Clinical trial results:
A Phase 1/2 Study of Brentuximab Vedotin (SGN-35) in Pediatric Patients With Relapsed or Refractory Systemic Anaplastic Large-Cell Lymphoma or Hodgkin Lymphoma.

Summary

EudraCT number	2011-001240-29
Trial protocol	DE GB NL IT ES
Global end of trial date	12 April 2018

Results information

Result version number	v1 (current)
This version publication date	27 October 2018
First version publication date	27 October 2018

Trial information

Trial identification

Sponsor protocol code	C25002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01492088
WHO universal trial number (UTN)	U1111-1158-2613
Other trial identifiers	RNEC: 133300410A0384, CCMO: NL38209.078.11

Notes:

Sponsors

Sponsor organisation name	Takeda Oncology
Sponsor organisation address	40 Landsdowne Street, Cambridge, MA, United States, 02139
Public contact	Medical Director, Clinical Science, Takeda, +1 877-825-3327, clinicaltrialregistry@tpna.com
Scientific contact	Medical Director, Clinical Science, Takeda, +1 877-825-3327, clinicaltrialregistry@tpna.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000980-PIP01-10
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 April 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial is to assess the safety and pharmacokinetics, and determine the pediatric maximum tolerated dose and/or or recommended phase 2 dose of brentuximab vedotin.

Protection of trial subjects:

All study participants or their guardians were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 April 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Regulatory reason
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 4
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Mexico: 1
Worldwide total number of subjects	36
EEA total number of subjects	31

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	0

months)	
Children (2-11 years)	12
Adolescents (12-17 years)	24
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 12 investigative sites in United States, France, Germany, Netherlands, United Kingdom, Italy, Spain and Mexico from 16-April-2012 to 12-April-2018.

Pre-assignment

Screening details:

Participants with diagnosis of relapsed or refractory (r/r) sALCL/HL were enrolled to receive brentuximab vedotin 1.4-1.8 mg/kg, intravenous infusion on Day 1 of every 21-day cycle for up to 16 cycles. Treatment beyond 16 cycles was permitted at joint discretion of sponsor and investigator for participants experiencing continued clinical benefit.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Brentuximab vedotin 1.4 mg/kg: Phase 1

Arm description:

Brentuximab vedotin 1.4 mg/kg, 30-minute IV infusion, Day 1 of every 21-day cycle, until there was evidence of disease progression or unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	Brentuximab vedotin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion, Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Brentuximab vedotin Intravenous Infusion

Arm title	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r HL only

Arm description:

Participants with r/r HL received brentuximab vedotin 1.8 mg/kg, 30-minute IV infusion, Day 1 of every 21-day cycle until there was evidence of disease progression or unacceptable toxicity (Up to 16 cycles). Treatment with brentuximab vedotin beyond 16 cycles was permitted at the joint discretion of the sponsor and the investigator for those participants experiencing continued clinical benefit.

Arm type	Experimental
Investigational medicinal product name	Brentuximab vedotin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion, Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Brentuximab vedotin Intravenous Infusion

Arm title	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r sALCL only

Arm description:

Participants with r/r systemic anaplastic large-cell lymphoma (sALCL) received brentuximab vedotin 1.8 mg/kg, 30-minute IV infusion, Day 1 of every 21-day cycle until there was evidence of disease progression or unacceptable toxicity (Up to 16 cycles). Treatment with brentuximab vedotin beyond 16

cycles was permitted at the joint discretion of the sponsor and the investigator for those participants experiencing continued clinical benefit.

Arm type	Experimental
Investigational medicinal product name	Brentuximab vedotin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion, Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Brentuximab vedotin Intravenous Infusion

Number of subjects in period 1	Brentuximab vedotin 1.4 mg/kg: Phase 1	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r HL only	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r sALCL only
Started	3	16	17
Completed	0	2	3
Not completed	3	14	14
Completed Post Treatment Followup (PTFU)	2	-	1
Death	1	6	2
Alive at Last Follow-up	-	6	11
Withdrawal by Patient	-	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Brentuximab vedotin 1.4 mg/kg: Phase 1
Reporting group description:	
Brentuximab vedotin 1.4 mg/kg, 30-minute IV infusion, Day 1 of every 21-day cycle, until there was evidence of disease progression or unacceptable toxicity.	
Reporting group title	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r HL only
Reporting group description:	
Participants with r/r HL received brentuximab vedotin 1.8 mg/kg, 30-minute IV infusion, Day 1 of every 21-day cycle until there was evidence of disease progression or unacceptable toxicity (Up to 16 cycles). Treatment with brentuximab vedotin beyond 16 cycles was permitted at the joint discretion of the sponsor and the investigator for those participants experiencing continued clinical benefit.	
Reporting group title	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r sALCL only
Reporting group description:	
Participants with r/r systemic anaplastic large-cell lymphoma (sALCL) received brentuximab vedotin 1.8 mg/kg, 30-minute IV infusion, Day 1 of every 21-day cycle until there was evidence of disease progression or unacceptable toxicity (Up to 16 cycles). Treatment with brentuximab vedotin beyond 16 cycles was permitted at the joint discretion of the sponsor and the investigator for those participants experiencing continued clinical benefit.	

Reporting group values	Brentuximab vedotin 1.4 mg/kg: Phase 1	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r HL only	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r sALCL only
Number of subjects	3	16	17
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	2	10
Adults (18-64 years)	3	14	7
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	14.7	14.5	11.5
standard deviation	± 1.15	± 2.68	± 3.18
Sex: Female, Male Units: Subjects			
Female	1	7	3
Male	2	9	14
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	4
Not Hispanic or Latino	3	14	12
Unknown or Not Reported	0	2	1
Race/Ethnicity, Customized Units: Subjects			

White	2	13	16
Asian	1	0	0
Other	0	2	1
Not Reported	0	1	0
Region of Enrollment Units: Subjects			
United States	2	1	1
France	0	2	0
Germany	0	4	1
Netherlands	0	1	2
United Kingdom	0	1	2
Italy	1	7	6
Spain	0	0	4
Mexico	0	0	1
Height Units: cm			
arithmetic mean	167.17	165.31	149.54
standard deviation	± 10.865	± 14.350	± 17.783
Weight Units: kg			
arithmetic mean	53.10	57.85	42.16
standard deviation	± 9.924	± 17.539	± 15.162
Body Surface Area Units: m^2			
arithmetic mean	1.562	1.617	1.313
standard deviation	± 0.0967	± 0.2938	± 0.3103

Reporting group values	Total		
Number of subjects	36		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	12		
Adults (18-64 years)	24		
From 65-84 years	0		
85 years and over	0		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Subjects			
Female	11		
Male	25		

Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	4		
Not Hispanic or Latino	29		
Unknown or Not Reported	3		
Race/Ethnicity, Customized Units: Subjects			
White	31		
Asian	1		
Other	3		
Not Reported	1		
Region of Enrollment Units: Subjects			
United States	4		
France	2		
Germany	5		
Netherlands	3		
United Kingdom	3		
Italy	14		
Spain	4		
Mexico	1		
Height Units: cm arithmetic mean standard deviation	- -		
Weight Units: kg arithmetic mean standard deviation	- -		
Body Surface Area Units: m^2 arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	Brentuximab vedotin 1.4 mg/kg: Phase 1

Reporting group description:

Brentuximab vedotin 1.4 mg/kg, 30-minute IV infusion, Day 1 of every 21-day cycle, until there was evidence of disease progression or unacceptable toxicity.

Reporting group title	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r HL only

Reporting group description:

Participants with r/r HL received brentuximab vedotin 1.8 mg/kg, 30-minute IV infusion, Day 1 of every 21-day cycle until there was evidence of disease progression or unacceptable toxicity (Up to 16 cycles). Treatment with brentuximab vedotin beyond 16 cycles was permitted at the joint discretion of the sponsor and the investigator for those participants experiencing continued clinical benefit.

Reporting group title	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r sALCL only

Reporting group description:

Participants with r/r systemic anaplastic large-cell lymphoma (sALCL) received brentuximab vedotin 1.8 mg/kg, 30-minute IV infusion, Day 1 of every 21-day cycle until there was evidence of disease progression or unacceptable toxicity (Up to 16 cycles). Treatment with brentuximab vedotin beyond 16 cycles was permitted at the joint discretion of the sponsor and the investigator for those participants experiencing continued clinical benefit.

Subject analysis set title	Brentuximab vedotin 1.8 mg/kg: Phase 1
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Brentuximab vedotin 1.8 mg/kg, 30-minute IV infusion, Day 1 of every 21-day cycle until there was evidence of disease progression or unacceptable toxicity (Up to 16 cycles). Treatment with brentuximab vedotin beyond 16 cycles was permitted at the joint discretion of the sponsor and the investigator for those participants experiencing continued clinical benefit.

Subject analysis set title	Brentuximab vedotin 1.8 mg/kg: Phase 1
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Brentuximab vedotin 1.8 mg/kg, 30-minute IV infusion, Day 1 of every 21-day cycle starting from Cycle 2 until there was evidence of disease progression or unacceptable toxicity (Up to 16 cycles). Treatment with brentuximab vedotin beyond 16 cycles was permitted at the joint discretion of the sponsor and the investigator for those participants experiencing continued clinical benefit.

Subject analysis set title	Brentuximab vedotin 1.8 mg/kg: Phase 1
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Brentuximab vedotin 1.8 mg/kg, 30-minute IV infusion, Day 1 of every 21-day cycle starting from Cycle 2 until there was evidence of disease progression or unacceptable toxicity (Up to 16 cycles). Treatment with brentuximab vedotin beyond 16 cycles was permitted at the joint discretion of the sponsor and the investigator for those participants experiencing continued clinical benefit.

Subject analysis set title	Brentuximab vedotin 1.8 mg/kg: Phase 1
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Brentuximab vedotin 1.8 mg/kg, 30-minute IV infusion, Day 1 of every 21-day cycle until there was evidence of disease progression or unacceptable toxicity (Up to 16 cycles). Treatment with brentuximab vedotin beyond 16 cycles was permitted at the joint discretion of the sponsor and the investigator for those participants experiencing continued clinical benefit.

Primary: Number of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs) (Phase 1)

End point title	Number of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs) (Phase 1)[1][2]

End point description:

An AE is defined as any untoward medical occurrence in a clinical investigation participant administered a drug; it does not necessarily have to have a causal relationship with treatment. A SAE is any experience that suggests a significant hazard, contraindication, side effect or precaution that results in

death, is life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or is medically significant. A treatment-emergent adverse event (TEAE) is defined as an adverse event with an onset that occurs after receiving study drug. AE severity was graded according to NCI CTCAE version 4.03. Safety population is defined as all participants who received at least 1 dose of study drug. Participants enrolled in Phase 1 of study were evaluated for this endpoint.

End point type	Primary

End point timeframe:

From the first dose through 30 days after the last dose of study medication (Up to 15 months)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics were planned for this endpoint.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be assessed in Phase 1 arm groups.

End point values	Brentuximab vedotin 1.4 mg/kg: Phase 1	Brentuximab vedotin 1.8 mg/kg: Phase 1		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3	9		
Units: participants				
TEAE	3	9		
SAE	0	4		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Abnormal Clinical Laboratory Values Reported as AEs (Phase 1)

End point title	Number of Participants with Abnormal Clinical Laboratory Values Reported as AEs (Phase 1)[3][4]

End point description:

Abnormal clinical laboratory values (serum chemistry and hematology) were reported as AEs if they were considered by the investigator to be a clinically significant change from Baseline or led to premature discontinuation of study treatment, dose modification, or other therapeutic intervention. Safety population is defined as all participants who received at least 1 dose of study drug. Participants enrolled in Phase 1 of study were evaluated for this endpoint.

End point type	Primary

End point timeframe:

From the first dose through 30 days after the last dose of study medication (Up to 15 months)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics were planned for this endpoint.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be assessed in Phase 1 arm groups.

End point values	Brentuximab vedotin 1.4 mg/kg: Phase 1	Brentuximab vedotin 1.8 mg/kg: Phase 1		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3	9		
Units: participants				
Gamma-glutamyltransferase increased	0	1		
Transaminases increased	0	1		
Lymphocyte count decreased	1	1		
Neutrophil count decreased	0	1		
Blood bicarbonate decreased	0	1		
Weight decreased	0	1		
Hypocalaemia	0	2		
Hyperuricaemia	0	1		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Clinically Significant Vital Signs Values Reported as AEs (Phase 1)

End point title	Number of Participants with Clinically Significant Vital Signs Values Reported as AEs (Phase 1)[5][6]

End point description:

Vital signs measurements included supine (after 3-5 minutes in this position) and standing (after 3-5 minutes in this position) measurements of diastolic and systolic blood pressure, heart rate, and oral temperature. Safety population is defined as all participants who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

From the first dose through 30 days after the last dose of study medication (Up to 15 months)

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics were planned for this endpoint.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be assessed in Phase 1 arm groups.

End point values	Brentuximab vedotin 1.4 mg/kg: Phase 1	Brentuximab vedotin 1.8 mg/kg: Phase 1		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3	9		
Units: participants	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Antibody-drug Conjugate (ADC) Serum Concentrations (Phase 1)

End point title	Antibody-drug Conjugate (ADC) Serum Concentrations (Phase 1)[7][8]

End point description:

Blood samples were collected and tested for serum concentrations of brentuximab vedotin antibody-drug conjugate. Data for this endpoint was not summarized for Phase 1 participants only, data was summarized together for Phase 1 and 2 participants in brentuximab 1.4 mg/kg and 1.8 mg/kg arms groups.

End point type	Primary

End point timeframe:

Cycle 1 and 8 pre-dose and 5 minutes, 24, 48, 96 and 312 hours post-dose; Cycle 2 pre-dose, 5 minutes and 24, 48 and 96 hours post-dose; Cycle 3 to 16 pre-dose and 5 minutes post-dose

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics were planned for this endpoint.

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be assessed in Phase 1 arm groups.

End point values	Brentuximab vedotin 1.4 mg/kg: Phase 1			
Subject group type	Reporting group			
Number of subjects analysed	0[9]			
Units: ng/mL				
arithmetic mean (standard deviation)	()			

Notes:

[9] - Data has been presented in endpoint 19.

Statistical analyses

No statistical analyses for this end point

Primary: Serum Concentration of Total Antibodies (Conjugated and Unconjugated) (Phase 1)

End point title	Serum Concentration of Total Antibodies (Conjugated and Unconjugated) (Phase 1)[10][11]

End point description:

Blood samples were collected and tested for conjugated and unconjugated antibodies. Data for thisendpoint was not summarized for Phase 1 participants only, data was summarized together for Phase 1 and 2 participants in brentuximab 1.4 mg/kg and 1.8 mg/kg arms groups.

End point type	Primary

End point timeframe:

Cycle 1 and 8 pre-dose and 5 minutes, 24, 48, 96 and 312 hours post-dose; Cycle 2 pre-dose, 5 minutes and 24, 48 and 96 hours post-dose; Cycle 3 to 16 pre-dose and 5 minutes post-dose

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics were planned for this endpoint.

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be assessed in Phase 1 arm groups.

End point values	Brentuximab vedotin 1.4 mg/kg: Phase 1			
Subject group type	Reporting group			
Number of subjects analysed	0[12]			
Units: ug/mL				
arithmetic mean (standard deviation)	()			

Notes:

[12] - Data has been presented in endpoint 20.

Statistical analyses

No statistical analyses for this end point

Primary: Monomethyl Auristatin E (MMAE) Plasma Concentrations (Phase 1)

End point title	Monomethyl Auristatin E (MMAE) Plasma Concentrations (Phase 1)[13][14]

End point description:

Blood samples were collected and tested for MMAE plasma concentrations. Data for this endpoint was not summarized for Phase 1 participants only, data was summarized together for Phase 1 and 2 participants in brentuximab 1.4 mg/kg and 1.8 mg/kg arms groups.

End point type	Primary

End point timeframe:

Cycle 1 and 8 pre-dose and 5 minutes, 24, 48, 96 and 312 hours post-dose; Cycle 2 pre-dose, 5 minutes and 24, 48 and 96 hours post-dose; Cycle 3 to 16 pre-dose and 5 minutes post-dose

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics were planned for this endpoint.

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be assessed in Phase 1 arm groups.

End point values	Brentuximab vedotin 1.4 mg/kg: Phase 1			
Subject group type	Reporting group			
Number of subjects analysed	0[15]			
Units: ng/mL				
arithmetic mean (standard deviation)	()			

Notes:

[15] - Data has been presented in endpoint 21.

Statistical analyses

No statistical analyses for this end point

Primary: Overall Response Rate (ORR) (Phase 1 and 2)

End point title	Overall Response Rate (ORR) (Phase 1 and 2)[16]

End point description:

Overall response rate is defined as the percentage of participants with complete remission (CR) or partial remission (PR) as assessed by an independent review facility (IRF) using International Working

Group (IWG) Revised Response Criteria for Malignant Lymphoma. CR is defined as the disappearance of all evidence of disease and PR is defined as regression of measurable disease and no new sites. Response-evaluable population included participants who received at least 1 dose of study drug, have measurable disease at baseline, and 1 postbaseline disease assessment. Data was summarized together for Phase 1 and 2 participants in brentuximab 1.8 mg/kg arm group.

End point type	Primary

End point timeframe:

Cycles 2, 4, 7, 10, 13 and 16 (21-day cycles) until disease progression, death or end of treatment (EOT) (Up to 15 months)

Notes:

[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics were planned for this endpoint.

End point values	Brentuximab vedotin 1.4 mg/kg: Phase 1	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r HL only	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r sALCL only	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	15	17	
Units: percentage of participants				
number (confidence interval 95%)	0 (0 to 71)	47 (21 to 73)	53 (28 to 77)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Antitherapeutic Antibodies (ATA) and Neutralizing ATA (nATA) (Phase 1 and 2)

End point title	Number of Participants with Antitherapeutic Antibodies (ATA) and Neutralizing ATA (nATA) (Phase 1 and 2)

End point description:

Blood samples were collected to assess the immunogenicity of brentuximab vedotin (ATA and nATA development) using a laboratory test. ATA-positive samples were further characterized as transiently ATA positive (defined as 1 or 2 post-Baseline ATA-positive responses), persistently ATA positive (defined as more than 2 post-Baseline ATA positive responses), and nATA positive or negative. Participants from the Safety Population, all enrolled participants who received at least one dose of brentuximab vedotin, with data available for analysis.

End point type	Secondary

End point timeframe:

Baseline up to EOT (Up to 15 months)

End point values	Brentuximab vedotin 1.4 mg/kg: Phase 1	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r HL only	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r sALCL only	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	16	17	
Units: participants				
ATA status: Transiently positive	1	4	7	

ATA status: Persistently positive	0	2	0	
nATA status: Positive	0	5	4	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR) (Phase 1)

End point title	Overall Response Rate (ORR) (Phase 1)[17]

End point description:

Overall response rate is defined as the percentage of participants with CR or PR as assessed by an IRF using IWG Revised Response Criteria for Malignant Lymphoma. CR is defined as the disappearance of all evidence of disease and PR is defined as regression of measurable disease and no new sites. Response-evaluable population included participants who received at least 1 dose of study drug, have measurable disease at baseline, and 1 postbaseline disease assessment. Participants enrolled in Phase 1 of the study were evaluated for this endpoint.

End point type	Secondary

End point timeframe:

Cycles 2, 4, 7, 10, 13 and 16 (21-day cycles) until disease progression, death or EOT (Up to 15 months)

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be assessed in Phase 1 arm groups.

End point values	Brentuximab vedotin 1.4 mg/kg: Phase 1	Brentuximab vedotin 1.8 mg/kg: Phase 1		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3	8		
Units: percentage of participants				
number (confidence interval 95%)	0 (0 to 71)	63 (24 to 91)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP) (Phase 1 and 2)

End point title	Time to Progression (TTP) (Phase 1 and 2)

End point description:

TTP is defined as the time in months from first dose until the first subsequent documentation of objective tumor progression. Progressive disease (PD) is defined as any new lesion or increase by ≥50% of previously involved sites from nadir. Safety population is defined as all participants who received at least 1 dose of study drug. TTP was censored on last radiological assessment of measured lesions documenting absence of PD for participants who did not have tumor progression. Safety population is defined as all participants who received at least 1 dose of study drug. TTP was censored on last radiological assessment of measured lesions documenting absence of PD for participants who did not have tumor progression. Here, 9999 indicates upper limit of confidence interval was not reached due to low number of participants with events.

End point type	Secondary

End point timeframe:

Cycles 2, 4, 7, 10, 13 and 16 (21-day cycles) until disease progression, death or EOT and then every 12 weeks for 12 months after EOT, until disease progression, or death (Up to 27 months)

End point values	Brentuximab vedotin 1.4 mg/kg: Phase 1	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r HL only	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r sALCL only	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	16	17	
Units: months				
median (confidence interval 95%)	2.7 (1.4 to 2.8)	4.8 (1.2 to 9999)	6.2 (2.8 to 9999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (Phase 1 and 2)

End point title	Time to Response (Phase 1 and 2)

End point description:

Time to response is defined as the time in months from the first dose of study treatment until the date of the first assessment of confirmed CR or PR. as assessed by an IRF using IWG revised response criteria for malignant lymphoma. CR is defined as the disappearance of all evidence of disease and PR is defined as regression of measurable disease and no new sites. Response-evaluable population included participants who received at least 1 dose of study drug, have measurable disease at baseline, and 1 postbaseline disease assessment. Time to response was censored on the last radiological assessment of measured lesions documenting absence of CR or PR for participants who did not have CR or PR. Here, 9999 indicates upper limit of confidence interval was not reached due to low number of participants with events. 99999 indicates median was not reached as no participant had response.

End point type	Secondary

End point timeframe:

Cycles 2, 4, 7, 10, 13 and 16 (21-day cycles) until disease progression, death or EOT (Up to 15 months)

End point values	Brentuximab vedotin 1.4 mg/kg: Phase 1	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r HL only	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r sALCL only	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	15	17	
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	2.7 (1.3 to 9999)	1.5 (1.2 to 9999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) (Phase 1 and 2)

End point title	Duration of Response (DOR) (Phase 1 and 2)

End point description:

DOR is defined as the time in months from the date of first documentation of a CR or PR to the date of first documentation of tumor progression or PD per IRF assessment according to IWG criteria or to death due to any cause, whichever comes first. CR is defined as the disappearance of all evidence of disease and PD is defined as any new lesion or increase by >50% of previously involved sites from nadir. Participants with response from the Safety Population, all enrolled participants who received at least one dose of brentuximab vedotin, with data available for analysis. Duration of response was censored at last observation documenting absence of PD for participants who did not have tumor progression. Here, 99999 indicates median and CI limits were not reached due to low number of participants with events.

End point type	Secondary

End point timeframe:

Cycles 2, 4, 7, 10, 13 and 16 (21-day cycles) until disease progression, death or EOT and then every 12 weeks for 12 months after EOT, until disease progression, or death or end of study (Up to 72 months)

End point values	Brentuximab vedotin 1.4 mg/kg: Phase 1	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r HL only	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r sALCL only	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[18]	7	9	
Units: months				
median (confidence interval 95%)	(to)	99999 (2.2 to 99999)	30.3 (3.4 to 30.3)	

Notes:

[18] - Number of Subjects Analyzed were Zero.

Statistical analyses

No statistical analyses for this end point

Secondary: Event Free Survival (EFS) (Phase 1 and 2)

End point title	Event Free Survival (EFS) (Phase 1 and 2)

End point description:

EFS is defined as the time in months from first dose until any cause of treatment failure: disease progression, premature discontinuation of treatment for any reason, or death due to any cause, whichever occurs first. PD is defined as any new lesion or increase by >50% of previously involved sites from nadir. Safety population is defined as all participants who received at least 1 dose of study drug. EFS was censored on the last follow-up date if none of the above events occur during the study.

End point type	Secondary

End point timeframe:

Cycles 2, 4, 7, 10, 13 and 16 (21-day cycles) until disease progression, death or EOT and then every 12 weeks for 12 months after EOT, until disease progression, or death (Up to 27 months)

End point values	Brentuximab vedotin 1.4 mg/kg: Phase 1	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r HL only	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r sALCL only	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	16	17	
Units: months				
median (confidence interval 95%)	2.7 (1.4 to 2.8)	2.1 (1.2 to 4.8)	4.8 (2.8 to 7.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) (Phase 1 and 2)

End point title	Progression Free Survival (PFS) (Phase 1 and 2)

End point description:

PFS is defined as time in months from start of study treatment to first documentation of objective tumor progression per IRF assessment or up to death due to any cause, whichever occurs first. and PD is defined as any new lesion or increase by >50% of previously involved sites from nadir. Safety population is defined as all participants who received at least 1 dose of study drug. PFS was censored on the day following the date of last radiological assessment of measured lesions documenting absence of PD for participants who did not have tumor progression. Here, 9999 indicates upper limit of CI was not reached due to low number of participants with events.

End point type	Secondary

End point timeframe:

Cycles 2, 4, 7, 10, 13 and 16 (21-day cycles) until disease progression, death or EOT and then every 12 weeks for 12 months after EOT, until disease progression, or death or end of study (Up to 72 months)

End point values	Brentuximab vedotin 1.4 mg/kg: Phase 1	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r HL only	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r sALCL only	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	16	17	
Units: months				
median (confidence interval 95%)	2.7 (1.4 to 2.8)	3.8 (1.2 to 9999)	6.2 (2.8 to 31.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) (Phase 1 and 2)

End point title	Overall Survival (OS) (Phase 1 and 2)

End point description:

OS is the time in months from start of study treatment to date of death due to any cause. Safety population is defined as all participants who received at least 1 dose of study drug. Here, 99999

indicates median was not reached due to low number of participants with events.

End point type	Secondary

End point timeframe:

Every 6 months after EOT, until the sooner of death, study closure, or 2 years after enrolment of the last participant (Up to 72 months)

End point values	Brentuximab vedotin 1.4 mg/kg: Phase 1	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r HL only	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r sALCL only	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	16	17	
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs) (Phase 1 and 2)

End point title	Number of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs) (Phase 1 and 2)

End point description:

An AE is defined as any untoward medical occurrence in a clinical investigation participant administered a drug; it does not necessarily have to have a causal relationship with this treatment. A SAE is any experience that suggests a significant hazard, contraindication, side effect or precaution that: results in death, is life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or is medically significant. A treatment-emergent adverse event (TEAE) is defined as an adverse event with an onset that occurs after receiving study drug. AE severity was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. Safety population is defined as all participants who received at least 1 dose of study drug. Data was summarized together for Phase 1 and 2 participants.

End point type	Secondary

End point timeframe:

From the first dose through 30 days after the last dose of study medication (up to 15 months)

End point values	Brentuximab vedotin 1.4 mg/kg: Phase 1	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r HL only	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r sALCL only	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	16	17	
Units: participants				
TEAEs	3	16	17	

SAEs	0	7	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Abnormal Clinical Laboratory Values Reported as AEs (Phase 1 and 2)

End point title	Number of Participants with Abnormal Clinical Laboratory Values Reported as AEs (Phase 1 and 2)

End point description:

Abnormal clinical laboratory values (serum chemistry and hematology) were reported as AEs if they were considered by the investigator to be a clinically significant change from Baseline or led to premature discontinuation of study treatment, dose modification, or other therapeutic intervention. Safety population is defined as all participants who received at least 1 dose of study drug. Data was summarized together for Phase 1 and 2 participants in brentuximab 1.8 mg/kg arm group.

End point type	Secondary

End point timeframe:

From the first dose through 30 days after the last dose of study medication (Up to 15 months)

End point values	Brentuximab vedotin 1.4 mg/kg: Phase 1	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r HL only	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r sALCL only	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	16	17	
Units: participants				
Gamma-glutamyltransferase increased	0	2	0	
Alanine aminotransferase increased	0	1	0	
Aspartate aminotransferase increased	0	1	0	
Transaminases increased	0	1	0	
Lymphocyte count decreased	1	0	2	
Neutrophil count decreased	0	0	2	
White blood cell count decreased	0	0	1	
Blood bicarbonate decreased	0	1	0	
Weight decreased	0	0	1	
C-reactive protein increased	0	1	0	
Blood alkaline phosphatase increased	0	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Clinically Significant Vital Signs Reported as AEs (Phase 1 and 2)

End point title	Number of Participants with Clinically Significant Vital Signs Reported as AEs (Phase 1 and 2)

End point description:

Vital signs measurements included supine (after 3-5 minutes in this position) and standing (after 3-5 minutes in this position) measurements of diastolic and systolic blood pressure, heart rate, and oral temperature. Safety population is defined as all participants who received at least 1 dose of study drug. Data was summarized together for Phase 1 and 2 participants in brentuximab 1.8 mg/kg arm group.

End point type	Secondary

End point timeframe:

From the first dose through 30 days after the last dose of study medication (Up to 15 months)

End point values	Brentuximab vedotin 1.4 mg/kg: Phase 1	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r HL only	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r sALCL only	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	16	17	
Units: participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Antibody-drug Conjugate (ADC) Serum Concentrations (Phase 1 and 2)

End point title	Antibody-drug Conjugate (ADC) Serum Concentrations (Phase 1 and 2)[19]

End point description:

Blood samples were collected and tested for serum concentrations of brentuximab vedotin antibody-drug conjugate. PK-evaluable population was defined as participants with sufficient dosing and PK data to reliably estimate PK parameters. Cycle 2 Day 2 values are collected in phase 1 participants only. Data was summarized together for all participants in brentuximab vedotin 1.8 mg/kg arm group. Here, 999999 indicates arithmetic mean and standard deviation was not estimable since the number of participants analyzed were '0'. n is the number of participants analyzed at the given time-point.

End point type	Secondary

End point timeframe:

Cycle 1 and 8 pre-dose and 5 minutes, 24, 48, 96 and 312 hours post-dose; Cycle 2 pre-dose, 5 minutes and 24, 48 and 96 hours post-dose; Cycle 3 to 16 pre-dose and 5 minutes post-dose

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data for this endpoint was planned to be assessed in combined form for Phase 2 arm groups.

End point values	Brentuximab vedotin 1.4 mg/kg: Phase 1	Brentuximab vedotin 1.8 mg/kg: Phase 1		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3	33[20]		
Units: ug/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 1, Pre-Dose (n=0,33)	999999 (± 999999)	99999 (± 99999)		
Cycle 1 Day 1, 5 Minutes Post-Dose (n=3,33)	23.1 (± 3.46)	31.8 (± 12.4)		
Cycle 1 Day 2, 24 Hours Post-Dose (n=3,32)	9.50 (± 1.73)	13.0 (± 5.34)		
Cycle 1 Day 3, 48 Hours Post-Dose (n=3,31)	5.67 (± 0.924)	12.0 (± 16.3)		
Cycle 1 Day 5, 96 Hours Post-Dose (n=3,31)	3.50 (± 1.41)	8.68 (± 13.4)		
Cycle 1 Day 14, 312 Hours Post-Dose (n=3,31)	0.844 (± 0.309)	2.19 (± 3.44)		
Cycle 2 Day 1, Pre-Dose (n=3,32)	0.149 (± 0.128)	0.395 (± 0.322)		
Cycle 2 Day 1, 5-minutes Post-Dose (n=3,30)	25.3 (± 7.56)	32.9 (± 9.80)		
Cycle 2 Day 2, 24 Hours Post-Dose (n=3,10)	8.80 (± 6.19)	10.4 (± 8.05)		
Cycle 2 Day 3, 48 Hours Post-Dose (n=3,29)	3.70 (± 1.95)	11.4 (± 16.8)		
Cycle 2 Day 5, 96 Hours Post-Dose (n=3,27)	2.04 (± 1.26)	9.61 (± 17.9)		
Cycle 3 Day 1, Pre-Dose (n=2,26)	0.116 (± 0.163)	0.491 (± 0.387)		
Cycle 3 Day 1, 5 minutes Post-Dose (n=2,26)	23.9 (± 2.83)	31.3 (± 9.79)		
Cycle 4 Day 1, Pre-dose (n=2,21)	0.218 (± 0.271)	0.691 (± 0.492)		
Cycle 4 Day 1, 5 minutes Post-Dose (n=2,21)	22.9 (± 4.60)	30.0 (± 12.2)		
Cycle 5 Day 1, Pre-Dose (n=2,21)	0.264 (± 0.321)	0.845 (± 0.564)		
Cycle 5 Day 1, 5 minutes Post-Dose (n=2,21)	22.5 (± 3.32)	30.6 (± 15.1)		
Cycle 6 Day 1, Pre-Dose (n=2,17)	0.312 (± 0.351)	1.06 (± 0.699)		
Cycle 6 Day 1, 5 minutes Post-Dose (n=2,17)	20.3 (± 4.38)	33.2 (± 16.1)		
Cycle 7 Day 1, Pre-Dose (n=2,17)	0.327 (± 0.337)	1.04 (± 0.618)		
Cycle 7 Day 1, 5 minutes Post-Dose (n=2,17)	17.9 (± 2.40)	32.3 (± 15.4)		
Cycle 8 Day 1, Pre-Dose (n=0,14)	999999 (± 999999)	1.25 (± 0.565)		
Cycle 8 Day 1, 5 minutes Post-Dose (n=0,13)	999999 (± 999999)	35.2 (± 10.5)		
Cycle 8 Day 2, 24 Hours Post-Dose (n=0,13)	999999 (± 999999)	14.0 (± 4.55)		
Cycle 8 Day 3, 48 Hours Post-Dose (n=0,13)	999999 (± 999999)	9.53 (± 2.96)		
Cycle 8 Day 5, 96 Hours Post-Dose (n=0,12)	999999 (± 999999)	6.44 (± 2.35)		

Cycle 8 Day 14, 312 Hours Post-Dose (n=0,13)	999999 (± 999999)	3.30 (± 4.63)		
Cycle 9 Day 1, Pre-Dose (n=0,14)	999999 (± 999999)	4.37 (± 11.7)		
Cycle 9 Day 1, 5 Minutes Post-Dose (n=0,13)	999999 (± 999999)	29.6 (± 11.3)		
Cycle 10 Day 1, Pre-Dose (n=0,11)	999999 (± 999999)	1.20 (± 0.455)		
Cycle 10 Day 1, 5 minutes Post-Dose (n=0,12)	999999 (± 999999)	35.7 (± 9.50)		
Cycle 11 Day 1, Pre-Dose (n=0,8)	999999 (± 999999)	1.84 (± 1.57)		
Cycle 11 Day 1, 5 minutes Post-Dose (n=0,8)	999999 (± 999999)	35.7 (± 10.8)		
Cycle 12 Day 1, Pre-Dose (n=0,6)	999999 (± 999999)	1.47 (± 0.665)		
Cycle 12 Day 1, 5 minutes Post-Dose (n=0,6)	999999 (± 999999)	40.0 (± 10.4)		
Cycle 13 Day 1, Pre-Dose (n=0,6)	999999 (± 999999)	6.28 (± 11.5)		
Cycle 13 Day 1, 5 minutes Post-Dose (n=0,6)	999999 (± 999999)	33.3 (± 16.1)		
Cycle 14 Day 1, Pre-Dose (n=0,6)	999999 (± 999999)	1.60 (± 0.600)		
Cycle 14 Day 1, 5 minutes Post-Dose (n=0,6)	999999 (± 999999)	37.0 (± 7.92)		
Cycle 15 Day 1, Pre-Dose (n=0,6)	999999 (± 999999)	1.48 (± 0.542)		
Cycle 15 Day 1, 5 minutes Post-Dose (n=0,6)	999999 (± 999999)	40.3 (± 10.6)		
Cycle 16 Day 1, Pre-Dose (n=0,6)	999999 (± 999999)	1.52 (± 0.361)		
Cycle 16 Day 1, 5 minutes Post-Dose (n=0,6)	999999 (± 999999)	41.5 (± 4.70)		

Notes:

[20] - Here, 99999 indicates data was below the limit of quantification.

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration of Total Antibodies (Conjugated and Unconjugated)

End point title	Serum Concentration of Total Antibodies (Conjugated and Unconjugated)[21]

End point description:

Blood samples were collected and tested for conjugated and unconjugated antibodies. PK-evaluable population was defined as participants with sufficient dosing and PK data to reliably estimate PK parameters. Cycle 2 Day 2 values are collected in phase 1 participants only. Data was summarized together for all participants in brentuximab vedotin 1.8 mg/kg arm group. Here, 999999 indicates arithmetic mean and standard deviation was not estimable since the number of participants analyzed were '0'. 99999 indicates data was below the limit of quantification. n is the number of participants analyzed at the given time-point.

End point type	Secondary

End point timeframe:

Cycle 1 and 8 pre-dose and 5 minutes, 24, 48, 96 and 312 hours post-dose; Cycle 2 pre-dose, 5 minutes and 24, 48 and 96 hours post-dose; Cycle 3 to 16 pre-dose and 5 minutes post-dose

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The data for this endpoint was planned to be assessed in combined form for Phase 2 arm groups.

End point values	Brentuximab vedotin 1.4 mg/kg: Phase 1	Brentuximab vedotin 1.8 mg/kg: Phase 1		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3	33[22]		
Units: ug/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 1, Pre-Dose (n=2,32)	99999 (± 99999)	99999 (± 99999)		
Cycle 1 Day 1, 5 Minutes Post-Dose (n=3,33)	26.3 (± 2.29)	34.7 (± 13.4)		
Cycle 1 Day 2, 24 Hours Post-Dose (n=3,33)	16.7 (± 1.50)	25.0 (± 9.59)		
Cycle 1 Day 3, 48 Hours Post-Dose (n=3,33)	12.7 (± 3.13)	18.5 (± 7.57)		
Cycle 1 Day 5, 96 Hours Post-Dose (n=3,33)	8.63 (± 5.11)	11.8 (± 5.02)		
Cycle 1 Day 14, 312 Hours Post-Dose (n=3,32)	2.23 (± 0.833)	3.50 (± 1.70)		
Cycle 2 Day 1, Pre-Dose (n=3,32)	0.470 (± 0.459)	1.16 (± 0.825)		
Cycle 2 Day 1, 5-minutes Post-Dose (n=3,31)	26.9 (± 7.98)	35.6 (± 12.0)		
Cycle 2 Day 2, 24 Hours Post-Dose (n=3,10)	17.1 (± 10.4)	17.2 (± 7.93)		
Cycle 2 Day 3, 48 Hours Post-Dose (n=3,31)	9.60 (± 5.39)	16.0 (± 6.73)		
Cycle 2 Day 3, 96 Hours Post-Dose (n=3,30)	6.43 (± 3.69)	10.2 (± 5.16)		
Cycle 3 Day 1, Pre-Dose (n=2,26)	0.415 (± 0.586)	1.62 (± 1.07)		
Cycle 3 Day 1, 5 minutes Post-Dose (n=2,26)	30.0 (± 5.87)	38.2 (± 13.1)		
Cycle 4 Day 1, Pre-dose (n=2,21)	0.875 (± 1.03)	1.95 (± 1.26)		
Cycle 4 Day 1, 5 minutes Post-Dose (n=2,21)	29.6 (± 8.13)	37.1 (± 15.6)		
Cycle 5 Day 1, Pre-Dose (n=2,21)	0.844 (± 0.928)	2.45 (± 1.68)		
Cycle 5 Day 1, 5 minutes Post-Dose (n=2,21)	29.4 (± 3.04)	38.0 (± 18.8)		
Cycle 6 Day 1, Pre-Dose (n=2,17)	1.05 (± 1.20)	2.99 (± 1.81)		
Cycle 6 Day 1, 5 minutes Post-Dose (n=2,17)	29.4 (± 5.37)	39.8 (± 19.8)		
Cycle 7 Day 1, Pre-Dose (n=2,17)	0.995 (± 0.998)	2.92 (± 1.62)		
Cycle 7 Day 1, 5 minutes Post-Dose (n=2,17)	24.0 (± 2.69)	41.0 (± 21.2)		
Cycle 8 Day 1, Pre-Dose (n=0,14)	999999 (± 999999)	3.29 (± 1.14)		
Cycle 8 Day 1, 5 minutes Post-Dose (n=0,14)	999999 (± 999999)	41.4 (± 9.47)		
Cycle 8 Day 2, 24 Hours Post-Dose (n=0,14)	999999 (± 999999)	28.2 (± 6.38)		

Cycle 8 Day 3, 48 Hours Post-Dose (n=0,14)	999999 (± 999999)	22.9 (± 5.67)		
Cycle 8 Day 5, 96 Hours Post-Dose (n=0,14)	999999 (± 999999)	17.3 (± 4.93)		
Cycle 8 Day 14, 312 Hours Post-Dose (n=0,13)	999999 (± 999999)	5.74 (± 2.02)		
Cycle 9 Day 1, Pre-Dose (n=0,14)	999999 (± 999999)	6.30 (± 12.0)		
Cycle 9 Day 1, 5 Minutes Post-Dose (n=0,13)	999999 (± 999999)	35.1 (± 11.3)		
Cycle 10 Day 1, Pre-Dose (n=0,12)	999999 (± 999999)	3.48 (± 1.13)		
Cycle 10 Day 1, 5 minutes Post-Dose (n=0,12)	999999 (± 999999)	41.4 (± 8.63)		
Cycle 11 Day 1, Pre-Dose (n=0,8)	999999 (± 999999)	3.96 (± 2.24)		
Cycle 11 Day 1, 5 minutes Post-Dose (n=0,8)	999999 (± 999999)	42.8 (± 8.85)		
Cycle 12 Day 1, Pre-Dose (n=0,6)	999999 (± 999999)	3.47 (± 1.28)		
Cycle 12 Day 1, 5 minutes Post-Dose (n=0,6)	999999 (± 999999)	44.8 (± 10.3)		
Cycle 13 Day 1, Pre-Dose (n=0,6)	999999 (± 999999)	11.3 (± 17.1)		
Cycle 13 Day 1, 5 minutes Post-Dose (n=3,32)	999999 (± 999999)	40.3 (± 19.2)		
Cycle 14 Day 1, Pre-Dose (n=0,6)	999999 (± 999999)	3.97 (± 1.14)		
Cycle 14 Day 1, 5 minutes Post-Dose (n=0,6)	999999 (± 999999)	44.5 (± 7.05)		
Cycle 15 Day 1, Pre-Dose (n=0,6)	999999 (± 999999)	4.02 (± 1.40)		
Cycle 15 Day 1, 5 minutes Post-Dose (n=0,6)	999999 (± 999999)	49.7 (± 6.88)		
Cycle 16 Day 1, Pre-Dose (n=0,6)	999999 (± 999999)	4.60 (± 1.67)		
Cycle 16 Day 1, 5 minutes Post-Dose (n=0,6)	999999 (± 999999)	49.7 (± 7.61)		

Notes:

[22] - Here, 99999 indicates data was below the limit of quantification.

Statistical analyses

No statistical analyses for this end point

Secondary: Monomethyl Auristatin E (MMAE) Plasma Concentrations (Phase 1 and 2)

End point title	Monomethyl Auristatin E (MMAE) Plasma Concentrations (Phase 1 and 2)[23]

End point description:

Blood samples were collected and tested for MMAE plasma concentrations. PK-evaluable population was defined as participants with sufficient dosing and PK data to reliably estimate PK parameters. Cycle 2 Day 2 values are collected in phase 1 participants only. Data was summarized together for all participants in brentuximab vedotin 1.8 mg/kg arm group. Here, 999999 indicates arithmetic mean and standard deviation was not estimable since the number of participants analyzed were '0'. 99999 indicates data was below the limit of quantification. n is the number of participants analyzed at the given time-point.

End point type	Secondary

End point timeframe:

Cycle 1 and 8 pre-dose and 5 minutes, 24, 48, 96 and 312 hours post-dose; Cycle 2 pre-dose, 5

minutes and 24, 48 and 96 hours post-dose; Cycle 3 to 16 pre-dose and 5 minutes post-dose

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The data for this endpoint was planned to be assessed in combined form for Phase 2 arm groups.

End point values	Brentuximab vedotin 1.4 mg/kg: Phase 1	Brentuximab vedotin 1.8 mg/kg: Phase 1		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3	33[24]		
Units: ng/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 1, Pre-Dose (n=2,32)	99999 (± 99999)	99999 (± 99999)		
Cycle 1 Day 1, 5 Minutes Post-Dose (n=3,32)	0.416 (± 0.480)	0.368 (± 0.309)		
Cycle 1 Day 2, 24 Hours Post-Dose (n=3,32)	4.63 (± 3.20)	4.88 (± 3.55)		
Cycle 1 Day 3, 48 Hours Post-Dose (n=3,32)	4.20 (± 1.95)	5.36 (± 3.72)		
Cycle 1 Day 5, 96 Hours Post-Dose (n=3,32)	2.80 (± 0.300)	4.43 (± 3.04)		
Cycle 1 Day 14, 312 Hours Post-Dose (n=3,31)	0.196 (± 0.0641)	0.530 (± 0.552)		
Cycle 2 Day 1, Pre-Dose (n=3,29)	0.0647 (± 0.0358)	0.0739 (± 0.0640)		
Cycle 2 Day 1, 5-minutes Post-Dose (n=3,29)	0.556 (± 0.562)	0.478 (± 0.461)		
Cycle 2 Day 2, 24 Hours Post-Dose (n=3,8)	5.63 (± 5.72)	3.71 (± 3.94)		
Cycle 2 Day 3, 48 Hours Post-Dose (n=3,30)	4.60 (± 3.70)	3.86 (± 3.18)		
Cycle 2 Day 5, 96 Hours Post-Dose (n=3,29)	2.60 (± 1.04)	2.70 (± 1.69)		
Cycle 3 Day 1, Pre-Dose (n=2,26)	0.0250 (± 0.0354)	0.0650 (± 0.0590)		
Cycle 3 Day 1, 5 minutes Post-Dose (n=2,25)	0.216 (± 0.0361)	0.514 (± 0.684)		
Cycle 4 Day 1, Pre-dose (n=2,19)	0.0565 (± 0.00495)	0.0866 (± 0.0784)		
Cycle 4 Day 1, 5 minutes Post-Dose (n=2,19)	0.234 (± 0.0742)	0.376 (± 0.449)		
Cycle 5 Day 1, Pre-Dose (n=2,18)	0.0820 (± 9999)	0.0862 (± 0.0729)		
Cycle 5 Day 1, 5 minutes Post-Dose (n=2,18)	0.334 (± 0.0955)	0.301 (± 0.248)		
Cycle 6 Day 1, Pre-Dose (n=2,15)	0.0680 (± 0.0156)	0.0841 (± 0.0632)		
Cycle 6 Day 1, 5 minutes Post-Dose (n=2,15)	0.247 (± 0.00707)	0.450 (± 0.663)		
Cycle 7 Day 1, Pre-Dose (n=2,16)	0.104 (± 0.0389)	0.0830 (± 0.0578)		
Cycle 7 Day 1, 5 minutes Post-Dose (n=2,15)	0.326 (± 0.0361)	0.310 (± 0.282)		
Cycle 8 Day 1, Pre-Dose (n=0,13)	999999 (± 999999)	0.101 (± 0.934)		

Cycle 8 Day 1, 5 minutes Post-Dose (n=0,12)	999999 (± 999999)	0.295 (± 0.151)		
Cycle 8 Day 2, 24 Hours Post-Dose (n=0,13)	999999 (± 999999)	1.96 (± 1.31)		
Cycle 8 Day 3, 48 Hours Post-Dose|	999999 (± 999999)	1.91 (± 1.29)		
Cycle 8 Day 5, 96 Hours Post-Dose (n=0,13)	999999 (± 999999)	2.00 (± 1.05)		
Cycle 8 Day 14, 312 Hours Post-Dose (n=0,12)	999999 (± 999999)	0.325 (± 0.214)		
Cycle 9 Day 1, Pre-Dose (n=0,13)	999999 (± 999999)	0.0819 (± 0.0496)		
Cycle 9 Day 1, 5 Minutes Post-Dose (n=0,12)	999999 (± 999999)	0.218 (± 0.128)		
Cycle 10 Day 1, Pre-Dose (n=0,12)	999999 (± 999999)	0.727 (± 0.0517)		
Cycle 10 Day 1, 5 minutes Post-Dose (n=0,12)	999999 (± 999999)	0.204 (± 0.0982)		
Cycle 11 Day 1, Pre-Dose (n=0,7)	999999 (± 999999)	0.0763 (± 0.0368)		
Cycle 11 Day 1, 5 minutes Post-Dose (n=0,7)	999999 (± 999999)	0.255 (± 0.133)		
Cycle 12 Day 1, Pre-Dose (n=0,5)	999999 (± 999999)	0.105 (± 0.0983)		
Cycle 12 Day 1, 5 minutes Post-Dose (n=0,5)	999999 (± 999999)	0.252 (± 0.116)		
Cycle 13 Day 1, Pre-Dose (n=0,6)	999999 (± 999999)	0.110 (± 0.0629)		
Cycle 13 Day 1, 5 minutes Post-Dose (n=0,6)	999999 (± 999999)	0.244 (± 0.130)		
Cycle 14 Day 1, Pre-Dose (n=0,6)	999999 (± 999999)	0.109 (± 0.0529)		
Cycle 14 Day 1, 5 minutes Post-Dose (n=0,6)	999999 (± 999999)	0.320 (± 0.138)		
Cycle 15 Day 1, Pre-Dose (n=0,6)	999999 (± 999999)	0.0843 (± 0.0548)		
Cycle 15 Day 1, 5 minutes Post-Dose (n=0,6)	999999 (± 999999)	0.404 (± 0.192)		
Cycle 16 Day 1, Pre-Dose (n=0,6)	999999 (± 999999)	0.139 (± 0.0926)		
Cycle 16 Day 1, 5 minutes Post-Dose (n=0,6)	999999 (± 999999)	0.381 (± 0.277)		

Notes:

[24] - Here, 99999 indicates data was below the limit of quantification.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose through 30 days after the last dose of study medication (Up to 15 months)

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the participant or observed by the investigator was recorded, irrespective of the relation to study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Brentuximab vedotin 1.4 mg/kg: Phase 1

Reporting group description:

Brentuximab vedotin 1.4 mg/kg, 30-minute IV infusion, Day 1 of every 21-day cycle, until there was evidence of disease progression or unacceptable toxicity.

Reporting group title	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r HL only

Reporting group description:

Participants with r/r HL received brentuximab vedotin 1.8 mg/kg, 30-minute IV infusion, Day 1 of every 21-day cycle until there was evidence of disease progression or unacceptable toxicity (Up to 16 cycles). Treatment with brentuximab vedotin beyond 16 cycles was permitted at the joint discretion of the sponsor and the investigator for those participants experiencing continued clinical benefit.

Reporting group title	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r sALCL only

Reporting group description:

Participants with r/r systemic anaplastic large-cell lymphoma (sALCL) received brentuximab vedotin 1.8 mg/kg, 30-minute IV infusion, Day 1 of every 21-day cycle until there was evidence of disease progression or unacceptable toxicity (Up to 16 cycles). Treatment with brentuximab vedotin beyond 16 cycles was permitted at the joint discretion of the sponsor and the investigator for those participants experiencing continued clinical benefit.

Serious adverse events	Brentuximab vedotin 1.4 mg/kg: Phase 1	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r HL only	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r sALCL only
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	7 / 16 (43.75%)	1 / 17 (5.88%)
number of deaths (all causes)	1	6	2
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Supraventricular tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest	Additional description: One treatment-emergent death occurred during treatment with brentuximab 1.8 mg/kg and was not related.		

subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			

subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Brentuximab vedotin 1.4 mg/kg: Phase 1	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r HL only	Brentuximab vedotin 1.8 mg/kg: Phase 1 and 2 r/r sALCL only
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	16 / 16 (100.00%)	17 / 17 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 16 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Flushing			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 3 (33.33%)	8 / 16 (50.00%)	7 / 17 (41.18%)
occurrences (all)	1	11	10
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	2 / 16 (12.50%)	1 / 17 (5.88%)
occurrences (all)	0	2	1
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	3
Feeling hot			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Oedema peripheral			

subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	2	0
Reproductive system and breast disorders			
Menstruation irregular			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 3 (0.00%)	3 / 16 (18.75%)	1 / 17 (5.88%)
occurrences (all)	0	4	2
Oropharyngeal pain			
subjects affected / exposed	0 / 3 (0.00%)	2 / 16 (12.50%)	0 / 17 (0.00%)
occurrences (all)	0	2	0
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	1 / 17 (5.88%)
occurrences (all)	0	1	1
Anxiety			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	2	0
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 16 (12.50%)	0 / 17 (0.00%)
occurrences (all)	0	2	0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	3	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	3	0
Transaminases increased			

subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Lymphocyte count decreased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 16 (0.00%)	2 / 17 (11.76%)
occurrences (all)	1	0	3
Neutrophil count decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	2 / 17 (11.76%)
occurrences (all)	0	0	2
White blood cell count decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Blood bicarbonate decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	2
C-reactive protein increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Joint dislocation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Muscle strain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 16 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Head injury			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Facial bones fracture			

subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Sinus tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	1 / 3 (33.33%)	5 / 16 (31.25%)	1 / 17 (5.88%)
occurrences (all)	2	5	1
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 3 (0.00%)	2 / 16 (12.50%)	2 / 17 (11.76%)
occurrences (all)	0	2	8
Neuropathy peripheral			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Peripheral motor neuropathy			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	3 / 17 (17.65%)
occurrences (all)	0	0	3
Migraine			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Dysgeusia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 16 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Tremor			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Vocal cord paralysis			

subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	4 / 16 (25.00%)	1 / 17 (5.88%)
occurrences (all)	0	6	3
Lymph node pain			
subjects affected / exposed	0 / 3 (0.00%)	2 / 16 (12.50%)	1 / 17 (5.88%)
occurrences (all)	0	2	1
Lymphadenopathy			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 16 (12.50%)	0 / 17 (0.00%)
occurrences (all)	0	2	0
Leukopenia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 16 (12.50%)	0 / 17 (0.00%)
occurrences (all)	0	6	0
Thrombocytopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	2
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Eye discharge			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 3 (66.67%)	7 / 16 (43.75%)	4 / 17 (23.53%)
occurrences (all)	2	9	5
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	2 / 16 (12.50%)	3 / 17 (17.65%)
occurrences (all)	0	3	3
Abdominal pain upper			

subjects affected / exposed	1 / 3 (33.33%)	2 / 16 (12.50%)	1 / 17 (5.88%)
occurrences (all)	1	2	2
Abdominal pain			
subjects affected / exposed	1 / 3 (33.33%)	2 / 16 (12.50%)	0 / 17 (0.00%)
occurrences (all)	1	2	0
Gastrointestinal pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	2 / 16 (12.50%)	3 / 17 (17.65%)
occurrences (all)	0	3	3
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	2 / 16 (12.50%)	0 / 17 (0.00%)
occurrences (all)	0	2	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Gastritis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	1 / 17 (5.88%)
occurrences (all)	0	1	1
Toothache			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Dyspepsia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal motility disorder			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Dysphagia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Odynophagia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Hepatobiliary disorders			

Hepatotoxicity			
subjects affected / exposed	0 / 3 (0.00%)	2 / 16 (12.50%)	0 / 17 (0.00%)
occurrences (all)	0	2	0
Hypertransaminasaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Hepatic pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	1 / 17 (5.88%)
occurrences (all)	0	1	1
Rash maculo-papular			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	2 / 17 (11.76%)
occurrences (all)	0	0	2
Blister			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	2
Dermatosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Dry skin			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	0 / 3 (0.00%)	2 / 16 (12.50%)	0 / 17 (0.00%)
occurrences (all)	0	2	0
Urticaria			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	1 / 17 (5.88%)
occurrences (all)	0	1	2
Alopecia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Night sweats			

subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	2	0
Drug eruption			
subjects affected / exposed	1 / 3 (33.33%)	0 / 16 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Erythema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Erythema multiforme			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Urinary tract pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	2 / 16 (12.50%)	1 / 17 (5.88%)
occurrences (all)	0	2	1
Musculoskeletal pain			
subjects affected / exposed	0 / 3 (0.00%)	2 / 16 (12.50%)	0 / 17 (0.00%)
occurrences (all)	0	2	0
Back pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	2
Neck pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Myalgia			

subjects affected / exposed	0 / 3 (0.00%)	4 / 16 (25.00%)	0 / 17 (0.00%)
occurrences (all)	0	5	0
Arthralgia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	1	1	0
Muscle spasms			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	1 / 17 (5.88%)
occurrences (all)	0	1	1
Groin pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	1 / 17 (5.88%)
occurrences (all)	0	1	1
Infections and infestations			
Rhinitis			
subjects affected / exposed	0 / 3 (0.00%)	3 / 16 (18.75%)	4 / 17 (23.53%)
occurrences (all)	0	3	5
Pharyngitis			
subjects affected / exposed	0 / 3 (0.00%)	3 / 16 (18.75%)	3 / 17 (17.65%)
occurrences (all)	0	4	4
Nasopharyngitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	1 / 17 (5.88%)
occurrences (all)	0	1	1
Sinusitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 3 (33.33%)	0 / 16 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Gingivitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Tooth abscess			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Clostridium difficile colitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1

Conjunctivitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	2	0
Herpes zoster			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Paronychia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 3 (0.00%)	3 / 16 (18.75%)	0 / 17 (0.00%)
occurrences (all)	0	3	0
Hypokalaemia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 16 (12.50%)	1 / 17 (5.88%)
occurrences (all)	0	3	1
Hyperuricaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Hypophosphataemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Hypoalbuminaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 July 2011	The amendment promoted participant safety by reducing the opportunity for potential drug-drug interactions, using an objective definition of dose-limiting toxicity (DLT), and specifying administration equipment that ensures drug compatibility.
06 February 2012	• The protocol excluded participants with signs or symptoms of progressive multifocal leukoencephalopathy (PML) and instructed for management of suspected PML as brentuximab vedotin discontinuation. • Information was added on management of infusion-related reactions, including instructions to immediately and permanently discontinue administration of brentuximab vedotin for Grade 3 or higher infusion-related reactions consistent with anaphylaxis. • Included information on occurrence of pulmonary toxicity and specifies that concomitant use of bleomycin with brentuximab vedotin is contraindicated. • The original protocol stated that brentuximab vedotin dose should be held in case of new or worsening events of Grade 2 or 3 neuropathy. To ensure participant's safety and conform to dosing guidelines, an exclusion criterion was added for participants with Grade 2/higher peripheral neuropathy at the time of screening. • Participants who were pregnant or both lactating and breastfeeding were not eligible for the study. This exclusion criterion was inadvertently omitted from original protocol and was added to this amendment. • A washout period of at least 14 days was required for participants who received local palliative radiation therapy; a washout period of at least 84 days was required for participants who received radiation therapy to more than 25% of bone marrow-containing spaces. Exclusion criteria was added to specify the restrictions on receiving radiation therapy prior to first dose of study drug. • Planned imaging assessments were revised in order to minimize radiation exposure in this pediatric population. Magnetic resonance imaging (MRI) was to be performed for neck, abdomen, and pelvis evaluations; computed tomography (CT) scans were to be used for chest evaluations only. • The definition of enrollment was changed to at the time of first dose of study drug. • The contact information for serious adverse events (SAEs) and events of pregnancy was revised.
12 June 2014	• Duration of follow-up was changed to align with content of pediatric investigation plan. PIP states that participants will be followed for safety and survival for 2 years after enrollment. References to follow-up revised to state that participants will be followed for progression-free survival and overall survival every 12 weeks for 12 months after End of Treatment visit. Thereafter, assessment for OS was to continue every 6 months until sooner of death or study closure or a maximum of 2 years after enrollment of last participant. • Described study procedures for participants who continue to receive brentuximab vedotin after Cycle 16 and further clarifies other study procedures associated with study conduct. • Clarified primary endpoint for phase 2 of study is best overall response rate Inclusion criterion for total bilirubin has been revised to include participants with total serum bilirubin ≤ 3 times upper limit of normal range (ULN) if abnormal value is due to indirect hyperbilirubinemia due to Gilbert's disease. • Participants with elevated alanine aminotransferase or aspartate aminotransferase values 5 times ULN may be enrolled if elevation can be reasonably ascribed to presence of metastatic disease in liver. • Exclusions of previous allogeneic stem cell transplant or autologous stem cell infusion was changed from within 6 months and 6 weeks before first dose of study drug, respectively, to within 3 months and 4 weeks before first dose of study drug, respectively. • Exclusion criterion for cytochrome P450 3A4 inhibitors was changed to exclude both strong and listed moderate inhibitors of CYP3A4 within 2 weeks before first dose of study drug, and a change to timing for exclusion of corticosteroids. • Following potential risks were added to Risks in Children section to align with updates to safety profile of brentuximab vedotin: Stevens-Johnson syndrome, pancreatitis, hepatotoxicity (elevated AST and ALT).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported