plateau was observed in the sALCL study population and possibly as well in the HL study population suggesting potentially maturity of the OS results at least in the sALCL study population. Nevertheless, further updated OS data from studies SG035-0003 and SG035-004 should be provided, including sub-analysis of patients ≥ 100 kg. The data should be presented in the context of historical controls.

The comparative benefit of brentuximab-vedotin has not been clearly established based on the uncontrolled trial and historical comparisons presented. The feasible and preferred option to obtain controlled data would have been to conduct a randomised, controlled confirmatory study in the HL population as studied in SG035-003. However, such a trial would be difficult to conduct at this time. As the main uncertainty relates to the patient population ineligible for ASCT, additional efficacy data for the relapsed/refractory HL population not eligible for ASCT should be provided by performing a single-arm study in a similar patient population investigating response rate, PFS, OS and proportion of patients proceeding to transplant and safety (n=approx 60 pts).

With regard to alternative confirmatory studies in sALCL, a randomised study against other second line treatments would be desirable, but this is not considered feasible due to the rarity of the disease; a further single-arm study looking at response rate, duration of response, rate of second ASCT and data in subpopulations (including but not necessarily restricted to ALK status and age) may serve this purpose instead.

2.5.4. Conclusions on the clinical efficacy

Based on the results as provided by the Applicant, the pivotal phase 2 studies are assumed to show efficacy of brentuximab-vedotin in terms of ORR and PFS in relapsed or refractory post-ASCT HL and sALCL, despite the absence of controlled data. The difference in intra-individual comparison of investigator-based PFS after brentuximab-vedotin with investigator-based PFS after the most recent prior therapy is considered a relevant treatment effect in the majority of the post-ASCT HL and sALCL patient populations studied. Taken into account that brentuximab-vedotin is studied in particular as further line treatment, the suggested effects are considered of clinical relevance.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

Regarding the relapsed, refractory HL patients not eligible for stem cell transplantation or multi-agent chemotherapy, the information provided by the applicant in the detailed case reports shows anti-

tumour activity of brentuximab vedotin. However, additional efficacy/safety data in the no-ASCT/no-multidrug patient population are essential. A further single arm study in the sALCL population to inform on subpopulations and rate of subsequent ASCT is also necessary.

Finally, updated OS data from the pivotal phase II studies should be submitted when available.

2.6. Clinical safety

Patient exposure

The applicant submitted safety data from 6 studies with 357 patients with CD30+ haematologic malignancies who received at least 1 dose of SGN35 (phase 1 dose escalation studies: SG035-0001 and SG035-0002, phase 1 studies SG035-007 and SG035-008A, pivotal phase 2 studies, SG035-0003 and SG035-0004.)

The median duration of treatment in study SG035-0003 was 27 weeks (range 3 to 56) and the median number of cycles administered per patient was 9 (range, 1 to 16). The median treatment duration with brentuximab-vedotin in study SG035-0004 was 20 weeks (range, 3 to 51); a median of 6 cycles (range, 1 to 16) have been administered per patient and slightly less than 50% of patients received 7 or more cycles.

A total of 261 patients received brentuximab vedotin at the proposed dsoe and schedule of 1.8mg/kg q3 week.

In addition, the applicant provided information on SAEs from 5 ongoing studies (SGN35-005, SGN35-006, SGN34-008B, SGN34-009 and SGN34-010) as well as a named patient programme (NPP).

Analysis of the 59 detailed case reports on the relapsed, refractory HL patients not eligible for stem cell transplantation or multi-agent chemotherapy on exposure of these patients to brentuximab vedotin showed that patients received a mean of 5.3 and a median of 4 cycles of brentuximab vedotin. If these numbers are corrected for the patients that did not fit the proposed indication, patients received a mean of 5.4 and a median of 4.5 cycles brentuximab vedotin (n=56). Exposure for the patients receiving the proposed brentuximab vedotin dose and schedule (n = 40) and the NPP cases series only (n = 26) was slightly higher than for the total no-prior-ASCT population (mean 5.7 cycles, median 5 cycles for both subsets).

Adverse events

An overall summary of all AEs across all clinical studies can be found in the following Table 29.

Table 29: Overall summary of adverse events

		HL SG035-0003 (N=102) n (%)	sALCL SG035-0004[a] (N=58) n (%)	Total Ph 2[b] (N=160) n (%)	Total Ph 1/Ph 2[c] (N=249) n (%)
Any treatment-emergent AE		100 (98)	58 (100)	158 (99)	245 (98)
Max. severity	Grade 1	11 (11)	6 (10)	17 (11)	28 (11)
	Grade 2	33 (32)	17 (29)	50 (31)	83 (33)
	Grade 3	41 (40)	20 (34)	61 (38)	97 (39)
	Grade 4	14 (14)	9 (16)	23 (14)	27 (11)
	Grade 5[d]	1 (1)	6 (10)	7 (4)	10 (4)
	≥ Grade 3	56 (55)	35 (60)	91 (57)	134 (54)
Treatment-related AE[e]		94 (92)	53 (91)	147 (92)	229 (92)
Discontinued due to AE		20 (20)	11 (19)	31 (19)	59 (24)
SAE		25 (25)	24 (41)	49 (31)	73 (29)
Treatment-related SAE[e]		14 (14)	10 (17)	24 (15)	36 (14)
Death		13 (13)	12 (21)	25 (16)	41 (16)
Within 30 days of last dose		0	6 (10)	6 (4)	8 (3)
Post 30 days of last dose[f]		13 (13)	12 (21)	19 (12)	33 (13)

a Interim CSR

b Studies SG035-0003 and SG035-0004

c Studies SG035-0001, SG035-0002, SG035-0003, and SG035-0004

d Two patients had Grade 5 AEs (disease progression in SG035-0001 and Hodgkin's disease recurrent in SG035-0003) that led to death more than 30 days after the last dose.

e Related to treatment with SGN-35 as determined by the investigator

f Data for deaths post 30 days of last dose include additional data available from the SG035-0004 study as of 14 January 2011; no additional SAEs were reported in the SG035-0004 study as of the cutoff date.

In study SG035-0003, the AEs that occurred in ≥20% of patients were peripheral sensory neuropathy (47%), fatigue (46%), nausea (42%), URTI (37%), diarrhoea (36%), pyrexia (29%), neutropenia (22%), vomiting (22%), and cough (21%).

Adverse events leading to dose reduction occurred in 11% of patients; the reason for dose reduction was peripheral neuropathy for all but 1 patient. The highest number of dose-reductions occurred at cycles 10 through 16. AEs leading to dose delays occurred in 47% of patients; the most common reasons for delays were neutropenia (16%), peripheral sensory neuropathy (13%) and thrombocytopenia (4%).

In study SG035-0004, the AEs that occurred in ≥20% of patients were nausea (38%), peripheral sensory neuropathy (38%) fatigue (34%), pyrexia (33%), diarrhoea (29%), and neutropenia (21%) and rash (21%). An AE grade ≥3 occurred in 60% of the patients.

Adverse events resulting in dose reduction occurred in 9% of patients; 2 patients out of the 5 patients had dose reductions for peripheral sensory neuropathy. Adverse events that led to dose delay occurred in 31% of patients; these AEs were neutropenia (12%), peripheral sensory neuropathy (7%), and thrombocytopenia (5%).

The most common AEs in the two pivotal phase II studies are summarised in the following Table 30.

Table 30: Treatement-emergent adverse events occurring in ≥ 10 % of patients in the phase II studies

Preferred Term	HL SG035-0003 (N=102) n (%)	sALCL SG035-0004 (N=58) n (%)	Total Ph 2 (N=160) n (%)
Peripheral sensory neuropathy	48 (47)	22 (38)	70 (44)
Fatigue	47 (46)	20 (34)	67 (42)
Nausea	43 (42)	22 (38)	65 (41)
Diarrhoea	37 (36)	17 (29)	54 (34)
Pyrexia	30 (29)	19 (33)	49 (31)
Upper respiratory tract infection	38 (37)	7 (12)	45 (28)
Neutropenia	22 (22)	12 (21)	34 (21)
Vomiting	22 (22)	10 (17)	32 (20)
Cough	21 (21)	10 (17)	31 (19)
Headache	19 (19)	9 (16)	28 (18)
Constipation	16 (16)	11 (19)	27 (17)
Pruritus	16 (16)	11 (19)	27 (17)
Myalgia	17 (17)	9 (16)	26 (16)
Rash	14 (14)	12 (21)	26 (16)
Arthralgia	19 (19)	5 (9)	24 (15)
Dyspnoea	13 (13)	10 (17)	23 (14)
Insomnia	14 (14)	9 (16)	23 (14)
Abdominal pain	17 (17)	5 (9)	22 (14)
Alopecia	13 (13)	8 (14)	21 (13)
Chills	13 (13)	7 (12)	20 (13)
Dizziness	11 (11)	9 (16)	20 (13)
Back pain	14 (14)	5 (9)	19 (12)
Decreased appetite	11 (11)	8 (14)	19 (12)
Lymphadenopathy	11 (11)	6 (10)	17 (11)
Night sweats	12 (12)	4 (7)	16 (10)
Pain in extremity	10 (10)	6 (10)	16 (10)
Thrombocytopenia	8 (8)	8 (14)	16 (10)

Treatment-related adverse events (Adverse Drug Reactions, ADRs) are summarised in the following Table 31.

Table 31: Adverse reactions for Adcetris reported in the phase 2 population

System Organ Class	Adverse Reactions
Infections and infestations disorders	
Very Common:	Infection[a]
Common:	Upper respiratory tract infection, herpes zoster, pneumonia
Uncommon:	Oral candidiasis, pneumocystis jiroveci pneumonia, staphylococcal bacteraemia
Blood and lymphatic system disorders	
Very common:	Neutropenia
Common:	Anaemia, thrombocytopenia
Metabolism and nutrition disorders	
Common	Hyperglycaemia
Uncommon:	Tumour lysis syndrome*
Nervous system disorders	
Very common:	Peripheral sensory neuropathy
Common:	Peripheral motor neuropathy, dizziness, demyelinating polyneuropathy*
Respiratory, thoracic and mediastinal disorders	
Common:	Cough, dyspnoea
Gastro-intestinal disorders	
Very common:	Diarrhoea, nausea, vomiting
Common:	Constipation
Skin and subcutaneous tissue disorders	
Very common:	Alopecia, pruritus
Common	Rash
Uncommon:	Stevens-Johnson syndrome*
Musculoskeletal and connective tissue disorders	
Very common:	Myalgia
Common:	Arthralgia, back pain
General disorders and administration site conditions	
Very common:	Fatigue, pyrexia, infusion-related reactions[b]
Common:	Chills

*Reported as a serious adverse reaction only

[a] Preferred terms that were reported under the Infections and Infestations SOC include upper respiratory tract infection, herpes zoster, and pneumonia.

[b] Preferred terms associated with infusion-related reactions were chills (4%), nausea, dyspnoea and pruritus (3% each), and cough (2%).

Serious adverse event / deaths / other significant events

Serious adverse events

In the phase 2 studies, 31% of patients had a serious adverse event (SAE), 28% had an SAE of grade 3 or higher, and 15% had an SAE that was determined by the investigator to be related to brentuximab-vedotin. The most common SAEs in the phase 2 population were abdominal pain, disease progression (recurrent ALCL), pulmonary embolism, and septic shock.

All SAEs reported in the two phase II trials are summarised in the following Table 32. SAEs grade 3 or higher and those considered as ADRs are also summarised in the table.

Table 32: Serious adverse events occurring in the Phase 2 Population

	HL SG035-0003 (N=102) n (%)			sALCL SG035-0004 (N=58) n (%)			Total Ph 2 (N=160) n (%)		
	Any	Grade ≥3	Rel	Any	Grade ≥3	Rel	Any	Grade ≥3	Rel
Any SAE	25 (25)	24 (24)	14 (14)	24 (41)	20 (34)	10 (17)	49 (31)	44 (28)	24 (15)
Abdominal pain	2 (2)	2 (2)	1 (1)	1 (2)	0	0	3 (2)	2 (1)	1 (1)
ALCL recurrent	0	0	0	3 (5)	3 (5)	0	3 (2)	3 (2)	0
Pulmonary embolism	2 (2)	2 (2)	1 (1)	1 (2)	1 (2)	1 (2)	3 (2)	3 (2)	2 (1)
Septic shock	1 (1)	1 (1)	0	2 (3)	1 (2)	0	3 (2)	2 (1)	0
Arrhythmia supraventricular	0	0	0	2 (3)	1 (2)	0	2 (1)	1 (1)	0
Cellulitis	1 (1)	1 (1)	0	1 (2)	1 (2)	0	2 (1)	2 (1)	0
Demyelinating polyneuropathy	2 (2)	2 (2)	2 (2)	0	0	0	2 (1)	2 (1)	2 (1)
Diarrhoea	1 (1)	0	0	1 (2)	1 (2)	1 (2)	2 (1)	1 (1)	1 (1)
Gastrointestinal haemorrhage	1 (1)	1 (1)	0	1 (2)	1 (2)	0	2 (1)	2 (1)	0
Mental status changes	1 (1)	0	1 (1)	1 (2)	0	0	2 (1)	0	1 (1)
Pain in extremity	0	0	0	2 (3)	2 (3)	0	2 (1)	2 (1)	0
Peripheral motor neuropathy	1 (1)	1 (1)	1 (1)	1 (2)	1 (2)	1 (2)	2 (1)	2 (1)	2 (1)
Pneumonia	1 (1)	1 (1)	1 (1)	1 (2)	1 (2)	1 (2)	2 (1)	2 (1)	2 (1)
Pneumonitis	2 (2)	2 (2)	1 (1)	0	0	0	2 (1)	2 (1)	1 (1)
Pneumothorax	2 (2)	1 (1)	0	0	0	0	2 (1)	1 (1)	0
Pyelonephritis	2 (2)	2 (2)	0	0	0	0	2 (1)	2 (1)	0
Pyrexia	2 (2)	2 (2)	2 (2)	0	0	0	2 (1)	2 (1)	2 (1)
Urinary tract infection	0	0	0	2 (3)	2 (3)	2 (3)	2 (1)	2 (1)	2 (1)
Abdominal pain upper	1 (1)	1 (1)	0	0	0	0	1 (1)	1 (1)	0
Acute myocardial infarction	0	0	0	1 (2)	1 (2)	0	1 (1)	1 (1)	0
Anaemia	0	0	0	1 (2)	1 (2)	0	1 (1)	1 (1)	0
Asthenia	0	0	0	1 (2)	0	0	1 (1)	0	0
Atrial fibrillation	0	0	0	1 (2)	1 (2)	0	1 (1)	1 (1)	0
Atrioventricular block complete	0	0	0	1 (2)	1 (2)	0	1 (1)	1 (1)	0
Bradycardia	0	0	0	1 (2)	1 (2)	0	1 (1)	1 (1)	0
Bronchitis	1 (1)	0	0	0	0	0	1 (1)	0	0
Candidiasis	1 (1)	0	0	0	0	0	1 (1)	0	0
Constipation	0	0	0	1 (2)	1 (2)	1 (2)	1 (1)	1 (1)	1 (1)
Decreased appetite	0	0	0	1 (2)	1 (2)	0	1 (1)	1 (1)	0

	HL SG035-0003 (N=102) n (%)			sALCL SG035-0004 (N=58) n (%)			Total Ph 2 (N=160) n (%)		
	Any	Grade ≥3	Rel	Any	Grade ≥3	Rel	Any	Grade ≥3	Rel
Deep vein thrombosis	0	0	0	1 (2)	1 (2)	0	1 (1)	1 (1)	0
Diabetic coma	1 (1)	1 (1)	0	0	0	0	1 (1)	1 (1)	0
Diffuse large b-cell lymphoma	1 (1)	0	0	0	0	0	1 (1)	0	0
Encephalopathy	0	0	0	1 (2)	1 (2)	0	1 (1)	1 (1)	0
Endocarditis staphylococcal	0	0	0	1 (2)	1 (2)	0	1 (1)	1 (1)	0
Flank pain	1 (1)	0	0	0	0	0	1 (1)	0	0
Fluid overload	0	0	0	1 (2)	1 (2)	0	1 (1)	1 (1)	0
Gastroenteritis viral	0	0	0	1 (2)	0	0	1 (1)	0	0
Generalised oedema	0	0	0	1 (2)	1 (2)	0	1 (1)	1 (1)	0
H1N1 influenza	1 (1)	1 (1)	0	0	0	0	1 (1)	1 (1)	0
Haematemesis	1 (1)	1 (1)	1 (1)	0	0	0	1 (1)	1 (1)	1 (1)
Haemoptysis	1 (1)	1 (1)	0	0	0	0	1 (1)	1 (1)	0
Haemorrhage intracranial	0	0	0	1 (2)	0	0	1 (1)	0	0
Hodgkin's disease recurrent	1 (1)	1 (1)	0	0	0	0	1 (1)	1 (1)	0
Hydronephrosis	0	0	0	1 (2)	0	0	1 (1)	0	0
Hypercalcaemia	0	0	0	1 (2)	0	0	1 (1)	0	0
Hyperglycaemia	1 (1)	1 (1)	1 (1)	0	0	0	1 (1)	1 (1)	1 (1)
Intestinal perforation	1 (1)	0	0	0	0	0	1 (1)	0	0
Klebsiella bacteraemia	0	0	0	1 (2)	1 (2)	0	1 (1)	1 (1)	0
Lower limb fracture	0	0	0	1 (2)	0	0	1 (1)	0	0
Lung infection	1 (1)	1 (1)	0	0	0	0	1 (1)	1 (1)	0
Muscular weakness	1 (1)	1 (1)	1 (1)	0	0	0	1 (1)	1 (1)	1 (1)
Mycosis fungoides	0	0	0	1 (2)	1 (2)	0	1 (1)	1 (1)	0
Myositis	0	0	0	1 (2)	1 (2)	1 (2)	1 (1)	1 (1)	1 (1)
Nausea	1 (1)	0	0	0	0	0	1 (1)	0	0
Neuralgia	0	0	0	1 (2)	0	1 (2)	1 (1)	0	1 (1)
Neutropenia	0	0	0	1 (2)	1 (2)	1 (2)	1 (1)	1 (1)	1 (1)
Peripheral sensory neuropathy	0	0	0	1 (2)	1 (2)	1 (2)	1 (1)	1 (1)	1 (1)
Pleural effusion	1 (1)	0		0	0	0	1 (1)	0	0
Pneumocystis jiroveci pneumonia	1 (1)	1 (1)	1 (1)	0	0	0	1 (1)	1 (1)	1 (1)
Pulmonary oedema	0	0	0	1 (2)	1 (2)	0	1 (1)	1 (1)	0
Rash papular	0	0	0	1 (2)	1 (2)	0	1 (1)	1 (1)	0
Renal failure	0	0	0	1 (2)	1 (2)	0	1 (1)	1 (1)	0
Renal failure acute	0	0	0	1 (2)	1 (2)	0	1 (1)	1 (1)	0

	HL SG035-0003 (N=102) n (%)			sALCL SG035-0004 (N=58) n (%)			Total Ph 2 (N=160) n (%)		
	Any	Grade ≥3	Rel	Any	Grade ≥3	Rel	Any	Grade ≥3	Rel
Respiratory failure	0	0	0	1 (2)	1 (2)	0	1 (1)	1 (1)	0
Retinal vein occlusion	0	0	0	1 (2)	0	1 (2)	1 (1)	0	1 (1)
Soft tissue infection	1 (1)	1 (1)	0	0	0	0	1 (1)	1 (1)	0
Spinal cord compression	0	0	0	1 (2)	1 (2)	0	1 (1)	1 (1)	0
Staphylococcal bacteraemia	1 (1)	1 (1)	1 (1)	0	0	0	1 (1)	1 (1)	1 (1)
Stevens-johnson syndrome	1 (1)	1 (1)	1 (1)	0	0	0	1 (1)	1 (1)	1 (1)
Sudden death	0	0	0	1 (2)	1 (2)	0	1 (1)	1 (1)	0
Superinfection bacterial	0	0	0	1 (2)	1 (2)	0	1 (1)	1 (1)	0
Syncope	0	0	0	1 (2)	1 (2)	0	1 (1)	1 (1)	0
Thrombocytopenia	1 (1)	1 (1)	1 (1)	0	0	0	1 (1)	1 (1)	1 (1)
Tracheal disorder	0	0	0	1 (2)	1 (2)	0	1 (1)	1 (1)	0
Tumour flare	0	0	0	1 (2)	1 (2)	1 (2)	1 (1)	1 (1)	1 (1)
Tumour lysis syndrome	0	0	0	1 (2)	1 (2)	1 (2)	1 (1)	1 (1)	1 (1)
Urinary tract infection staphylococcal	1 (1)	1 (1)		0	0	0	1 (1)	1 (1)	0
Vomiting	0	0	0	1 (2)	1 (2)	1 (2)	1 (1)	1 (1)	1 (1)
Wrist fracture	1 (1)	1 (1)	0	0	0	0	1 (1)	1 (1)	0

Abbreviations: Rel= Related (as assessed by the investigator). Final classification of SAEs as ADRs was determined by the applicant

Preferred terms are sorted by descending frequency of the "Any" column corresponding to the Phase 2 Population.

Deaths

There were 6 deaths in the phase 2 studies that occurred within 30 days of the last dose of brentuximab-vedotin. These deaths all occurred in systemic ALCL patients and were considered unrelated to treatment and were attributable to ALCL recurrent (3 patients), acute myocardial infarction and acute renal failure (1 patient), respiratory failure (1 patient), and sudden death (1 patient). During the follow-up period (more than 30 days after the last dose of brentuximab-vedotin), 25 patients died; a Grade 5 adverse event was recorded for 1 of these patients (Hodgkin's disease recurrent). Of the 31 deaths total in the phase 2 studies, 18 were considered by the investigator to be related to the disease under study.

In the phase 1 dose-escalation studies, 2 patients died within 30 days of the last dose of SGN-35: 1 patient died from febrile neutropenia and septic shock (Study SG035-0001) and 1 patient died from pneumonia influenza (Study SG035-0002). During the follow-up period in the phase 1 dose-escalation studies, there were 14 patient deaths (SG035-0001: 7 patients; SG035-0002: 7 patients).

In the phase 1 study assessing cardiac ventricular repolarization (SGN35-007), no patients died within Cycle 1. In the phase 1 clinical pharmacology study (Study SGN5-008A), 1 patient with a history of

allogeneic stem cell transplant died after receiving 1 dose of SGN-35 from intracranial hemorrhage, CMV infection, and pancytopenia, all of which were considered by the investigator to be related to treatment.

Other significant events

Progressive Multifocal Leukoencephalopathy (PML)

To date, 2 of the patients included in the pivotal HL study suffered from progressive multifocal leukoencephalopathy (PML) following brentuximab-vedotin. This severe debilitating disease resulted in the death of one of them. World-wide, in total 3 patients suffered from confirmed PML on a total of about 2,000 brentuximab-vedotin-treated patients. The incidence of PML among transplantation recipients has been reported to be ~1.24 per 1,000 post-transplantation person-years (Mateen *et al*, 2011).

The exact cause of death of another patient who suffered from fatal seizures could not be established as autopsy was not performed. Of note is that seizures are a symptom of PML as well.

Immunological events

Patients were tested for antitherapeutic antibody (ATA) against SGN-35 at baseline (within 2 hours prior to the first dose), pre-dose in each subsequent treatment cycle (C_{trough}; approximately 3 weeks following the previous dose), and at the end-of-treatment visit. A summary of the ATA findings (ATA incidence and status) according to baseline ATA status from studies SG035-0003 and SG035-0004 is presented in the following Table 33. Study SG035-0001 was not included in the overall analysis because a different assay for ATA detection was used, study SG035-0002 was not included because of a different dosing schedule used and results from studies SGN35-007 and SGN35-008 were not included due to the short duration of data available from those studies.

The majority of phase 2 patients (95%) were negative for anti-SGN35 antibodies (ATA) at baseline. The presence of ATA did not correlate with a substantial reduction in brentuximab-vedotin serum levels and did not result in a decrease in the efficacy of brentuximab-vedotin. However, patients with persistently positive ATA had higher incidence of infusion-related reaction compared to patients with transiently or never positive ATA.

Table 33: Immunogenicity in the phase II studies

Baseline ATA Status	Postbaseline ATA Status	Number of Patients (N = 156) n (%)
Baseline negative		148 (95)
	Negative postbaseline	96 (62)
	Transiently positive postbaseline	42 (27)
	Persistently positive postbaseline	10 (6)
Baseline positive		8 (5)
	Negative postbaseline	2 (1)
	Transiently positive postbaseline	5 (3)
	Persistently positive postbaseline	1 (1)

Confirmed ATA-positive samples from SG035-0003 and SG035-0004 were assayed for the presence of neutralizing antibodies. Of 58 patients with ATA-positive samples, 18 (31%) patients were negative for the presence of neutralizing antibodies, 36 (62%) had at least one sample that was positive for the presence of neutralizing antibodies, and 4 (7%) were of unknown status due to insufficient sample.

In the detailed case reports of the relapsed/refractory HL patients that have previously not been treated with ASCT, the applicant did not report on the presence of ATA. One of the 56 patients was

described to have suffered from a grade ≥3 drug hypersensitivity reaction, which was classified as unrelated to the treatment.

Laboratory findings

The highest incidences of new or worsening clinical laboratory values of any grade were observed for low leukocytes (58%), neutrophils (54%), haemoglobin (29%), lymphocytes (25%) and platelets (23%); and high glucose (40%), aspartate aminotransferase (AST [37%]), and alanine aminotranferase (ALT [34%]).

The clinical laboratory parameters for which the highest percentages of patients in the Phase 2 population had a postbaseline worsening of 2 or more grades were low neutrophils (30%), leukocytes (22%) lymphocytes (11%) and high glucose (9%). The clinical laboratory parameters for which the most patients (>5%) in the phase 2 population had new or worsening shifts to Grade 3 were low neutrophils (11%), lymphocytes (11%), platelets (6%), leukocytes (5%), high glucose (6%), and high ALT and AST (1%).

In the 56 detailed case reports concerning the patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL) following at least two prior therapies when autologous stem cell transplant or multi-agent chemotherapy is no longer a treatment option, the grade ≥3 clinical laboratory parameters were neutropenia (15%), lymphopenia (8%), thrombocytopenia (8%), leukopenia (2%) and hyperglycaemia (2%).

Safety in special populations

A clinical study to evaluate the effects of renal impairment and hepatic impairment on brentuximab vedotin and MMAE pharmacokinetics is ongoing. In the phase 2 studies, effects regarding age and race are inconclusive due to the small number of patients who were <18 or >65 years or older, or non-white.

Safety related to drug-drug interactions and other interactions

Clinical data (study SGN35-008A) from co-administration of brentuximab-vedotin with rifampicin, a CYP3A4 inducer, or ketoconazole, a strong CYP3A4 inhibitor, indicate that MMAE is a substrate of CYP3A4. Patients who are receiving strong CYP3A4 inhibitors concomitantly with brentuximab-vedotin should be closely monitored for adverse events because of the potential for modest increases in MMAE levels.

Discontinuation due to adverse events

In the phase 2 population, AEs led to treatment discontinuation in 19% of patients. The most common AEs were peripheral sensory neuropathy (6%), peripheral motor neuropathy (2%), and disease recurrence (1%).

In the relapsed or refractory HL patients that have previously not been treated with ASCT, AEs led to treatment discontinuation in 9% of the patients, with the most common AE being disease progression (i.e. 5% of the total number of patients).

2.6.1. Discussion on clinical safety

Across six clinical studies that were submitted to support this application, a total of 357 patients have received at least one dose of brentuximab-vedotin. Based on the epidemiology of the conditions for

which brentuximab-vedotin is intended, a limited safety base of this size is acceptable, but exposure is somewhat limited.

In the pivotal studies, patients with HL and sALCL were generally similar with respect to the AE incidence and severity, but the percentage of patients with treatment-emergent upper respiratory tract infection were higher in HL patients (37%) relative to sALCL patients (12%). It is conceivable that this difference is due to impairment in cell-mediated immunity in classical Hodgkin's lymphoma patients (Franzke *et al*, 2006).

Previously two other anti-CD30 therapeutic mAb without drug conjugate have been evaluated for their anti-neoplastic effect in CD30+haematologic malignancies.

Forero-Torres *et al* (2009) evaluated SGN30 in a phase 2 study in 38 patients with refractory/recurrent HL. No objective responses were observed in the HL group. Anaemia grade ≥3 was reported in 4% of the patients. Treatment-related SAE were reported in 13% of the patients. AE leading to discontinuation were reported in 4% of the patients.

Ansell *et al* (2007) evaluated in a phase I/II study MDX-060 in patients with relapsed HL. The treatment was well tolerated. Grade ≥3 treatment related AE were dyspnoea (3%), acute respiratory distress syndrome (1%), elevation of liver transaminases (1%), epistaxis (1%), GvHD (1%), and cardiac tamponade (1%).

In the light of the low efficacy and low toxicity of the anti-CD30 mAbs SGN-30 and MDX-060, the efficacy, but also toxicity, of brentuximab-vedotin is most likely to be mainly due to its drug conjugate, the anti-tubulin agent monomethyl auristatin E (MMAE). MMAE blocks polymerisation of tubulin and the maximum concentrations were typically observed 2 days post-dose and MMAE declined with an apparent terminal half-life of ~4 days at the 1.8 mg/kg dose level.

The use of brentuximab vedotin is contraindicated in case of hypersensitivity to the active substance or to any of the excipients of Adcetris. Combined use of bleomycin and brentuximab vedotin causes pulmonary toxicity and is also contraindicated.

The phase 2 studies revealed the following key safety concerns of brentuximab-vedotin treatment in HL and sALCL patients:

Peripheral neuropathy

Peripheral neuropathy was the most common AE occurring in 55% of the patients (39% sensory only, 3% motor only and 12% with both) leading to treatment discontinuation (12%), and dose reductions (10%).

A by-patient graphical representation of the onset, severity, duration, and resolution of all treatment-emergent peripheral neuropathy events per MedDRA SMQ was provided by the Applicant (data not shown).

In HL patients, all grade 3 peripheral neuropathy events were preceded by lower grades of either sensory or motor neuropathy. In addition, grade 3 events did not typically present prior to 6 months of continuous brentuximab-vedotin treatment. The median time to onset of Grade 3 events is 38.0 weeks. No Grade 4 peripheral neuropathy events were observed.

For the sALCL patients it was shown that no event exceeded grade 3 in severity, and all PN events had improved to at least grade 2 or lower by the end of the observation period (± 580 days). The first patients of this study population showed onset of grade 3 PN at around 2 months after initiation of the treatment with brentuximab-vedotin, which appears to be earlier than in the HL study population. The

dosage of brentuximab-vedotin used per cycle was equal in both studies and as such can not explain the possible difference in onset of the PN between the two diseases.

Supporting data from nerve conduction study findings in patients from studies SG035-0003, SG035-0004 and SGN35-007 (data not shown) are consistent with findings of peripheral sensory neuropathy and demyelinating polyneuropathy. No repeat nerve conduction studies were documented in association with a brentuximab-vedotin-induced event. Follow-up data at the individual patient level are therefore not available.

The incidence and severity of neuropathy, as well as the nature of the events (i.e. sensory events were more common than motor events and a distal pattern of development was more common than a proximal pattern of development), is similar to that observed with other microtubule inhibitor-based chemotherapies (including vinca alkaloids, taxanes, and epothilones). Also consistent with the clinical experience with microtubule inhibitors was the observation that neuropathy appeared to be a cumulative effect. Onset of motor neuropathy was later than non-motor events, suggesting that in most cases motor neuropathy occurs with higher cumulative exposure.

In general, peripheral neuropathy was managed by early recognition, dose delay, and subsequent dose reduction to 1.2 mg/kg, and was reversible, with symptom improvement or resolution in more than 60% of patients who experienced peripheral neuropathy events. Importantly, no grade 4 AE has been reported and peripheral sensory/motoric neuropathy appeared to resolve at least to a certain extent.

Patients should be monitored for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paraesthesia, discomfort, a burning sensation, neuropathic pain or weakness. Patients experiencing new or worsening peripheral neuropathy may require a delay and a dose reduction of brentuximab vedotin or discontinuation of treatment, as recommended in section 4.2 of the SmPC.

Myelosuppression

Grade 3 and 4 neutropenia occurred in 13% and 7% of patients, respectively; however it was typically of short duration and managed by dose delays with growth factor support in some cases.

Since the relative dose intensity in the phase 2 population was >90%, dose withholding / reduction had only a minimal impact on overall brenutuximab-vedotin dosing.

Complete blood counts should be monitored prior to administration of each dose of this treatment. Patients should be monitored closely for fever and managed according to best medical practice if febrile neutropenia develops. Moreover, neutropenia should be managed by dose delays as described in section 4.2 of the SmPC.

Other safety concerns

Serious infections such as pneumonia, staphylococcal bacteraemia, and herpes zoster, and opportunistic infections such as Pneumocystis jiroveci pneumonia and oral candidiasis have been reported in patients treated with brentuximab vedotin. Patients should be carefully monitored during treatment for the emergence of possible serious and opportunistic infections.

Infusion-related reactions occurred in approximately 10% of patients and were typically managed by dose interruptions. Infusion-related reactions are more frequent and more severe in patients with antibodies to brentuximab vedotin.

Patients should be carefully monitored during and after infusion. If anaphylaxis occurs, administration of brentuximab vedotin should be immediately and permanently discontinued and appropriate medical therapy should be administered.

If an infusion-related reaction occurs, the infusion should be interrupted and appropriate medical management instituted. The infusion may be restarted at a slower rate after symptom resolution. Patients who have experienced a prior infusion-related reaction should be premedicated for subsequent infusions. Premedication may include paracetamol, an antihistamine and a corticosteroid.

Further safety concerns associated with brentuximab-vedotin treatment are infections and hyperglycaemia. It is unclear whether the one reported case of Stevens Johnson Syndrome was associated with brentuximab-vedotin treatment. If Stevens-Johnson syndrome occurs, treatment with brentuximab vedotin should be discontinued and appropriate medical therapy should be administered. Hyperglycaemia has been reported during clinical trials in patients with an elevated Body Mass Index (BMI) with or without a history of diabetes mellitus. However, any patient who experiences an event of hyperglycaemia should have their serum glucose closely monitored. Anti-diabetic treatment should be administered as appropriate.

At this time two confirmed cases of progressive multifocal leukoencephalopathy (PML) and 1 suspect case of PML have been reported in the 2,000 patients treated world-wide. The incidence of PML among transplantation recipients has been reported with ~1.24 per 1,000 post-transplantation person-years (Mateen *et al*, 2011).

Patients should be closely monitored for new or worsening neurological, cognitive, or behavioural signs or symptoms, which may be suggestive of PML. Brentuximab vedotin dosing should be held for any suspected case of PML. Suggested evaluation of PML includes neurology consultation, gadolinium-enhanced magnetic resonance imaging of the brain and cerebrospinal fluid analysis for JCV DNA by polymerase chain reaction or a brain biopsy with evidence of JCV. A negative JCV PCR does not exclude PML. Additional follow up and evaluation may be warranted if no alternative diagnosis can be established. Brentuximab vedotin dosing should be permanently discontinued if a diagnosis of PML is confirmed.

The physician should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g., cognitive, neurological, or psychiatric symptoms).

The safety data on heavily pre-treated patients with relapsed-refractory HL who had not been transplanted with autologous haematopoietic stem cells, presented by the Applicant during the Oral Explanantion, suggest a comparable safety profile as observed in the pivotal HL study, SG035-0003. However, it should be noted that this preliminary conclusion is based on only 40 patients (having received the recommended dose of brentuximab vedotin) in total.

From the safety information on these relapsed or refractory HL patients not previously treated with ASCT, 72 AEs grade I and II were observed in 56 patients that received any dose of brentuximab vedotin. This analysis was somewhat hampered by the fact that the grade I and II AEs were not specified per patient, hence AEs reported in the 3 patients (of the 59) excluded as having received only one therapy prior to brentuximab vedotin could not be identified. However, this exclusion should only lead to minor numerical adjustments. The distribution of the AEs among the described studies seemed comparable although patient number per study was low and there was heterogeneity regarding the dose and the number of cycles of brentuximab vedotin administered. In total, 59 grade ≥3 AEs were observed of which 7 were described to be related to brentuximab vedotin. Of 15 other grade ≥3 events relationship to study treatment was not reported. These AEs occurred in the patients included in the SGN35-007 phase 1 QTc study, the TB-BC010088 phase 1/2 Japan-only study and the NPPs. Overall, as no new safety concerns have been identified, it is unlikely that further specification would have affected the safety profile to a large extent.

Immunogenicity of SGN-35 can not be evaluated fully as the ECL screening assay for the detection of ATA against brentuximab vedotin in serum of treated patients is insufficient in terms of sensitivity,

drug tolerance and interference by sCD30 and rheumatoid factor. Under reporting of antibodies is possible. The screening assay for the detection of ATA against brentuximab vedotin in serum should be further optimised.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Additional safety data needed in the context of a conditional MA

Due to the relatively small size of the studied population, a post-authorisation safety study (PASS) in the studied HL and sALCL populations (comprising at least 500 patients including at least 50 sALCL patients) is expected to provide comprehensive safety data to further inform the benefit/risk balance of Adcetris.

2.6.2. Conclusions on the clinical safety

The anti-CD30 antibody drug conjugate contains a microtubule inhibitor. This group of chemotherapeutic agents are known to be associated with peripheral neuropathy, most frequently sensory in nature, and haematological toxicities.

In the phase 2 HL and sALCL study populations, treatment-related adverse events were common, leading to treatment discontinuation in 19% of patients and to dose modifications in 46% of patients. The most common brentuximab-vedotin treatment-related AE in the pivotal studies were peripheral neuropathy (55%, leading to treatment discontinuation (12%), and dose reductions (10%)), myelosuppression, infections and infusion reactions. The majority of AEs were managed by dose delays or reduction. One of the patients suffering from PML upon the use of brentuximab-vedotin died.

The single arm study design in the pivotal studies makes it difficult to determine attribution of AEs in general, even more so in a heavily pre-treated patient population with disease-related immune dysfunctions (Franzke *et al*, 2006).

The safety data on 56 heavily pre-treated patients with relapsed-refractory HL without ASCT presented by the applicant indicated that the safety profile is comparable with the pivotal HL study population. However, the heterogeneity between the patients and the not complete report on AEs should be noted.

The CHMP considers the following measures necessary to address the missing safety data in the context of a conditional MA:

A Post-Authorisation Safety Study (PASS) in both studied HL and sALCL patient populations (n=500) should be performed including a sufficient number of sALCL patients (i.e. at least n=50).

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted a risk management plan.

Table 34: Summary of the risk management plan

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Important Identified Risks		
Progressive Multifocal Leuko-encephalopathy	• Routine Pharmacovigilance	SmPC Section 4.4, Special warnings and precautions for use; SmPC Section 4.8, Undesirable effects Progressive multifocal leukoencephalopathy (PML) has been reported in patients who received this treatment after receiving multiple prior chemotherapy regimens. PML is a rare demyelinating disease of the central nervous system that results from reactivation of latent JC virus (JCV) and is often fatal. Patients should be closely monitored for new or worsening neurological, cognitive, or behavioural signs or symptoms that may be suggestive of PML. Brentuximab vedotin dosing should be held for any suspected case of PML. Suggested evaluation of PML includes neurology consultation, gadolinium-enhanced magnetic resonance imaging of the brain, and cerebrospinal fluid analysis for JCV DNA by polymerase chain reaction or a brain biopsy with evidence of JCV. A negative JC-V PCR does not exclude PML. Additional follow up and evaluation may be warranted if no alternative diagnosis can be established. Brentuximab vedotin dosing should be permanently discontinued if a diagnosis of PML is confirmed. The physician should be particularly alert to symptoms suggestive of PML that the patient may not notice (eg, cognitive, neurological, or psychiatric symptoms).
Pulmonary toxicity associated with combination use of bleomycin and brentuximab vedotin	• Routine Pharmacovigilance • Termination of administration of the combination within and without the clinical development programme	SmPC Section 4.3, Contraindications The use of bleomycin and brentuximab vedotin in combination is contraindicated due to associated pulmonary toxicity reported in a phase 1 study. The brentuximab vedotin + ABVD combination cohort of the trial has been terminated and no further dosing with this combination is planned.
Peripheral Neuropathy (Sensory and Motor)	• Routine Pharmacovigilance • Ongoing SGN35-0003 study • Ongoing SGN35-0004 study • Ongoing SGN35-005 study • Planned SGN35-014 study • Planned cutaneous T cell lymphoma study (C25001) • Postauthorisation safety study (MA25101)	SmPC Section 4.2, Posology and method of administration; SmPC Section 4.4, Special warnings and precautions for use; SmPC Section 4.8, Undesirable effects Brentuximab vedotin treatment may cause a peripheral neuropathy that is predominantly sensory. Cases of peripheral motor neuropathy have also been reported. Brentuximab vedotin-induced peripheral neuropathy is typically an effect of cumulative exposure to this medicinal product and is reversible in most cases. In clinical studies, the majority of patients had improvement or resolution of their symptoms. Neuropathy appeared to be mitigated by dose delay and subsequent reduction or brentuximab vedotin discontinuation. Patients should be monitored for symptoms of neuropathy, such as hypoaesthesia, hyperaesthesia, paraesthesia, discomfort, a burning sensation, neuropathic pain or weakness. Patients experiencing

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
		new or worsening peripheral neuropathy may require a delay and a dose reduction of brentuximab vedotin or discontinuation of treatment (refer to SmPC Section 4.2).
Neutropenia	• Routine Pharmacovigilance • Postauthorisation safety study (MA25101)	SmPC Section 4.2, Posology and method of administration; SmPC Section 4.4, Special warnings and precautions for use; SmPC Section 4.8, Undesirable effects Prolonged (≥ 1 week) Grade 3 or Grade 4 neutropenia can occur with brentuximab vedotin. Patients should be monitored with complete blood counts prior to administration of each dose. If Grade 3 or Grade 4 neutropenia develops refer to SmPC Section 4.2.
Thrombocytopenia	• Routine Pharmacovigilance	SmPC Section 4.4, Special warnings and precautions for use; SmPC Section 4.8, Undesirable effects Grade 3 or Grade 4 thrombocytopenia can occur with brentuximab vedotin. Patients should be monitored with complete blood counts prior to administration of each dose.
Anaemia	• Routine Pharmacovigilance	SmPC Section 4.8, Undesirable effects Grade 3 or Grade 4 anaemia can occur with brentuximab vedotin. Patients should be monitored with complete blood counts prior to administration of each dose.
Infection Including Bacteraemia/ Sepsis/Septic Shock	• Routine Pharmacovigilance • Postauthorisation safety study (MA25101)	SmPC Section 4.4, Special warnings and precautions for use; SmPC Section 4.8, Undesirable effects Serious infection such as pneumonia, staphylococcal bacteraemia, and herpes zoster, have been reported in patients treated with brentuximab vedotin. Patients should be carefully monitored during treatment for the emergence of possible serious infection.
Opportunistic Infection	• Routine Pharmacovigilance • Postauthorisation safety study (MA25101)	SmPC Section 4.4, Special warnings and precautions for use; SmPC Section 4.8, Undesirable effects Serious opportunistic infection such as *Pneumocystis jiroveci* pneumonia and oral candidiasis have been reported in patients treated with brentuximab vedotin. Patients should be carefully monitored during treatment with brentuximab vedotin for the emergence of possible serious opportunistic infection.
Infusion-Related Reactions	• Routine Pharmacovigilance • Planned SGN35-014 study • Planned cutaneous T-cell lymphoma study (C25001) • Postauthorisation safety study (MA25101)	SmPC Section 4.4, Special warnings and precautions for use; SmPC Section 4.8, Undesirable effects Immediate and delayed infusion-related reactions (IRRs), as well as anaphylaxis, have been reported. Patients should be carefully monitored during and after infusion. If anaphylaxis occurs, administration of brentuximab vedotin should be immediately and permanently discontinued and appropriate medical therapy should be administered. If an IRR occurs, the infusion should be interrupted and appropriate medical management instituted. The infusion may be restarted at a slower rate after symptom resolution. Patients who have experienced a prior IRR should be premedicated for subsequent infusions. Premedication may include paracetamol,

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
		an antihistamine, and a corticosteroid. Infusion-related reactions are more frequent and more severe in patients with antibodies to brentuximab vedotin. Symptoms of anaphylaxis may include, but are not limited to, urticaria, angioedema, hypotension, and bronchospasm. Routine pharmacovigilance will be used to monitor IRRs. The sponsor commits to monitor hypersensitivity reactions (either an IRR or an allergic reaction). In addition, the monitoring of ATAs in the clinical trial setting will be performed, including the determination of ATA isotype (using the redeveloped assay), in patients enrolled in company-sponsored clinical trials who experience a hypersensitivity reaction (either an IRR or an allergic reaction) and who test positive for ATAs. The RMP will be updated regarding the occurrence and the effects of ATAs, as appropriate.
Hyperglycaemia	• Routine Pharmacovigilance • Postauthorisation safety study (MA25101)	SmPC Section 4.4, Special warnings and precautions for use; SmPC Section 4.8, Undesirable effects Hyperglycaemia has been reported during clinical trials in patients with an elevated body mass index (BMI) with or without a history of diabetes mellitus. However, any patient who experiences an event of hyperglycaemia should have their serum glucose closely monitored. Antidiabetic treatment should be administered as appropriate.
Stevens-Johnson Syndrome	• Routine Pharmacovigilance	SmPC Section 4.4, Special warnings and precautions for use; SmPC Section 4.8, Undesirable effects Stevens-Johnson syndrome has been reported with brentuximab vedotin. If Stevens-Johnson syndrome occurs, treatment with brentuximab vedotin should be discontinued and appropriate medical therapy should be administered.
Tumour Lysis Syndrome	• Routine Pharmacovigilance	SmPC Section 4.4, Special warnings and precautions for use; SmPC Section 4.8, Undesirable effects Tumour lysis syndrome (TLS) has been reported with brentuximab vedotin. Patients with rapidly proliferating tumour and high tumour burden are at risk of TLS. These patients should be monitored closely and managed according to best medical practice. Management of TLS may include aggressive hydration, monitoring of renal function, correction of electrolyte abnormalities, antihyperuricaemic therapy, and supportive care.
Antitherapeutic Antibodies	• Routine Pharmacovigilance • Planned SGN35-014 study • Planned cutaneous T-cell lymphoma study (C25001)	SmPC Section 4.4, Special warnings and precautions for use; SmPC Section 4.8, Undesirable Effects Immediate and delayed infusion-related reactions, as well as anaphylaxis, have been reported. Patients should be carefully monitored during and after infusion. If anaphylaxis occurs, administration of brentuximab vedotin should be immediately and permanently discontinued and appropriate medical

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
		therapy should be administered. Symptoms of anaphylaxis may include, but are not limited to, urticaria, angioedema, hypotension, and bronchospasm. If an IRR occurs, the infusion should be interrupted and appropriate medical management instituted. The infusion may be restarted at a slower rate after symptom resolution. Patients who have experienced a prior IRR should be premedicated for subsequent infusions. Premedication may include paracetamol, an antihistamine, and a corticosteroid. Infusion-related reactions are more frequent and more severe in patients with antibodies to brentuximab vedotin. Patients with relapsed or refractory HL and sALCL in two phase 2 studies were tested for antibodies to brentuximab vedotin every 3 weeks using a sensitive electro-chemiluminescent immunoassay. Approximately 35% of subjects in these studies developed antibodies to brentuximab vedotin. Of these patients, the majority became positive prior to Dose 2, 7% were persistently ATA-positive, and 62% of the ATA-positive patients had neutralizing antibodies. One percent (1%) of patients experienced adverse reactions consistent with IRRs that led to discontinuation of treatment. The presence of antibodies to brentuximab vedotin did not correlate with a clinically meaningful reduction in serum brentuximab vedotin levels and did not result in a decrease in the efficacy of brentuximab vedotin While the presence of antibodies to brentuximab vedotin does not necessarily predict the development of an IRR, there was a higher incidence of IRRs in patients with persistently positive ATA (30%) relative to patients with transiently positive ATA (12%), and never-positive ATA (7%). Routine pharmacovigilance will be used to monitor ATAs. The sponsor commits to monitor hypersensitivity reactions (either an IRR or an allergic reaction). In addition, the monitoring of ATAs in the clinical trial setting will be performed, including the determination of ATA isotype (using the redeveloped assay), in patients enrolled in company-sponsored clinical trials who experience a hypersensitivity reaction (either an IRR or an allergic reaction) and who test positive for ATAs. The RMP will be updated regarding the occurrence and the effects of ATAs, as appropriate.
Important Potential Risks		
Reproductive Toxicity	• Routine Pharmacovigilance	SmPC Section 4.6, Fertility, pregnancy and lactation; SmPC Section 5.3, Preclinical safety data Brentuximab vedotin should not be used during pregnancy unless the benefit for the mother outweighs the potential risks to the foetus. If a pregnant woman

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
		needs to be treated she should be clearly advised on the potential risks to the foetus. There are no data from the use of brentuximab vedotin in pregnant women and there have been no studies on the effects of brentuximab vedotin on human female fertility. Studies in animals have shown reproductive toxicity. Brentuximab vedotin caused embryo-fetal lethality in pregnant female rats. There are no data as to whether brentuximab vedotin or its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. If a breastfeeding woman needs to be treated, a decision should be made whether to discontinue breastfeeding or to discontinue/abstain from brentuximab vedotin therapy, taking into account a potential risk of breastfeeding for the child and the benefit of therapy for the woman. Women of childbearing potential must use two methods of effective contraception during treatment with brentuximab vedotin and until 30 days following the last dose. The effects of brentuximab vedotin on human male fertility have not been studied. However, results of repeat-dose toxicity studies in rats indicate the potential for brentuximab vedotin to impair male reproductive function and fertility. In nonclinical studies, brentuximab vedotin has resulted in testicular toxicity, and may alter male fertility. Testicular atrophy and degeneration were partially reversible following a 16-week treatment-free period. MMAE has been shown to have aneugenic properties. Therefore, men being treated with brentuximab vedotin are advised advised to have sperm samples frozen and stored prior to treatment and not to father a child during and up to 6 months following the last dose.
Thymus Depletion (Paediatric)	• Routine Pharmacovigilance • Study in cynomolgus monkey (aged 2-3 years) • Planned Study C25002 • Planned Study C25004	SmPC Section 4.2, Posology and method of administration SmPC Section 5.3, Preclinical safety data The safety and efficacy of children younger than 18 years have not yet been established. No data are available. In nonclinical studies, lymphoid depletion and reduced thymic weight were observed, consistent with the pharmacologic disruption of microtubules caused by MMAE derived from brentuximab vedotin.
Febrile Neutropenia	• Routine Pharmacovigilance • Postauthorisation safety study (MA25101)	SmPC Section 4.2, Posology and method of administration; SmPC Section 4.4, Special warnings and precautions for use; SmPC Section 4.8, Undesirable effects Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection with an absolute neutrophil count < 1.0×10^9/L, fever ≥ 38.5°C) has been reported during treatment with brentuximab vedotin. Complete blood counts should

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
		be monitored prior to administration of each dose. Patients should be monitored closely for fever and managed according to best medical practice if febrile neutropenia develops.
Interaction with Drugs Modifying CYP3A4 Activity	• Routine Pharmacovigilance	SmPC Section 4.5, Interaction with other medicinal products and other forms of interaction; SmPC Section 5.2, Pharmacokinetic properties Co-administration of brentuximab vedotin with strong CYP3A4 and P-gp inhibitors may increase the incidence of neutropenia. If neutropenia develops, refer to SmPC Section 4.2, Posology and method of administration (SmPC Section 4.5, Interaction with other medicinal products and other forms of interaction). Co-administration of brentuximab vedotin with CYP3A4 inducers is not expected to have an impact on safety or efficacy (SmPC Section 4.5, Interaction with other medicinal products and other forms of interaction). The levels of MMAE metabolites have not been measured in human plasma. At least 1 metabolite of MMAE has been shown to be active in vivo.
Important Missing Information		
Safety in Paediatrics	• Routine Pharmacovigilance • In addition, the agreed PIP includes the following planned studies: – Study in cynomolgus monkeys (aged 2-3 years) – Study C25002: Phase 1 in paediatric patients (5 to < 18 years) – Study C25004: Phase 1 in paediatric patients (5 to < 18 years)	SmPC Section 4.2, Posology and method of administration; SmPC Section 5.2, Pharmacokinetic properties The safety and efficacy of children younger than 18 years of age have not yet been formally established. No data are available. Clinical studies of brentuximab vedotin did not include sufficient numbers of patients younger than 18 years of age to determine whether the PK profile differs from that of adult patients.
Safety in Elderly	• Routine Pharmacovigilance • Postauthorisation safety study (MA25101)	SmPC Section 4.2, Posology and method of administration; SmPC Section 5.2, Pharmacokinetic properties The safety and efficacy in elderly patients aged 65 and older have not been established. No data are available. Clinical studies of brentuximab vedotin did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects.
Safety in Patients with Renal, Hepatic, or Cardiac Impairment	• Routine Pharmacovigilance • In addition, Seattle Genetics is conducting a study in patients with hepatic or renal impairment (SGN35-008 [Part B])	SmPC Section 4.2, Posology and method of administration; SmPC Section 4.4, Special warnings and precautions for use; SmPC Section 5.1, Pharmacodynamic properties; SmPC Section 5.2, Pharmacokinetic properties Patients with renal or hepatic impairment should be carefully monitored. There is limited experience in patients with renal and hepatic impairment. Population pharmacokinetic

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
		(PK) analysis indicated that MMAE clearance might be affected by moderate and severe renal impairment and by low serum albumin concentrations. The kidney is a route of excretion of the unchanged active metabolite MMAE. Data are not yet available from studies in patients with renal impairment. Population pharmacokinetic (PK) analysis indicated that MMAE clearance might be affected by moderate and severe renal impairment, and by low serum albumin concentrations. The liver is a major route of elimination of the unchanged active metabolite MMAE. Data are not yet available on the effect of hepatic impairment on the pharmacokinetics, safety, or efficacy of brentuximab vedotin Results of a phase 1 study designed to evaluate the effect of brentuximab vedotin on cardiac ventricular repolarization, showed the absence of clinically relevant QT prolongation due to brentuximab vedotin administered at a dose of 1.8 mg/kg in patients with CD30-expressing malignancies.
Long Term Safety	• Routine Pharmacovigilance • Postauthorisation safety study (MA25101)	As additional data on long term safety with the use of brentuximab vedotin becomes available, additional language will be proposed in the appropriate section(s) of the SmPC.

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
Pharmacokinetic data in renal and hepatic impaired patients from study SGN-35-008b should be submitted	31/07/2014
Redevelopment of the electrochemiluminescent (ECL) antitherapeutic antibody (ATA) assay	31/12/2012
Determination of MMAE and metabolites in blood and urine after cycle 1 and cycle 3 with and without rifampicin arm (Study C25005)	31/12/2014
The study report of the randomised, double-blind, placebo-controlled AETHERA study of single-agent brentuximab vedotin in patients at high risk for residual HL following transplant should be submitted	30/06/2014
The study report of a randomised, controlled trial to examine patients with newly diagnosed mature T-cell lymphoma (MTCL), including 75% (± 5%) of patients with sALCL (n=±300), should be submitted (SGN35-014)	30/09/2019

No additional risk minimisation activities were required beyond those included in the product information.

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Relapsed/Refractory Hodgkin's lymphoma (HL) post-ASCT: The primary efficacy endpoint in the study on HL (SG035-0003) was overall response rate (ORR). ORR is a measure of anti-tumour activity and it may be considered as an acceptable endpoint to demonstrate clinical benefit in patients with relapsed or refractory HL post-ASCT for conditional approval, provided that the effect is sufficiently large.

Currently, the applicant provided updated efficacy results for Study SG035-0003 (HL) with 1 August 2011 (2 April 2012 for OS) as data cut off date, which showed that:

- the ORR was 75% (76/102) with a CR rate of 33% (34/102) by IRF analysis

- the estimated median duration of response per IRF by Kaplan-Meier analysis was 6.7 months [95% CI (3.6, 14.8)] (range 1.2 to 26.1 months)

- the median duration of response in patients with CR has not been reached [95% CI (10.8, -)]; the current duration of response ranges from 1.4 to 26.1 months

- the estimated median PFS per IRF by Kaplan-Meier analysis was 5.6 months [95% CI (5.0, 9.0 months)] (range, 1.2 to 27.3 months)

- at the time of the last analysis (2 April 2012), 40 of 102 patients were known to have died. The median overall survival (OS) by Kaplan-Meier analysis has not been reached [95% CI (27, – months)].

These data indicate a benefit that is at least comparable to historical controls and perhaps better. The chance to obtain CR and another option for potentially curative stem cell transplantation is meaningful.

Relapsed/Refractory HL in patients ineligible for ASCT or multi-agent chemotherapy: The applicant provided safety and efficacy data for 56 patients with relapsed or refractory HL who had received at least 2 chemotherapy cycles and no ASCT, 40 of whom received the proposed schedule. Overall response rate, complete response rate and the percentage of patients that become eligible for transplantation are considered currently the most important read-outs for the anti-tumour activity of brentuximab-vedotin in this patient population ineligible for ASCT or multidrug chemotherapy:

- ORR seemed lower as compared to the results as observed in the study SG035-0003, regardless of dose and schedule (46% ORR for the 56 no-prior-ASCT patients, 57% ORR for the 40 proposed-dose-and-schedule no-prior-ASCT patients versus 75% ORR for study SG035-0003 patients).

- The CR rates were also lower, i.e. 21% CR for all no-prior-ASCT patients, 23% CR for proposed-dose-and-schedule no-prior-ASCT patients versus 33% CR for study SG035-0003 patients. In the Named Patient Programme (NPP) population only, that is considered to reflect day-to-day clinical practice, these response rates were similar.

- With regard to patients becoming eligible for stem cell transplantation, 20% of the 40 proposed-dose-and-schedule patients (27% when considering only the 26 NPPs patients) have become eligible for stem cell transplantation upon treatment with brentuximab vedotin

The applicant provided very limited PFS/OS data in the case reports, insufficient for any conclusion. Overall, these data indicate that brentuximab vedotin shows anti-tumour activity in the relapsed or refractory HL patients not eligible for stem cell transplantation or muli-agent chemotherapy.

Systemic Anaplastic Large Cell Lymphoma (sALCL): To support the indication relapsed or refractory sALCL a pivotal phase 2 trial (SG035-0004) in 58 patients was submitted. In this study the same endpoints and the assessment of the endpoints were used as in the study in patients with Hodgkin's lymphoma.

The most updated efficacy results with 13 July 2011 (2 April 2012 for OS) as data cut off date showed that:

- the ORR was 86% (50/58) with a CR rate of 59% (34/58)

- the estimated median duration of response per IRF by Kaplan-Meier analysis was 13.2 months [95% CI (5.7,-)] (range, 0.1 to 21.7 months). Of the 50 patients who had an objective response, 27 had had disease progression or had died.

- among patients who achieved a best response of CR, the estimated median duration of response per IRF by Kaplan-Meier analysis was not reached [95% CI (13.0 months, -)] (range, 0.7 to 21.7 months). Of the 34 patients who had a CR, 13 had had disease progression or had died.

- the estimated median PFS per IRF by Kaplan-Meier analysis was 14.3 months [95% CI (6.9,-)] (range, 0.8 to 23.6 months).

- at the time of the last analysis (2 April 2012), 21 of 58 patients were known to have died. The median overall survival by Kaplan-Meier analysis was not reached [95% CI (21.3 , -)]. The estimated overall survival rate at 12 months was 71% [95% CI (57, 80)].

In both pivotal studies, the intra-individual analysis of the PFS in the study populations suggests that brentuximab-vedotin provides a main clinical benefit compared to prior treatment regimens. When optimal treatment is given to patients, any next line therapy usually results in lower efficacy, both in relapsed or refractory HL or sALCL.

Uncertainty in the knowledge about the beneficial effects

In the absence of a controlled trial where the effect of brentuximab-vedotin is compared to established regimens in the proposed indications (regimens consisting of e.g. gemcitabine, vinorelbine or a combination thereof), it is difficult to interpret the claimed effects in terms of PFS and OS.

The median overall survival (OS) in the Hodgkin's lymphoma population and in the sALCL population has not been reached. However, an OS plateau is observed in the sALCL study population and possibly as well in the HL study population (cut of date 2 April 2012). This suggests maturity of the OS results at least in the sALCL study population, although definitive conclusions can not be drawn at this time.

The patient population with relapsed or refractory HL after at least two prior therapies not eligible for ASCT or multi-agent chemotherapy was not included in the pivotal studies. Very limited efficacy and safety date were provided from 56 patients meeting these criteria enrolled in the phase I studies and the named patient programmes. Little PFS/OS data were provided for these patients. This may be explained by the fact that the data were obtained from 6 different studies in combination with the immaturity of the data and the fact that 20% of the patients proceeded to stem cell transplantation. Importantly, the applicant provided a biological rationale to extrapolate the results from the pivotal SG035-003 (HL) and SG035-004 (sALCL) studies to HL patients ineligible for ASCT/multidrug chemotherapy, in that CD30 expression is consistent throughout the HL and sALCL populations and it is not subject to change upon therapy (including ASCT), which is supported. Nevertheless, efficacy data in this patient population are relatively limited.

The optimal duration of the treatment with brentuximab-vedotin has not been studied as such. The pivotal studies aimed at administrating 16 cycles of 1.8 mg/kg brentuximab–vedotin with an interval of 3 weeks. In both the HL and the sALCL patient population, 83% of the patients did not receive the target number of cycles. The median number of cycles administered to the patients treated was 7 and the number of cycles to achieve complete response ranged between 2 and 4. At this time it is unknown how many cycles are required to obtain a durable response or whether patients can be cured by the administration of brentuximab-vedotin as a single agent.

Risks

Unfavourable effects

The safety profile of brentuximab-vedotin was consistent across studies. In the phase 2 population of 160 patients practically all patients experienced AEs: 92% were treatment related, 57% were ≥ grade 3. The most frequent grade ≥3 treatment emergent AEs were related to myelosuppression, peripheral sensory neuropathy and hyperglycaemia.

Serious AEs were experienced by 49 patients, or 31%. Forty-four patients or 28% had grade ≥3 SAEs.

15% of patients had treatment related SAEs as determined by the investigator and 28% had a SAE grade 3 or higher. The most common SAE preferred terms (3 patients or 2% each) were abdominal pain, disease progression (recurrent sALCL), pulmonary embolism, and septic shock. Important treatment-related SAEs were demyelinating polyneuropathy, peripheral motor neuropathy, pneumonia, pyrexia and urinary tract infection.

Thirty-one patients or 19% died. Seven deaths (4% of the phase 2 population) could not be attributed to the disease. Six deaths or 4% occurred within 30 days after start of treatment. None of these were attributed to the drug.

AEs led to treatment discontinuation in 19% of patients and to dose modifications (delays, reductions, or adjustments) in 46% of patients. The most important of these AEs were peripheral sensory neuropathy, peripheral motor neuropathy and disease progression.

The most common treatment emergent AE was peripheral sensory neuropathy. Peripheral neuropathy was assessed by the investigator, using the peripheral neuropathy (PN) standardised MedDRA Query. Any PN treatment-emergent AE was reported in 84 patients (53% of the phase 2 population); these were grade 3 or higher in 18 patients, or 11% of the phase 2 population. Higher grade events occurred later in the course of therapy than did lower grade events, presumably reflecting the influence of increasing cumulative doses. Resolution of treatment emergent peripheral neuropathy before end of treatment occurred in 16 patients, or 19% of patients with peripheral neuropathy. At last follow-up after end of treatment this number had increased to 26 patients. Median duration of follow-up after end of treatment was ten weeks. In 30 out of 84 patients, peripheral neuropathy had resolved fully on the last follow-up visit and 22 had improved. 32 patients of these 84 patients experiencing peripheral neuropathy did not improve. Irreversible sensory neuropathy may be a disabling condition and it was cited as a major reason for discontinuing due to AEs, indicating the impact of this AE. Occurrence of this side effect might lead to dose reductions. Treatment emergent motor neuropathy was reported in 20 of 160 patients in the phase 2 trials (12.5%). Seven of these had grade 3. AEs potentially associated with autonomic neuropathy were reviewed in the phase 2 population. The most common AEs in the phase 2 populations that were potentially associated with autonomic neuropathy were constipation, abdominal pain, dizziness.

Grade 3 and 4 neutropenia occurred in 13% and 7% of patients, respectively. Most cases were manageable with dose delays and sometimes with treatment with growth factors.

Infusion related reactions occurred in 11% of patients and were managed by dose interruptions.

Infections were observed in 58% of patients in the phase 2 studies. The majority of infections was grade 1 or 2, and occurred with an incidence comparable to that reported in similar populations. The most frequent infection was grade 1 or 2 upper respiratory tract infection (URTI); the incidence of pneumonia was lower than that reported in the literature for comparable populations. Grade 3 or 4 infections occurred in < 10% of patients, and no Grade 5 infections were reported during phase 2 studies.

Progressive multifocal leukoencephalopathy (PML) constitutes a very serious adverse event that may be related to the use of brentuximab-vedotin. To date, two confirmed cases and one suspect case have been documented of which one patient with Hodgkin lymphoma has died.

No new safety concerns were identified from the data as supplied by the applicant in the detailed case reports of relapsed or refractory HL patients not eligible for ASCT or multidrug therapy. Overall, the safety profile seemed comparable between the pivotal study population and the relapsed/refractory HL population ineligible for ASCT or multidrug chemotherapy despite some shortcomings in the reporting of the data discussed in the clinical safety section.

Uncertainty in the knowledge about the unfavourable effects

Across six clinical studies that were submitted to support this application, a total of 357 patients have received at least one dose of brentuximab-vedotin. Based on the epidemiology of the conditions for which brentuximab-vedotin is intended, a limited safety base of this size is acceptable, but exposure is somewhat limited. Moreover, the attributability of AEs to study drugs is severely limited by the single arm study design. Whether or not AEs were to be attributed to the drug was determined by the investigator in the trials and by the applicant in the integrated presentation of ADRs in section 4.8 of the SmPC. Scoring AEs can be biased in single arm studies, even despite the use of standardised scoring systems like the one used in the assessment of peripheral neuropathy. The number of patients who received brentuximab-vedotin at the proposed dose and schedule was limited, i.e. 17% in both the HL and sALCL study populations.

The precise mechanism of testicular toxicity in rats is not known and there is uncertainty on the presence of CD30 in human spermatogonia/early spermatocytes. It remains therefore uncertain whether the testicular toxicity would occur in humans as well. This has not been studied. Men treated with brentuximab-vedotin should not father a child during treatment and until 6 months after treatment.

The incidence of neutropenia grade 3 or higher was increased in presence of rifampicin which may be explained by increased formation of active metabolites. This uncertainty will be addressed by a phase 1 study to quantify MMAE and metabolites in human plasma and urine with and without rifampicin, which is included in the RMP.

Pharmacokinetics of MMAE was greatly influenced by serum albumin levels. MMAE concentrations increased substantially at low albumin levels, possibly due to reduced MMAE clearance. Pharmacokinetic data from patients with renal and hepatic impairment in the SGN-35-008b study will address this uncertainty which is included in the RMP.

As already indicated, the incidence of PML in patients treated (3/2000) with brentuximab-vedotin to date is considered 'uncommon' (MeDRA). However, there is a rather large uncertainty as regards the true incidence of PML. PML has been included as an important identified risk in the RMP.

Immunogenicity of SGN-35 could not be evaluated fully as the ECL screening assay for the detection of ATA against brentuximab vedotin in serum of treated patients is insufficient in terms of sensitivity, drug tolerance and interference by sCD30 and rheumatoid factor. Under reporting of antibodies is possible. The screening assay for the detection of ATA against brentuximab vedotin in serum should be further optimised. Formation of anti-therapeutic antibodies (ATA) is included in the RMP and development of the ECL ATA assay is an additional pharmacovigilane activity addressing this concern.

Benefit-risk balance

Importance of favourable and unfavourable effects

The patient population with relapsed or refractory HL after at least two prior therapies and *not treated with ASCT* has been studied in 18 patients in two early Phase I studies, in 7 patients from a Phase I QTc study, in 5 Japanese patients and in 26 patients from the Named Patient Programmes, in total 56 patients. The information in the provided detailed case reports was obtained from a very heterogeneous set of patients and is in several aspects immature and limited, but still contained useful data. Within this context, the CHMP concluded that brentuximab vedotin showed anti-tumour activity in the relapsed, refractory HL patients not eligible for stem cell transplantation or multi-agent chemotherapy. Moreover, the safety profile was shown to be acceptable and comparable with that observed in the pivotal HL study population. Despite the limitations of the provided data, the preliminary conclusion that brentuximab vedotin offers an around 1 in 5 chance for stem cell transplantation and as such an opportunity for prolonged PFS and potentially cure of the disease, should be considered to be a main finding. In addition, an ORR of 55% and a CR of 23% for the proposed dose and schedule for patients in this population not becoming eligible for ASCT upon brentuximab vedotin can be considered clinically relevant in itself.

In relapsed or refractory HL patients already *treated with ASCT* treatment with brentuximab-vedotin led to 75% ORR with 33% CR. In patients with relapsed or refractory sALCL treatment with brentuximab-vedotin led to 86% ORR with 59% CR. The studied patients included both patients who had undergone ASCT (12/58) and those who had not. Obtaining CR is an important advantageous 'interim' outcome for further curative treatment options, i.e. stem cell transplantation. Possibly PR has the same role although there is a higher degree of uncertainty. Also, clinical benefit in terms of resolution of B-symptoms was obtained.

Based on the updated PFS data, the median PFS observed was 5.6 months in HL patients, and 14.3 months in sALCL patients. The results in HL patients after ASCT were at least as good as observed with conventional chemotherapy and sometimes even better (see Devizzi *et al*, 1994; Little *et al*, 1998; Crump, 2008; Blum *et al*, 2010). However, historical comparisons always entail a high risk for introducing bias and a randomised, controlled study would have been preferred at this stage. In patients with sALCL the PFS of 13.2 months is impressive and comparison with historical controls is hampered by the lack of available data. More information was obtained from the intra-individual analysis of the PFS results as obtained with brentuximab-vedotin after the previous line of treatment although here, ideally, comparison should have been made with best previous treatment. The data available did suggest a clinical benefit for the majority of the patients, i.e. 59% and 60% for the HL and sALCL population, respectively.

The median overall survival (OS) by Kaplan-Meier analysis has not been reached in both patient groups. In the HL population, 62/108 patients were alive at the time of the last analysis and in the sALCL population, the estimated overall survival rate at 12 months was 71% (37/58 patients alive at 12 months). Within the context of the high mortality risk, these results can be considered as potentially favourable, but inconclusive and further follow-up is needed.

Frequently reported AEs were neurotoxicity, myelosuppression and infections. The high rates of grade 3 AEs and SAEs indicate that brentuximab-vedotin should be considered toxic. AEs were a reason for discontinuation in almost a fifth of the phase 2 population. Mortality was high at 19%, but mostly disease related. Myelosuppression, in particular neutropenia, was reversible and comparable with that seen with chemotherapy. The most common treatment emergent AE was peripheral sensory neuropathy that may be irreversible in 20% of the patients. Treatment emergent motor neuropathy was also reported in 12.5% of the patients. The risk of developing PML post-treatment is considered balanced by the natural course of HL and sALCL when found refractory or relapsed after multiple treatment regimens.

In view of the grave prognosis of the diseases presently proposed to be indicated for brentuximab-vedotin, the observed adverse events, with the incidence observed at this time, are considered an acceptable risk, but follow-up data are needed to assess this further, in particular the risk for neurotoxicity and PML.

Benefit-risk balance

The anti-tumour activity of brentuximab-vedotin has been established in the HL and sALCL study populations as well as in the relapsed or refractory HL patients ineligible for ASCT/multidrug chemotherapy. The different clinical endpoints demonstrated clinical benefit in terms of disease control, resolution of B-symptoms and in terms of enabling further potentially curative treatment options. Moreover, the safety profile as reported is considered to entail acceptable risks. However, the lack of a control arm in the pivotal studies results in the need for confirmation of the benefit/risk profile of brentuximab-vedotin.

Overall, the provided evidence in its entirety was considered convincing and the benefits in the relapsed/refractory HL and sALCL patients and in the population with relapsed/refractory HL after at least two prior therapies and not eligible for autologous stem cell transplantation or multi-drug therapy can be considered established and considered to outweigh the risks associated with its use.

The inclusion criteria of both pivotal trials specified that only patients with proven CD30-positive malignancies were allowed. While sALCL is always CD30-positive, a subset of Hodgkin's lymphomas is CD30 negative. It is therefore appropriate that the indication in the treatment of patients with relapsed or refractory Hodgkin's lymphoma (HL) only includes patients with CD30-positive HL.

Discussion on the benefit-risk balance

Relapsed sALCL patients that have chemosensitive disease may become eligible for stem cell transplantation with contemporary chemotherapy which may be an alternative treatment option. This is different for the refractory sALCL patients, where the use of brentuximab-vedotin, due to its novel working mechanism, may render these patients eligible for stem cell transplantation and as such may offer a chance for cure or prolonged survival of the disease. This raises the question whether the sALCL patients should be restricted to refractory sALCL patients only, but it may not always be possible to make a distinction between relapsed and refractory patients, both before and after stem cell transplantation. Therefore, it is proposed not to make this distinction.

Lack of controlled data warrants further clinical studies to provide comprehensive data on the benefit-risk balance. The Applicant has proposed the following programme of clinical studies to meet this requirement.

- The ongoing AETHERA study, which examines in a randomized and blinded setting the single-agent potential for brentuximab-vedotin to treat patients at high risk for residual HL following transplant. This study compares the same brentuximab-vedotin dose and regimen as explored in SG035-0003 against placebo and will build a comparative safety database (n=322). Definitive report will be filled in June 2014.
- A Post-Authorisation Safety Study (PASS) in both studied HL and sALCL patient populations (n=500). Duration will be 3 years. Applicant should commit to include a sufficient number of sALCL patients (i.e. at least n=50).
- Further OS follow up of the patients included in study SG035-0003 and in study SG035-004: For SG035-003, a report will be filled annually to report on OS until 2015 or until enough survival events accrue that no need for follow-up remains, whichever occurs earlier. Likewise for SG035 004, a report will be filled annually to report on OS until 2016 or until enough survival events accrue that no need for follow-up remains, whichever occurs earlier.
- A randomised, controlled trial will examine patients with newly diagnosed mature T-cell lymphoma (MTCL), including 75% (± 5%) of patients with sALCL. (n=±300). This trial will provide safety data in the sALCL population. Study will complete and report in the 2018-2019 timeframe.

However, the CHMP considered that the AETHERA study and the study in MTCL target different patient population than the currently intended ones.

The CHMP considered that Adcetris falls under the scope of Article 2 of Commission Regulation (EC) No. 507/2006 as eligible for a Conditional Marketing Authorisation as it belongs to:

a) Medicinal products designated as orphan medicinal products in accordance with Article 3 of Regulation (EC) No 141/2000;

b) Medicinal products which aim at the treatment, the prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases.

Furthermore, the requirements listed in Article 4 of the Regulation apply to brentuximab vedotin on the basis of the following reasons:

a) The risk-benefit balance of the product is positive:

In the patients with relapsed or refractory CD30+ Hodgkin lymphoma following autologous stem cell transplant or patients with relapsed or refractory systemic anaplastic large cell lymphoma brentuximab vedotin showed efficacy in terms of a significant increase in ORR and PFS, despite the absence of confirmatory controlled data. The intra-individual comparisons of investigator-based PFS after brentuximab vedotin with investigator-based PFS after the most recent prior therapy are considered a relevant treatment effect in the majority of the post-ASCT HL and sALCL patient populations studied. Regarding the relapsed-refractory HL patients for whom autologous stem cell transplantation or multi-drug chemotherapy is not an option, anti-tumour activity is considered to be established on the basis of the response rates. Importantly, for all these indications the chance to obtain CR and an(other) option for a potentially curative stem cell transplantation is of major importance. Taking into account that brentuximab vedotin is proposed in particular as a late line treatment, the suggested effects are considered of clinical relevance. Together with an acceptable safety-profile in patients in any of the three proposed indications and considering the overall grave prognosis of the patients involved, the benefit-risk balance is considered positive.

b) It is likely that the applicant will be able to provide comprehensive clinical data:

The applicant will provide further comprehensive clinical data to confirm efficacy and safety of brentuximab vedotin in the proposed indications. More specifically:

- Updated Overall Survival data from the pivotal studies SG035-0003, SG035-004 will be provided, including a sub-analysis in patients ≥ 100 kg. The data should be presented annually in the context of historical controls until 2015 and 2016, respectively, or until enough OS events have occurred, whichever occurs earlier

- a Post-Authorisation Safety Study (PASS) in both studied relapsed/refractory HL and sALCL patient populations (n=500) including a sufficient number of sALCL patients (i.e. at least n=50) will provide comprehensive safety data to inform the benefit/risk

- in HL patients with relapsed/refractory disease ineligible for ASCT a single-arm study investigating response rate, duration of response, rate of (second) ASCT and data in subpopulations (including but not necessarily restricted to ALK status and age) will be provided by Q2 2016 as as a randomised clinical trial is not feasible in this patient population

- for the relapsed/refractory sALCL population, an additional single-arm study looking at response rate, duration of response, rate of second ASCT and data in subpopulations (including, but not necessarily restricted, to ALK status and age) will be provided by Q1 2016, as a randomised clinical trial is not feasible in this patient population

c) Fulfilment of unmet medical need in the proposed indications:

Currently there are no approved treatment options for the patients that fit the proposed indications. Brentuximab vedotin provides a chance to reach CR and an(other) option for a potentially curative stem cell transplantation, which is considered of clinical relevance. Therefore, unmet medical needs will be fulfilled.

d) The benefits to patients of the immediate availability outweigh the risks inherent in the fact that additional data are still required:

In the favourable benefit-risk profile, the chance to obtain CR and an(other) option for potentially curative stem cell transplantation is a main finding for the proposed HL and sALCL patient populations that are currently without a good treatment option besides palliative care. In combination with an overall grave prognosis of these patients, the immediate availability of Adcetris on the market outweighs the risk inherent in the fact that additional data are still required.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Adcetris in the treatment of treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL) following autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT or multi-agent chemotherpay are not a treatment option and in the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL) is favourable and therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

Risk Management System

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 1.0 of the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
Further Overall Survival follow up of the patients included in study SG035-0003 and in study SG035-004 should be provided, including sub-analysis of patients ≥ 100 kg. The data should be presented in the context of historical controls.	SG035-003 annual reports until 2015 or when the overall survival data is sufficiently mature (at least 50% OS events observed), whichever occurs earlier. SG035-004 annual reports until 2016 or when the overall survival data is sufficiently mature (at least 50% OS events observed), whichever occurs earlier
A Post-Authorisation Safety Study (PASS) in both studied HL and sALCL patient populations (n=500) should be performed including a sufficient number of sALCL patients (i.e. at least n=50, Study MA25101).	Report on interim analysis: 30/04/2016 Final study report: 31/12/2018

To perform a single-arm study in a similar patient population as the sALCL population investigating response rate, duration of response, rate of (second) ASCT and data in subpopulations (including but not necessarily restricted to ALK status and age) based on a CHMP agreed protocol (Study C25006).	Protocol submission by: Q4 2012 Final study Report by: Q1 2016
To perform a single-arm studying r/r HL population not eligible for ASCT investigating response rate, PFS, OS, proportion of patients proceeding to transplant and safety (n=approx 60 pts) based on a CHMP agreed protocol.	Protocol submission by: Q1 2013 Final study report by: Q2 2016

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality, non-clinical and clinical properties of the active substance, the CHMP considers that brentuximab vedotin is to be qualified as a new active substance (see appendix 1).

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