Clinical trial results:
A Single-arm Study of Brentuximab Vedotin in Patients with Relapsed or Refractory Hodgkin Lymphoma who are not Suitable for Stem Cell Transplantation or Multiagent Chemotherapy

Summary

EudraCT number	2013-000232-10
Trial protocol	CZ ES DE PL
Global end of trial date	12 March 2020

Results information

Result version number	v1 (current)
This version publication date	26 March 2021
First version publication date	26 March 2021

Trial information

Trial identification

Sponsor protocol code	C25007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1154-2250
Other trial identifiers	NMRR: NMRR-13-1246-18099, REec: REec-2014-0619

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	95 Hayden Avenue, Lexington, MA, United States, 02421
Public contact	Study Director, Takeda, +1 877-825-3327, TrialDisclosures@takeda.com
Scientific contact	Study Director, Takeda, +1 877-825-3327, TrialDisclosures@takeda.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 March 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This phase 4, single-arm, open-label, multicenter study is designed to evaluate the efficacy and safety of brentuximab vedotin as a single agent in adult participants with histologically confirmed CD30+ relapsed or refractory classical Hodgkin Lymphoma who have not received a prior stem cell transplantation (SCT) and are considered to be not suitable for SCT or multiagent chemotherapy at the time of study entry.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 March 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	18 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Czechia: 3
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Malaysia: 8
Country: Number of subjects enrolled	Poland: 26
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Thailand: 10
Country: Number of subjects enrolled	Turkey: 9
Worldwide total number of subjects	60
EEA total number of subjects	33

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 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	55
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 18 investigative sites in Czech Republic, Germany, Malaysia, Poland, Spain, Thailand and Turkey, from 14 March 2014 to 12 March 2020.

Pre-assignment

Screening details:

Participants with a diagnosis of relapsed or refractory Hodgkin Lymphoma were enrolled in 1 treatment group to receive brentuximab vedotin 1.8 mg/kg, 30-minute intravenous (IV) infusion on Day 1 of every 3-week cycle and were followed for progression free survival (PFS) and overall survival (OS) up to the End of study (approximately 6 years).

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

Arm title	Brentuximab Vedotin 1.8 mg/kg

Arm description:

Brentuximab vedotin 1.8 mg/kg, 30-minute IV infusion, Day 1 of every 3-week cycle, until there is evidence of disease progression or unacceptable toxicity occurs (Up to 16 cycles). The dose could be decreased or delayed or discontinued in participants who develop treatment-associated non-hematologic toxicity, hematologic toxicity or peripheral neuropathy to brentuximab vedotin.

Arm type	Experimental
Investigational medicinal product name	Brentuximab Vedotin
Investigational medicinal product code	
Other name	ADCETRIS SGN-35
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Brentuximab vedotin, IV infusion

Number of subjects in period 1	Brentuximab Vedotin 1.8 mg/kg
Started	60
Completed	25
Not completed	35
Adverse event, serious fatal	22
Consent withdrawn by subject	3
Symptomatic Deterioration	1
Progressive disease	3
Lost to follow-up	1
Withdrawal of Informed Consent	2
Reason not Specified	2

Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Brentuximab Vedotin 1.8 mg/kg

Reporting group description:

Brentuximab vedotin 1.8 mg/kg, 30-minute IV infusion, Day 1 of every 3-week cycle, until there is evidence of disease progression or unacceptable toxicity occurs (Up to 16 cycles). The dose could be decreased or delayed or discontinued in participants who develop treatment-associated non-hematologic toxicity, hematologic toxicity or peripheral neuropathy to brentuximab vedotin.

Reporting group values	Brentuximab Vedotin 1.8 mg/kg	Total	
Number of subjects	60	60	
Age categorical Units: Subjects			
Adults (18-64 years)	55	55	
From 65-84 years	5	5	
Age Continuous Units: years			
arithmetic mean	35.4		
standard deviation	± 13.83	-	
Sex: Female, Male Units: participants			
Female	24	24	
Male	36	36	
Region of Enrollment Units: Subjects			
Czech Republic	3	3	
Germany	2	2	
Malaysia	8	8	
Poland	26	26	
Spain	2	2	
Thailand	10	10	
Turkey	9	9	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	18	18	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	42	42	
More than one race	0	0	
Unknown or Not Reported	0	0	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	2	
Not Hispanic or Latino	58	58	
Unknown or Not Reported	0	0	

Baseline Height			
Units: cm			
arithmetic mean	171.0		
standard deviation	± 9.66	-	
Baseline Weight			
Units: kg			
arithmetic mean	70.3		
standard deviation	± 19.41	-	
Body Mass Index (BMI)			
BMI = weight (kg)/[height (m)^2]			
Units: kg/m^2			
arithmetic mean	23.864		
standard deviation	± 5.4085	-	

End points

End points reporting groups

Reporting group title	Brentuximab Vedotin 1.8 mg/kg

Reporting group description:

Brentuximab vedotin 1.8 mg/kg, 30-minute IV infusion, Day 1 of every 3-week cycle, until there is evidence of disease progression or unacceptable toxicity occurs (Up to 16 cycles). The dose could be decreased or delayed or discontinued in participants who develop treatment-associated non-hematologic toxicity, hematologic toxicity or peripheral neuropathy to brentuximab vedotin.

Primary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)[1]

End point description:

Objective 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. Intent-to-Treat (ITT) Population included all participants who were enrolled in the study.

End point type	Primary

End point timeframe:

Baseline until disease progression, death or end of study (EOS) (Up to 24 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: Statistical analyses were not available for this endpoint.

End point values	Brentuximab Vedotin 1.8 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	60			
Units: percentage of participants				
number (confidence interval 95%)	50 (37 to 63)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR is defined as the time in months from the date of first documentation of a CR or PR response to the date of first documentation of tumor progression or progressive disease (PD) per IRF assessment according to IWG criteria. CR is defined as the disappearance of all evidence of disease. PR is defined as regression of measurable disease and no new sites. PD is defined as any new lesion or increase by >50% of previously involved sites from nadir. ITT Population included all participants who were enrolled in the study. DOR was censored on the date of last disease assessment documenting absence of PD for those that were lost to follow-up, withdrew consent, started a new anticancer therapy other than stem cell transplantation (SCT), or discontinued treatment due to undocumented PD after last disease assessment. All responders were evaluated in this endpoint.

End point type	Secondary

End point timeframe:

From first documented complete or partial remission until disease progression (Up to 24 months)

End point values	Brentuximab Vedotin 1.8 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: months				
median (confidence interval 95%)	4.6 (3.42 to 7.85)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

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. ITT Population included all participants who were enrolled in the study. For a participant that has not progressed and has not died, PFS is censored at the last response assessment that is SD or better.

End point type	Secondary

End point timeframe:

Baseline until disease progression, death or end of treatment (EOT), and then every 3 months up to approximately 6 years

End point values	Brentuximab Vedotin 1.8 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	60			
Units: months				
median (confidence interval 95%)	4.8 (2.96 to 5.32)			

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Remission Rate

End point title	Complete Remission Rate

End point description:

Complete remission rate is defined as percentage of participants with CR per IRF response assessment based on IWG criteria are reported. CR is defined as the disappearance of all evidence of disease. ITT Population included all participants who were enrolled in the study. In the absence of confirmation of death, survival time is censored at the last date the participant is known to be alive, including study closure.

End point type	Secondary

End point timeframe:

Baseline until disease progression, death or EOS (Up to approximately 6 years)

End point values	Brentuximab Vedotin 1.8 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	60			
Units: percentage of participants				
number (confidence interval 95%)	13 (6 to 25)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Complete Remission

End point title	Duration of Complete Remission

End point description:

Duration of CR is defined as the time from the date of first documentation of a CR or to the date of first documentation of tumor progression or progressive disease (PD) per IRF assessment according to IWG criteria. 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. ITT Population included all participants who were enrolled in the study. DOR was censored on the date of last disease assessment documenting absence of PD for those that were lost to follow-up, withdrew consent, started a new anticancer therapy other than SCT, or discontinued treatment due to undocumented PD after last disease assessment. Only participants with CR were analyzed for this outcome measure. 9999 = Not estimable. Upper limit of CI was not estimable due to the low number of participants with events.

End point type	Secondary

End point timeframe:

From first documented complete remission until disease progression (up to approximately 6 years)

End point values	Brentuximab Vedotin 1.8 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	8[2]			
Units: months				
median (confidence interval 95%)	6.1 (2.10 to 9999)			

Notes:

[2] - Number analyzed is the number of participants with data available at the given time-point.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is the time in months from start of study treatment to date of death due to any cause. ITT Population included all participants who were enrolled in the study. In the absence of confirmation of death, survival time is censored at the last date the participant is known to be alive, including study closure. 9999 indicates median and 95% confidence interval (CI) was not estimable due to the low number of participants with events.

End point type	Secondary

End point timeframe:

Every 3 months for 18 months after EOT, thereafter, every 6 months until the sooner of death, study closure, or 5 years after enrollment of the last participant (up to approximately 6 years)

End point values	Brentuximab Vedotin 1.8 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	60			
Units: months				
median (confidence interval 95%)	9999 (9999 to 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Received Hematopoietic SCT

End point title	Percentage of Participants who Received Hematopoietic SCT

End point description:

ITT Population included all participants who were enrolled in the study.

End point type	Secondary

End point timeframe:

Baseline up to EOS (up to approximately 6 years)

End point values	Brentuximab Vedotin 1.8 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	60			
Units: percentage of participants				
number (not applicable)	53			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events (AEs), Drug-Related AEs, Grade 3 or Higher AEs, Serious Adverse Events (SAEs), Drug-Related SAEs and Grade 3 or Higher SAEs

End point title	Number of Participants with Adverse Events (AEs), Drug-Related AEs, Grade 3 or Higher AEs, Serious Adverse Events (SAEs), Drug-Related SAEs and Grade 3 or Higher SAEs

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 A serious 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. AEs Grade 3 and higher are severe. Safety Population was defined as all enrolled participants who received at least one dose of brentuximab vedotin.

End point type	Secondary

End point timeframe:

From first dose through 30 days after the last dose of study medication (Up to 24 months)

End point values	Brentuximab Vedotin 1.8 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	60			
Units: participants				
Any AEs	52			
Grade 3 or higher AEs	21			
Drug-related AEs	41			
Drug-related Grade 3 or higher AEs	11			
SAEs	11			
Drug-related SAEs	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Abnormal Clinical Laboratory Values Reported as AEs

End point title	Number of Participants with Abnormal Clinical Laboratory Values Reported as AEs

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 was defined as all enrolled participants who received at least one dose of brentuximab vedotin.

End point type	Secondary

End point timeframe:

From the first dose through 30 days after the last dose of study medication (Up to 24 months)

End point values	Brentuximab Vedotin 1.8 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	60			
Units: participants				
Neutrophil count decreased	2			
Lymphocyte count decreased	1			
Alanine aminotransferase increased	2			
Aspartate aminotransferase increased	2			
Gamma-glutamyltransferase increased	1			
Blood thyroid stimulating hormone increased	1			
Platelet count decreased	1			
Haemoglobin decreased	1			
Blood alkaline phosphatase increased	1			
Blood lactate dehydrogenase increased	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Antibody-drug Conjugate (ADC) Serum Concentrations

End point title	Antibody-drug Conjugate (ADC) Serum Concentrations

End point description:

Blood samples were collected and tested for serum concentrations of brentuximab vedotin antibody-drug conjugate. Pharmacokinetic (PK)-evaluable Population was defined as participants with sufficient dosing and PK data to reliably estimate PK parameters. 'n' indicates number analysed is the number of participants with data available at the given time-point.

End point type	Secondary

End point timeframe:

Cycle 1 pre-dose and 10 minutes, 24 hours and 336 hours post-dose; Cycle 2 pre-dose and 10 minutes post-dose; Cycle 3 pre-dose and 10 minutes, 24 hours and 336 hours post-dose; Cycle 4 to 16 pre-dose and 10 minutes post-dose; EOT (Up to 24 months)

End point values	Brentuximab Vedotin 1.8 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	60			
Units: ng/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 1, Pre-Dose (n=59)	0.00 (± 0.000)			
Cycle 1 Day 1, 10 minutes Post-Dose (n=58)	35504.65 (± 10226.104)			
Cycle 1 Day 2, 24 hours Post-Dose (n=59)	14517.67 (± 4481.312)			
Cycle 1 Day 15, 336 hours Post-Dose (n=55)	1410.43 (± 1946.525)			
Cycle 2 Day 1, Pre-Dose (n=52)	526.42 (± 350.467)			
Cycle 2 Day 1, 10 minutes Post-Dose (n=53)	37118.32 (± 11678.088)			
Cycle 3 Day 1, Pre-Dose (n=49)	2283.30 (± 7552.322)			
Cycle 3 Day 1, 10 minutes Post-Dose (n=51)	35878.77 (± 12724.898)			
Cycle 3 Day 2, 24 hours Post-Dose (n=54)	14737.82 (± 4512.358)			
Cycle 3 Day 15, 336 hours Post-Dose (n=46)	1586.45 (± 680.955)			
Cycle 4 Day 1, Pre-Dose (n=51)	1313.56 (± 2566.360)			
Cycle 4 Day 1, 10 minutes Post-Dose (n=51)	42915.34 (± 28221.764)			
Cycle 5 Day 1, Pre-Dose (n=43)	1117.01 (± 637.637)			
Cycle 5 Day 1, 10 minutes Post-Dose (n=41)	36418.77 (± 10041.935)			
Cycle 6 Day 1, Pre-Dose (n=37)	1231.45 (± 714.383)			
Cycle 6 Day 1, 10 minutes Post-Dose (n=38)	39000.95 (± 12484.458)			
Cycle 7 Day 1, Pre-Dose (n=38)	1285.91 (± 712.625)			
Cycle 7 Day 1, 10 minutes Post-Dose (n=36)	38814.82 (± 12471.299)			
Cycle 8 Day 1, Pre-Dose (n=22)	1413.98 (± 782.391)			
Cycle 8 Day 1, 10 minutes Post-Dose (n=24)	39027.22 (± 9919.251)			
Cycle 9 Day 1, Pre-Dose (n=15)	1277.18 (± 594.603)			
Cycle 9 Day 1, 10 minutes Post-Dose (n=14)	38359.15 (± 13421.064)			
Cycle 10 Day 1, Pre-Dose (n=11)	1498.44 (± 754.721)			
Cycle 10 Day 1, 10 minutes Post-Dose (n=11)	39890.12 (± 5376.038)			
Cycle 11 Day 1, Pre-Dose (n=9)	1511.35 (± 461.907)			

Cycle 11 Day 1, 10 minutes Post-Dose (n=9)	39132.17 (± 6316.541)			
Cycle 12 Day 1, Pre-Dose (n=10)	1479.38 (± 397.816)			
Cycle 12 Day 1, 10 minutes Post-Dose (n=10)	39955.13 (± 7821.656)			
Cycle 13 Day 1, Pre-Dose (n=9)	1423.56 (± 415.744)			
Cycle 13 Day 1, 10 minutes Post-Dose (n=9)	37609.69 (± 4563.601)			
Cycle 14 Day 1, Pre-Dose (n=8)	1185.62 (± 422.664)			
Cycle 14 Day 1, 10 minutes Post-Dose (n=8)	38282.29 (± 10324.023)			
Cycle 15 Day 1, Pre-Dose (n=8)	2279.42 (± 2919.545)			
Cycle 15 Day 1, 10 minutes Post-Dose (n=8)	39068.14 (± 7981.110)			
Cycle 16 Day 1, Pre-Dose (n=8)	1452.23 (± 429.731)			
Cycle 16 Day 1, 10 minutes Post-Dose (n=8)	38414.73 (± 9427.315)			
End of Treatment (n=49)	1515.30 (± 6413.367)			

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)

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. 'n' indicates Number analysed is the number of participants with data available at the given time-point.

End point type	Secondary

End point timeframe:

Cycle 1 pre-dose and 10 minutes, 24 hours and 336 hours post-dose; Cycle 2 pre-dose and 10 minutes post-dose; Cycle 3 pre-dose and 10 minutes, 24 hours and 336 hours post-dose; Cycle 4 to 16 pre-dose and 10 minutes post-dose; EOT (Up to 24 months)

End point values	Brentuximab Vedotin 1.8 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	60			
Units: ng/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 1, Pre-Dose (n=58)	0.00 (± 0.000)			

Cycle 1 Day 1, 10 minutes Post-Dose (n=57)	37329.59 (± 17724.247)			
Cycle 1 Day 2, 24 hours Post-Dose (n=57)	23248.90 (± 8228.938)			
Cycle 1 Day 15, 336 hours Post-Dose (n=59)	2791.49 (± 1413.452)			
Cycle 2 Day 1, Pre-Dose (n=56)	1254.86 (± 774.586)			
Cycle 2 Day 1, 10 minutes Post-Dose (n=54)	39801.87 (± 12914.837)			
Cycle 3 Day 1, Pre-Dose (n=54)	2645.22 (± 5685.914)			
Cycle 3 Day 1, 10 minutes Post-Dose (n=52)	36461.28 (± 11144.634)			
Cycle 3 Day 2, 24 hours Post-Dose (n=50)	27071.46 (± 8069.489)			
Cycle 3 Day 15, 336 hours Post-Dose (n=49)	4033.28 (± 1760.094)			
Cycle 4 Day 1, Pre-Dose (n=52)	2600.73 (± 2275.881)			
Cycle 4 Day 1, 10 minutes Post-Dose (n=50)	41823.31 (± 11761.223)			
Cycle 5 Day 1, Pre-Dose (n=43)	2690.61 (± 1254.886)			
Cycle 5 Day 1, 10 minutes Post-Dose (n=42)	43786.57 (± 15470.979)			
Cycle 6 Day 1, Pre-Dose (n=39)	2806.17 (± 1021.877)			
Cycle 6 Day 1, 10 minutes Post-Dose (n=39)	44936.89 (± 13827.929)			
Cycle 7 Day 1, Pre-Dose (n=38)	3889.94 (± 6201.351)			
Cycle 7 Day 1, 10 minutes Post-Dose (n=36)	41840.20 (± 12552.597)			
Cycle 8 Day 1, Pre-Dose (n=24)	2932.19 (± 1089.138)			
Cycle 8 Day 1, 10 minutes Post-Dose (n=24)	42013.77 (± 12754.334)			
Cycle 9 Day 1, Pre-Dose (n=15)	2959.26 (± 970.811)			
Cycle 9 Day 1, 10 minutes Post-Dose (n=14)	37300.95 (± 13442.910)			
Cycle 10 Day 1, Pre-Dose (n=11)	3189.16 (± 1484.258)			
Cycle 10 Day 1, 10 minutes Post-Dose (n=11)	38910.05 (± 6169.552)			
Cycle 11 Day 1, Pre-Dose (n=10)	3393.07 (± 1160.604)			
Cycle 11 Day 1, 10 minutes Post-Dose (n=10)	41238.25 (± 8081.750)			
Cycle 12 Day 1, Pre-Dose (n=10)	3270.44 (± 965.895)			
Cycle 12 Day 1, 10 minutes Post-Dose (n=10)	37550.64 (± 12459.906)			
Cycle 13 Day 1, Pre-Dose (n=9)	3406.00 (± 1067.414)			
Cycle 13 Day 1, 10 minutes Post-Dose (n=9)	35694.80 (± 3720.378)			
Cycle 14 Day 1, Pre-Dose (n=8)	2723.01 (± 1286.457)			
Cycle 14 Day 1, 10 minutes Post-Dose (n=8)	40848.64 (± 8704.538)			

Cycle 15 Day 1, Pre-Dose (n=8)	3111.63 (± 941.200)			
Cycle 15 Day 1, 10 minutes Post-Dose (n=8)	37091.56 (± 6644.258)			
Cycle 16 Day 1, Pre-Dose (n=8)	3159.38 (± 1017.679)			
Cycle 16 Day 1, 10 minutes Post-Dose (n=8)	39266.07 (± 9358.163)			
End of Treatment (n=50)	2340.49 (± 6715.837)			

Statistical analyses

No statistical analyses for this end point

Secondary: Monomethyl Auristatin E (MMAE) Serum Concentrations

End point title	Monomethyl Auristatin E (MMAE) Serum Concentrations

End point description:

Blood samples were collected and tested for MMAE serum concentrations. PK-evaluable Population was defined as participants with sufficient dosing and PK data to reliably estimate PK parameters. 'n' indicates number analysed is the number of participants with data available at the given time-point.

End point type	Secondary

End point timeframe:

Cycle 1 pre-dose and 10 minutes, 24 hours and 336 hours post-dose; Cycle 2 pre-dose and 10 minutes post-dose; Cycle 3 pre-dose and 10 minutes, 24 hours and 336 hours post-dose; Cycle 4 to 16 pre-dose and 10 minutes post-dose; EOT (Up to 24 months)

End point values	Brentuximab Vedotin 1.8 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	60			
Units: pg/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 1, Pre-Dose (n=59)	0.78 (± 5.976)			
Cycle 1 Day 1, 10 minutes Post-Dose (n=58)	591.09 (± 662.608)			
Cycle 1 Day 2, 24 hours Post-Dose (n=59)	6056.44 (± 3850.457)			
Cycle 1 Day 15, 336 hours Post-Dose (n=59)	746.12 (± 1123.502)			
Cycle 2 Day 1, Pre-Dose (n=57)	140.11 (± 111.036)			
Cycle 2 Day 1, 10 minutes Post-Dose (n=55)	539.38 (± 593.150)			
Cycle 3 Day 1, Pre-Dose (n=54)	130.62 (± 84.152)			
Cycle 3 Day 1, 10 minutes Post-Dose (n=52)	484.88 (± 701.402)			
Cycle 3 Day 2, 24 hours Post-Dose (n=51)	3076.75 (± 2330.510)			
Cycle 3 Day 15, 336 hours Post-Dose (n=49)	442.63 (± 259.360)			

Cycle 4 Day 1, Pre-Dose (n=52)	150.95 (± 123.841)			
Cycle 4 Day 1, 10 minutes Post-Dose (n=52)	497.20 (± 520.110)			
Cycle 5 Day 1, Pre-Dose (n=43)	153.95 (± 123.337)			
Cycle 5 Day 1, 10 minutes Post-Dose (n=42)	392.50 (± 320.346)			
Cycle 6 Day 1, Pre-Dose (n=39)	158.89 (± 109.024)			
Cycle 6 Day 1, 10 minutes Post-Dose (n=39)	369.53 (± 260.871)			
Cycle 7 Day 1, Pre-Dose (n=38)	185.91 (± 147.311)			
Cycle 7 Day 1, 10 minutes Post-Dose (n=37)	363.83 (± 237.883)			
Cycle 8 Day 1, Pre-Dose (n=24)	136.37 (± 86.947)			
Cycle 8 Day 1, 10 minutes Post-Dose (n=24)	303.43 (± 202.351)			
Cycle 9 Day 1, Pre-Dose (n=15)	142.30 (± 114.794)			
Cycle 9 Day 1, 10 minutes Post-Dose (n=14)	224.52 (± 159.833)			
Cycle 10 Day 1, Pre-Dose (n=11)	100.78 (± 57.270)			
Cycle 10 Day 1, 10 minutes Post-Dose (n=11)	253.73 (± 113.311)			
Cycle 11 Day 1, Pre-Dose (n=10)	158.09 (± 169.963)			
Cycle 11 Day 1, 10 minutes Post-Dose (n=10)	302.60 (± 175.869)			
Cycle 12 Day 1, Pre-Dose (n=10)	175.02 (± 141.192)			
Cycle 12 Day 1, 10 minutes Post-Dose (n=10)	382.52 (± 428.255)			
Cycle 13 Day 1, Pre-Dose (n=9)	146.76 (± 61.758)			
Cycle 13 Day 1, 10 minutes Post-Dose (n=9)	258.78 (± 108.871)			
Cycle 14 Day 1, Pre-Dose (n=8)	82.13 (± 22.661)			
Cycle 14 Day 1, 10 minutes Post-Dose (n=8)	204.29 (± 121.162)			
Cycle 15 Day 1, Pre-Dose (n=8)	133.78 (± 59.213)			
Cycle 15 Day 1, 10 minutes Post-Dose (n=8)	246.63 (± 98.399)			
Cycle 16 Day 1, Pre-Dose (n=8)	163.39 (± 114.821)			
Cycle 16 Day 1, 10 minutes Post-Dose (n=8)	264.63 (± 103.269)			
End of Treatment (n=50)	139.72 (± 220.211)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Antitherapeutic Antibodies (ATA)

End point title	Number of Participants With Antitherapeutic Antibodies (ATA)

End point description:

Blood samples were collected to assess the immunogenicity of brentuximab vedotin (ATA development) using a laboratory test. Confirmed ATA-positive response was categorized as transient (defined as 1 or 2 post-Baseline confirmed ATA-positive responses) and persistent (defined as more than 2 post-Baseline confirmed ATA positive responses) and neutralizing ATA (nATA) status. The confirmed ATA-positive samples were assessed for ATA titer and delineated into having high or low titers. 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:

Day 1 of every 3-week cycle up to 16 cycles and EOT (Up to 24 months)

End point values	Brentuximab Vedotin 1.8 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: participants				
ATA Positive	21			
Transient Positive	17			
Persistently Positive	4			
ATA Titer Low (≤25)	21			
ATA Titer High (>25)	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose of study drug up to 30 days post last dose of study drug (Up to 24 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 1.8 mg/kg

Reporting group description:

Brentuximab vedotin 1.8 mg/kg, 30-minute IV infusion, Day 1 of every 3-week cycle, until there is evidence of disease progression or unacceptable toxicity occurs (Up to 16 cycles). The dose could be decreased or delayed or discontinued in participants who develop treatment-associated non-hematologic toxicity, hematologic toxicity or peripheral neuropathy to brentuximab vedotin.

Serious adverse events	Brentuximab Vedotin 1.8 mg/kg		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 60 (18.33%)		
number of deaths (all causes)	22		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hodgkin's disease			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Vena cava thrombosis			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Tachycardia			

subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Serum sickness-like reaction			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Anaphylactic reaction			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Anxiety			

subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Device related sepsis			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	1 / 1		
Dengue fever			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Brentuximab Vedotin 1.8 mg/kg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	51 / 60 (85.00%)		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Lymphoedema			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	5		
Catheter site inflammation			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Chest pain			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Chills			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Extravasation			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Oedema			

subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	11 / 60 (18.33%)		
occurrences (all)	15		
Soft tissue inflammation			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Temperature regulation disorder			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Vaccination site pain			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Genital haemorrhage			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	5		
Dyspnoea			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Dyspnoea exertional			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	2		
Nasal congestion			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Upper respiratory tract inflammation			

subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences (all)	2		
Insomnia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences (all)	2		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences (all)	2		
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Blood thyroid stimulating hormone increased			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Haemoglobin decreased			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Lymphocyte count decreased			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		

Neutrophil count decreased subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 2		
Platelet count decreased subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 2		
Weight decreased subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Injury, poisoning and procedural complications			
Contusion subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Ligament sprain subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Procedural pain subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Cardiac disorders			
Tachycardia subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 2		
Nervous system disorders			
Autonomic neuropathy subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Dysgeusia subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Facial nerve disorder subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Headache subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 2		

Neuropathy peripheral subjects affected / exposed occurrences (all)	6 / 60 (10.00%) 9		
Paraesthesia subjects affected / exposed occurrences (all)	3 / 60 (5.00%) 4		
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	7 / 60 (11.67%) 8		
Polyneuropathy subjects affected / exposed occurrences (all)	5 / 60 (8.33%) 5		
Somnolence subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	5 / 60 (8.33%) 6		
Leukocytosis subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Leukopenia subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Neutropenia subjects affected / exposed occurrences (all)	6 / 60 (10.00%) 8		
Thrombocytopenia subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 2		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Eye disorders			

Diplopia subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 2		
Constipation subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 2		
Diarrhoea subjects affected / exposed occurrences (all)	6 / 60 (10.00%) 7		
Nausea subjects affected / exposed occurrences (all)	5 / 60 (8.33%) 9		
Toothache subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Vomiting subjects affected / exposed occurrences (all)	4 / 60 (6.67%) 6		
Hepatobiliary disorders Liver disorder subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 2		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	3 / 60 (5.00%) 4		
Dermatitis subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Dermatitis acneiform subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Dermatitis allergic			

subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Dermatitis contact			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences (all)	3		
Pruritus generalised			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences (all)	2		
Rash macular			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Rash maculo-papular			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Rash papular			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Rash pruritic			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Renal and urinary disorders			
Renal tubular disorder			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		

Endocrine disorders			
Autoimmune thyroiditis			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	5		
Back pain			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences (all)	3		
Bone pain			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Infections and infestations			
Breast cellulitis			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Bronchitis			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	4		
Conjunctivitis			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Coxsackie viral infection			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Dengue fever			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Device related infection			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		

Herpes zoster subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Hordeolum subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Influenza subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Klebsiella infection subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Nasopharyngitis subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 3		
Oral herpes subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 3		
Pseudomonas infection subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Sinusitis subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Subcutaneous abscess subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 2		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	5 / 60 (8.33%) 6		
Viral infection subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 2		
Metabolism and nutrition disorders Decreased appetite			

subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	4		
Hyperuricaemia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	3		
Hyperglycaemia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	4		
Hypomagnesaemia			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported