



Clinical trial results:

An Open-Label Study of Brentuximab Vedotin+Adriamycin, Vinblastine, and Dacarbazine in Pediatric Patients With Advanced Stage Newly Diagnosed Hodgkin Lymphoma

Summary

EudraCT number	2015-004112-38
Trial protocol	IT ES
Global end of trial date	24 September 2021

Results information

Result version number	v1 (current)
This version publication date	08 April 2022
First version publication date	08 April 2022

Trial information

Trial identification

Sponsor protocol code	C25004
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02979522
WHO universal trial number (UTN)	U1111-1171-0984

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-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	09 September 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	24 September 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to assess the safety, tolerability, and anti-tumor activity, as well as confirm the recommended dose of brentuximab vedotin (ADCETRIS) in combination with a multiagent chemotherapy regimen, doxorubicin (Adriamycin), vinblastine, and dacarbazine, in pediatric participants with advanced stage newly diagnosed classical CD30+ Hodgkin Lymphoma (HL).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 September 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 12
Country: Number of subjects enrolled	Brazil: 30
Country: Number of subjects enrolled	Italy: 15
Country: Number of subjects enrolled	Japan: 2
Worldwide total number of subjects	59
EEA total number of subjects	15

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)	11
Adolescents (12-17 years)	48

Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants with advanced stage newly diagnosed, classical CD30+ Hodgkin Lymphoma (HL) took part in the study at 14 investigative sites in the United States, Italy, Brazil and Japan from 06 September 2017 to 24 September 2021.

Pre-assignment

Screening details:

Participants with advanced stage newly diagnosed, classical CD30+ HL were received brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine(A+AVD). Data for Phase 2 endpoints is reported for Phase 2 participants only and all participants treated in Phase 1 with additional enrolled participants in Phase 2.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase 1: Brentuximab Vedotin 48 mg/m ² + AVD

Arm description:

Brentuximab vedotin 48 mg/m² (A), intravenous infusion, once on Days 1 and 15 of each 28-day cycle approximately 1 hour after administration of doxorubicin 25 mg/m², vinblastine 6 mg/m², and dacarbazine 375 mg/m² (AVD), intravenous infusion, once on Days 1 and 15 of each 28-day cycle for up to 6 cycles.

Arm type	Experimental
Investigational medicinal product name	Brentuximab vedotin
Investigational medicinal product code	
Other name	Adcetris
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use

Dosage and administration details:

Brentuximab vedotin 48 mg/m² infusion once on Days 1 and 15 of each 28-day cycle for up to 6 cycles.

Investigational medicinal product name	Vinblastine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Vinblastine 6 mg/m² infusion once on Days 1 and 15 of each 28-day cycle for up to 6 cycles.

Investigational medicinal product name	Dacarbazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dacarbazine 375 mg/m² infusion once on Days 1 and 15 of each 28-day cycle for up to 6 cycles.

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	Adriamycin
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Doxorubicin 25 mg/m ² infusion once on Days 1 and 15 of each 28-day cycle for up to 6 cycles.	
Arm title	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD

Arm description:

Brentuximab vedotin 48 mg/m² (A), intravenous infusion, once on Days 1 and 15 of each 28-day cycle approximately 1 hour after administration of doxorubicin 25 mg/m², vinblastine 6 mg/m², and dacarbazine 375 mg/m² (AVD), intravenous infusion, once on Days 1 and 15 of each 28-day cycle for up to 6 cycles.

Arm type	Experimental
Investigational medicinal product name	Brentuximab vedotin
Investigational medicinal product code	
Other name	Adcetris
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use

Dosage and administration details:

Brentuximab vedotin 48 mg/m² infusion once on Days 1 and 15 of each 28-day cycle for up to 6 cycles.

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	Adriamycin
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Doxorubicin 25 mg/m² infusion once on Days 1 and 15 of each 28-day cycle for up to 6 cycles.

Investigational medicinal product name	Vinblastine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Vinblastine 6 mg/m² infusion once on Days 1 and 15 of each 28-day cycle for up to 6 cycles.

Investigational medicinal product name	Dacarbazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dacarbazine 375 mg/m² infusion once on Days 1 and 15 of each 28-day cycle for up to 6 cycles.

Number of subjects in period 1	Phase 1: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD
Started	8	51
Completed	8	51

Baseline characteristics

Reporting groups

Reporting group title	Phase 1: Brentuximab Vedotin 48 mg/m ² + AVD
Reporting group description: Brentuximab vedotin 48 mg/m ² (A), intravenous infusion, once on Days 1 and 15 of each 28-day cycle approximately 1 hour after administration of doxorubicin 25 mg/m ² , vinblastine 6 mg/m ² , and dacarbazine 375 mg/m ² (AVD), intravenous infusion, once on Days 1 and 15 of each 28-day cycle for up to 6 cycles.	
Reporting group title	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD
Reporting group description: Brentuximab vedotin 48 mg/m ² (A), intravenous infusion, once on Days 1 and 15 of each 28-day cycle approximately 1 hour after administration of doxorubicin 25 mg/m ² , vinblastine 6 mg/m ² , and dacarbazine 375 mg/m ² (AVD), intravenous infusion, once on Days 1 and 15 of each 28-day cycle for up to 6 cycles.	

Reporting group values	Phase 1: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Total
Number of subjects	8	51	59
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)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	12.4	13.9	
standard deviation	± 3.81	± 2.88	-
Gender categorical Units: Subjects			
Female	4	24	28
Male	4	27	31
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	21	23
Not Hispanic or Latino	6	26	32
Unknown or Not Reported	0	4	4
Race/Ethnicity Units: Subjects			
Asian	0	3	3
Black or African American	0	12	12
White	8	26	34

Brown or Mulatto	0	9	9
Unknown or Not Reported	0	1	1
Region of Enrollment			
Units: Subjects			
United States	2	10	12
Japan	0	2	2
Italy	5	10	15
Brazil	1	29	30
Weight			
Units: kilograms (kg)			
arithmetic mean	45.91	49.91	
standard deviation	± 18.867	± 15.649	-

Subject analysis sets

Subject analysis set title	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD
Subject analysis set type	Full analysis

Subject analysis set description:

Brentuximab vedotin 48 mg/m² (A), intravenous infusion, once on Days 1 and 15 of each 28-day cycle approximately 1 hour after administration of doxorubicin 25 mg/m², vinblastine 6 mg/m², and dacarbazine 375 mg/m² (AVD), intravenous infusion, once on Days 1 and 15 of each 28-day cycle for up to 6 cycles.

Reporting group values	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD		
Number of subjects	59		
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	0		
standard deviation	± 0		
Gender categorical			
Units: Subjects			
Female			
Male			
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino			
Not Hispanic or Latino			
Unknown or Not Reported			

Race/Ethnicity Units: Subjects			
Asian Black or African American White Brown or Mulatto Unknown or Not Reported			
Region of Enrollment Units: Subjects			
United States Japan Italy Brazil			
Weight Units: kilograms (kg) arithmetic mean standard deviation	\pm		

End points

End points reporting groups

Reporting group title	Phase 1: Brentuximab Vedotin 48 mg/m ² + AVD
Reporting group description: Brentuximab vedotin 48 mg/m ² (A), intravenous infusion, once on Days 1 and 15 of each 28-day cycle approximately 1 hour after administration of doxorubicin 25 mg/m ² , vinblastine 6 mg/m ² , and dacarbazine 375 mg/m ² (AVD), intravenous infusion, once on Days 1 and 15 of each 28-day cycle for up to 6 cycles.	
Reporting group title	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD
Reporting group description: Brentuximab vedotin 48 mg/m ² (A), intravenous infusion, once on Days 1 and 15 of each 28-day cycle approximately 1 hour after administration of doxorubicin 25 mg/m ² , vinblastine 6 mg/m ² , and dacarbazine 375 mg/m ² (AVD), intravenous infusion, once on Days 1 and 15 of each 28-day cycle for up to 6 cycles.	
Subject analysis set title	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD
Subject analysis set type	Full analysis
Subject analysis set description: Brentuximab vedotin 48 mg/m ² (A), intravenous infusion, once on Days 1 and 15 of each 28-day cycle approximately 1 hour after administration of doxorubicin 25 mg/m ² , vinblastine 6 mg/m ² , and dacarbazine 375 mg/m ² (AVD), intravenous infusion, once on Days 1 and 15 of each 28-day cycle for up to 6 cycles.	

Primary: Phase 1: Recommended Dose of Brentuximab Vedotin in Combination With Doxorubicin, Vinblastine, and Dacarbazine in a Pediatric Population

End point title	Phase 1: Recommended Dose of Brentuximab Vedotin in Combination With Doxorubicin, Vinblastine, and Dacarbazine in a Pediatric Population ^{[1][2]}
End point description: The recommended dose was determined after considering all safety data in phase 1 and assessing for dose limiting toxicities (DLTs) which are defined as the dose range at which less than or equal to (\leq) 1 of 6 evaluable participants experience DLT within the defined observation period (Cycle 1 + 28 days). This outcome measure is planned to be assessed only for participants treated in Phase 1 arm. The DLT-evaluable population included participants who had received at least 1 dose of study drug therapy and experienced a DLT or no DLT during the DLT observation period. Participants who received granulocyte colony stimulating factor (G-CSF) during the DLT observation period were excluded from the DLT-Evaluable Population.	
End point type	Primary
End point timeframe: From the first dose (Cycle 1) up to Day 56 (Cycle length=28 days)	

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 was available 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: The endpoint was planned to be reported in Phase 1 only.

End point values	Phase 1: Brentuximab Vedotin 48 mg/m ² + AVD			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: mg/m ²				
number (not applicable)	48			

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1: Percentage of Participants Who Experienced Adverse Events (AEs) From the First Dose of Protocol Therapy Through 30 Days After Administration of the Last Dose of Protocol Therapy

End point title	Phase 1: Percentage of Participants Who Experienced Adverse Events (AEs) From the First Dose of Protocol Therapy Through 30 Days After Administration of the Last Dose of Protocol Therapy ^{[3][4]}
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End point description:

AE means any untoward medical occurrence in a participant administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This outcome measure is planned to be assessed only for participants treated in Phase 1 arm. The safety population included participants who had received at least 1 dose of any study drug (A+AVD regimen).

End point type	Primary
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End point timeframe:

From first dose in Cycle 1 Day 1 until 30 days after the last dose of study drug in Cycle 6 Day 15 (up to Cycle 7 Day 15) (Cycle length=28 days)

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: Statistical analyses was available 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: The endpoint was planned to be reported in Phase 1 only.

End point values	Phase 1: Brentuximab Vedotin 48 mg/m ² + AVD			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: percentage of participants				
number (not applicable)	100			

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1: Percentage of Participants Who Experienced Serious Adverse Events (SAEs) From the First Dose of Protocol Therapy Through 30 Days After

Administration of the Last Dose of Protocol Therapy

End point title	Phase 1: Percentage of Participants Who Experienced Serious Adverse Events (SAEs) From the First Dose of Protocol Therapy Through 30 Days After Administration of the Last Dose of Protocol Therapy ^{[5][6]}
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End point description:

AE means any untoward medical occurrence in a participant administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. SAE is defined as any untoward medical occurrence that at any dose results in death, Is life-threatening, requires inpatient hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability or incapacity, Is a congenital anomaly/birth defect, Is a medically important event. The safety population included participants who had received at least 1 dose of any study drug (A+AVD regimen).

End point type	Primary
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End point timeframe:

From first dose in Cycle 1 Day 1 until 30 days after the last dose of study drug in Cycle 6 Day 15 (up to Cycle 7 Day 15) (Cycle length=28 days)

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: Statistical analyses was available 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: The endpoint was planned to be reported in Phase 1 only.

End point values	Phase 1: Brentuximab Vedotin 48 mg/m ² + AVD			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: percentage of participants				
number (not applicable)	13			

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Percentage of Participants Who Achieved a Complete Remission (CR) Per Independent Review Facility (IRF) Assessment Per International Working Group (IWG) Criteria at End of Treatment (EOT) Visit

End point title	Phase 2: Percentage of Participants Who Achieved a Complete Remission (CR) Per Independent Review Facility (IRF) Assessment Per International Working Group (IWG) Criteria at End of Treatment (EOT) Visit ^{[7][8]}
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End point description:

CR was defined as the disappearance of all evidence of disease as assessed by IRF as per IWG Criteria. The confidence interval was based on exact binomial distribution (Clopper-Pearson method). This outcome measure was planned to be assessed for all participants treated at the recommended dose in Phase 2. As prespecified in the statistical analysis plan (SAP), data for Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. Response-evaluable population included participants who received at least one dose of study drug, have measurable disease at baseline, and have at least one post-baseline disease assessment based on an independent review facility.

End point type	Primary			
End point timeframe:				
At end of treatment (EOT) visit 30 days after the last dose of study drug (at Month 7)				
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: Statistical analyses was available 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: The endpoint was planned to be reported in Phase 2 only.				
End point values	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	51	59		
Units: percentage of participants				
number (confidence interval 95%)	75 (60 to 86)	76 (63 to 86)		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Percentage of Participants Whose Disease Was Positron Emission Tomography (PET) Negative After 2 Cycles of Protocol Therapy Per IRF Assessment

End point title	Phase 2: Percentage of Participants Whose Disease Was Positron Emission Tomography (PET) Negative After 2 Cycles of Protocol Therapy Per IRF Assessment ^{[9][10]}
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End point description:

The Deauville score according to IRF assessment of response was used to evaluate the results of PET scans. PET negative after Cycle 2 was defined as an IRF Deauville score of (1 or 2 or 3). This outcome measure was planned to be assessed for all participants treated at the recommended dose in Phase 2. As prespecified in SAP, data for Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. Response-evaluable population included participants who received at least one dose of study drug, have measurable disease at baseline, and have at least one post-baseline disease assessment based on an independent review facility.

End point type	Primary
End point timeframe:	
From first dose of study drug up to Cycle 2 Day 25 (Each Cycle length=28 days)	

Notes:

[9] - 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 was available for this endpoint.

[10] - 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 endpoint was planned to be reported in Phase 2 only.

End point values	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	51	59		
Units: percentage of participants				
number (not applicable)	90	90		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Percentage of Participants Who Achieved a Partial Remission (PR) Per IRF Assessment Per IWG Criteria at EOT Visit

End point title	Phase 2: Percentage of Participants Who Achieved a Partial Remission (PR) Per IRF Assessment Per IWG Criteria at EOT Visit ^{[11][12]}
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End point description:

PR was defined as regression of measurable disease and no new sites as assessed by IRF as per IWG criteria. Percentage of participants in the response-evaluable population who achieved a partial response based on the IRF assessment at the EOT visit based on the IWG criteria are reported. The confidence interval was based on exact binomial distribution (Clopper-Pearson method). This outcome measure was planned to be assessed for all participants treated at the recommended dose in Phase 2. As prespecified in SAP, data for Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. Response-evaluable population included participants who received at least one dose of study drug, have measurable disease at baseline, and have at least one post-baseline disease assessment based on an independent review facility.

End point type	Primary
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End point timeframe:

At EOT visit 30 days after the last dose of study drug (at Month 7)

Notes:

[11] - 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 was available for this endpoint.

[12] - 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 endpoint was planned to be reported in Phase 2 only.

End point values	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	51	59		
Units: percentage of participants				
number (confidence interval 95%)	12 (6 to 20)	12 (5 to 23)		

Statistical analyses

Primary: Phase 2: Percentage of Participants Who Achieved an Overall Response Rate (ORR) Per IRF Assessment Per IWG Criteria at EOT Visit

End point title	Phase 2: Percentage of Participants Who Achieved an Overall Response Rate (ORR) Per IRF Assessment Per IWG Criteria at EOT Visit ^{[13][14]}
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End point description:

Overall response rate was defined as the percentage of participants with CR or PR as assessed by IRF using IWG criteria. CR was defined as the disappearance of all evidence of disease and PR was defined as regression of measurable disease and no new diseases. The confidence interval was based on exact binomial distribution (Clopper-Pearson method). This outcome measure was planned to be assessed for all participants treated at the recommended dose in Phase 2. As prespecified in SAP, data for Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. Response-evaluable population included participants who received at least one dose of study drug, have measurable disease at baseline, and have at least one post-baseline disease assessment based on an independent review facility.

End point type	Primary
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End point timeframe:

At EOT visit 30 days after the last dose of study drug (at Month 7)

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: Statistical analyses was available 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: The endpoint was planned to be reported in Phase 2 only.

End point values	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	51	59		
Units: percentage of participants				
number (confidence interval 95%)	86 (74 to 94)	88 (77 to 95)		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Percentage of Participants Who Were Able to Complete 6 Cycles of Protocol Therapy at the Recommended Dose

End point title	Phase 2: Percentage of Participants Who Were Able to Complete 6 Cycles of Protocol Therapy at the Recommended Dose ^{[15][16]}
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End point description:

This outcome measure was planned to be assessed for all participants treated at the recommended dose in Phase 2. As prespecified in SAP, data for Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. The safety population included participants who had received at least 1 dose of any study drug (A+AVD regimen).

End point type	Primary
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End point timeframe:

From first dose of study drug up to Cycle 6 (Each Cycle length=28 days)

Notes:

[15] - 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 was available for this endpoint.

[16] - 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 endpoint was planned to be reported in Phase 2 only.

End point values	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	51	59		
Units: percentage of participants				
number (not applicable)	100	100		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1: Mean Maximum Observed Serum Concentration (Cmax) of Brentuximab Vedotin Total Conjugated and Therapeutic Antibody (TAB)

End point title	Phase 1: Mean Maximum Observed Serum Concentration (Cmax) of Brentuximab Vedotin Total Conjugated and Therapeutic Antibody (TAB) ^{[17][18]}
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End point description:

This outcome measure is planned to be assessed only for participants treated in Phase 1 arm. The PK population included participants with sufficient data to enable calculation of at least 1 PK parameter. 'n'= Number analysed is number of participants with data available for analysis at the given time point.

End point type	Primary
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End point timeframe:

Days 1 and 15 of Cycles 1 and 3 pre-infusion and up to 30 minutes after the end of infusion (Cycle length=28 days)

Notes:

[17] - 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 was available for this endpoint.

[18] - 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 endpoint was planned to be reported in Phase 1 only.

End point values	Phase 1: Brentuximab Vedotin 48 mg/m ² + AVD			
Subject group type	Reporting group			
Number of subjects analysed	8 ^[19]			
Units: microgram per milliliter(mcg/mL)				

arithmetic mean (standard deviation)				
Conjugate Brentuximab Vedotin at Cycle 1 Day 1	22.6 (± 1.51)			
Conjugate Brentuximab Vedotin at Cycle 1 Day 15	23.1 (± 3.85)			
Conjugate Brentuximab Vedotin at Cycle 3 Day 1	26.7 (± 3.65)			
Conjugate Brentuximab Vedotin at Cycle 3 Day 15	27.3 (± 7.14)			
TAbs at Cycle 1 Day 1	24.9 (± 3.84)			
TAbs at Cycle 1 Day 15	25.5 (± 5.28)			
TAbs at Cycle 3 Day 1	29.6 (± 4.05)			
TAbs at Cycle 3 Day 15	28.1 (± 7.45)			

Notes:

[19] - n= 7,6,8,7,7,6,6,6

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Mean Maximum Observed Plasma Concentration (Cmax) of Monomethyl Auristatin E (MMAE)

End point title	Phase 1: Mean Maximum Observed Plasma Concentration (Cmax) of Monomethyl Auristatin E (MMAE) ^[20]
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End point description:

This outcome measure is planned to be assessed only for participants treated in Phase 1 arm. The PK population included participants with sufficient data to enable calculation of at least 1 PK parameter. 'n'= Number analyzed is number of participants with data available for analysis at the given time point.

End point type	Secondary
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End point timeframe:

Days 1 and 15 of Cycles 1 and 3 pre-infusion and up to 30 minutes after the end of infusion (Cycle length=28 days)

Notes:

[20] - 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 endpoint was planned to be reported in Phase 1 only.

End point values	Phase 1: Brentuximab Vedotin 48 mg/m ² + AVD			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: nanogram per milliliter (ng/ml)				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n=8)	5.51 (± 0.677)			
Cycle 1 Day 15 (n=6)	2.08 (± 0.677)			
Cycle 3 Day 1 (n=8)	1.38 (± 0.514)			
Cycle 3 Day 15 (n=7)	1.19 (± 0.366)			

Statistical analyses

Secondary: Phase 1: Mean Area Under the Serum Concentration-Time Curve From Day 0 to Day 15 (AUC0-15) of Brentuximab Vedotin and TAb

End point title	Phase 1: Mean Area Under the Serum Concentration-Time Curve From Day 0 to Day 15 (AUC0-15) of Brentuximab Vedotin and TAb ^[21]
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End point description:

This outcome measure is planned to be assessed only for participants treated in Phase 1 arm. The PK population included participants with sufficient data to enable calculation of at least 1 PK parameter, with data available for analyses. 'n'= Number analyzed is number of participants with data available for analysis at the given time point.

End point type	Secondary
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End point timeframe:

Days 1 and 15 of Cycles 1 and 3 pre-infusion and up to 30 minutes after the end of infusion (Cycle length=28 days)

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 endpoint was planned to be reported in Phase 1 only.

End point values	Phase 1: Brentuximab Vedotin 48 mg/m ² + AVD			
Subject group type	Reporting group			
Number of subjects analysed	7 ^[22]			
Units: day*microgram per milliliter(day*mcg/mL)				
arithmetic mean (standard deviation)				
AUC0-15d of Brentuximab Vedotin at Cycle 1 Day 1	42.3 (± 3.10)			
AUC0-15d of Brentuximab Vedotin at Cycle 1 Day 15	48.8 (± 5.83)			
AUC0-15d of Brentuximab Vedotin at Cycle 3 Day 1	72.7 (± 27.8)			
AUC0-15d of Brentuximab Vedotin at Cycle 3 Day 15	64.8 (± 13.5)			
AUC0-15d of TAb at Cycle 1 Day 1 (n=7)	80.6 (± 13.0)			
AUC0-15d of TAb at Cycle 1 Day 15 (n=6)	103 (± 14.6)			
AUC0-15d of TAb at Cycle 3 Day 1 (n=6)	127 (± 10.2)			
AUC0-15d of TAb at Cycle 3 Day 15 (n=6)	128 (± 34.4)			

Notes:

[22] - n=7,6,7,6,7,6,6,6

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Mean Area Under the Plasma Concentration-Time Curve From Day 0 to Day 15 (AUC0-15) of MMAE

End point title	Phase 1: Mean Area Under the Plasma Concentration-Time
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End point description:

This outcome measure is planned to be assessed only for participants treated in Phase 1 arm. The PK population included participants with sufficient data to enable calculation of at least 1 PK parameter, with data available for analyses. 'n'= Number analyzed is number of participants with data available for analysis at the given time point.

End point type	Secondary
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End point timeframe:

Days 1 and 15 of Cycles 1 and 3 pre-infusion and up to 30 minutes after the end of infusion (Cycle length=28 days)

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 endpoint was planned to be reported in Phase 1 only.

End point values	Phase 1: Brentuximab Vedotin 48 mg/m ² + AVD			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: day* nanogram per milliliter (day*ng/mL)				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n=7)	29.8 (± 21.2)			
Cycle 1 Day 15 (n=3)	13.1 (± 2.99)			
Cycle 3 Day 1 (n=7)	8.88 (± 2.53)			
Cycle 3 Day 15 (n=4)	7.17 (± 2.17)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Median Time to Reach Cmax (Tmax) of Brentuximab Vedotin and TAb in Serum

End point title	Phase 1: Median Time to Reach Cmax (Tmax) of Brentuximab Vedotin and TAb in Serum ^[24]
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End point description:

This outcome measure is planned to be assessed only for participants treated in Phase 1 arm. The PK population included participants with sufficient data to enable calculation of at least 1 PK parameter. 'n'= Number analyzed is number of participants with data available for analysis at the given time point.

End point type	Secondary
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End point timeframe:

Cycle 1-6: Days 1 and 15 pre-infusion and up to 30 minutes after the end of infusion (Cycle length=28 days)

Notes:

[24] - 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 endpoint was planned to be reported in Phase 1 only.

End point values	Phase 1: Brentuximab Vedotin 48 mg/m ² + AVD			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: hour				
median (full range (min-max))				
Tmax of Brentuximab Vedotin at Cycle 1 Day 1 (n=7)	1.00 (0.570 to 1.05)			
Tmax of Brentuximab Vedotin at Cycle 1 Day 15 n=6	0.915 (0.580 to 1.00)			
Tmax of Brentuximab Vedotin at Cycle 3 Day 1 (n=8)	1.00 (0.630 to 1.17)			
Tmax of Brentuximab Vedotin at Cycle 3 Day 15 n=7	0.830 (0.580 to 1.00)			
Tmax of TAb at Cycle 1 Day 1 (n=7)	1.00 (0.570 to 1.05)			
Tmax of TAb at Cycle 1 Day 15 n=6	0.915 (0.580 to 1.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Median Time to Reach Cmax (Tmax) of MMAE in Plasma

End point title	Phase 1: Median Time to Reach Cmax (Tmax) of MMAE in Plasma ^[25]
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End point description:

This outcome measure is planned to be assessed only for participants treated in Phase 1 arm. The PK population included participants with sufficient data to enable calculation of at least 1 PK parameter. 'n'= Number analyzed is number of participants with data available for analysis at the given time point.

End point type	Secondary
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End point timeframe:

Days 1 and 15 of Cycles 1 and 3 pre-infusion and up to 30 minutes after the end of infusion (Cycle length=28 days)

Notes:

[25] - 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 endpoint was planned to be reported in Phase 1 only.

End point values	Phase 1: Brentuximab Vedotin 48 mg/m ² + AVD			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: hour				
median (full range (min-max))				
Cycle 1 Day 1 (n=8)	44.9 (21.1 to 69.1)			
Cycle 1 Day 15 (n=6)	43.1 (41.2 to 45.9)			

Cycle 3 Day 1 (n=8)	48.0 (42.3 to 66.9)			
Cycle 3 Day 15 (n=7)	48.2 (20.8 to 67.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Percentage of Participants Who Achieved a CR Per IRF Assessment Per IWG Criteria at EOT Visit

End point title	Phase 1: Percentage of Participants Who Achieved a CR Per IRF Assessment Per IWG Criteria at EOT Visit ^[26]
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End point description:

CR was defined as the disappearance of all evidence of disease as assessed by IRF as per IWG Criteria. The confidence interval was based on exact binomial distribution (Clopper-Pearson method). This outcome measure was planned to be assessed only for participants treated in Phase 1 arm. Response-evaluable population included participants who received at least one dose of study drug, have measurable disease at baseline, and have at least one post-baseline disease assessment based on an independent review facility.

End point type	Secondary
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End point timeframe:

At EOT visit 30 days after the last dose of study drug (at Month 7)

Notes:

[26] - 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 endpoint was planned to be reported in Phase 1 only.

End point values	Phase 1: Brentuximab Vedotin 48 mg/m ² + AVD			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: percentage of participants				
number (confidence interval 95%)	88 (47 to 100)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Percentage of Participants Who Achieved a PR Per IRF Assessment Per IWG Criteria at EOT Visit

End point title	Phase 1: Percentage of Participants Who Achieved a PR Per IRF Assessment Per IWG Criteria at EOT Visit ^[27]
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End point description:

PR was defined as regression of measurable disease and no new diseases as per IWG Criteria based on IRF. The confidence interval was based on exact binomial distribution (Clopper-Pearson method). This outcome measure was planned to be assessed only for participants treated in Phase 1 arm. Response-evaluable population included participants who received at least one dose of study drug, have measurable disease at baseline, and have at least one post-baseline disease assessment based on an

independent review facility.

End point type	Secondary
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End point timeframe:

At EOT visit 30 days after the last dose of study drug (at Month 7)

Notes:

[27] - 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 endpoint was planned to be reported in Phase 1 only.

End point values	Phase 1: Brentuximab Vedotin 48 mg/m ² + AVD			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: percentage of participants				
number (confidence interval 95%)	13 (1 to 53)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Percentage of Participants Who Achieved an ORR Per IRF Assessment Per IWG Criteria at EOT Visit

End point title	Phase 1: Percentage of Participants Who Achieved an ORR Per IRF Assessment Per IWG Criteria at EOT Visit ^[28]
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End point description:

Overall response rate was defined as the percentage of participants with CR or PR as assessed by an IRF using IWG Revised Response Criteria. CR was defined as the disappearance of all evidence of disease and PR was defined as regression of measurable disease and no new sites. The confidence interval was based on exact binomial distribution (Clopper-Pearson method). This outcome measure was planned to be assessed only for participants treated in Phase 1 arm. Response-evaluable population included participants who received at least one dose of study drug, have measurable disease at baseline, and have at least one post-baseline disease assessment based on an independent review facility.

End point type	Secondary
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End point timeframe:

At EOT visit 30 days after the last dose of study drug (at Month 7)

Notes:

[28] - 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 endpoint was planned to be reported in Phase 1 only.

End point values	Phase 1: Brentuximab Vedotin 48 mg/m ² + AVD			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: percentage of participants				
number (confidence interval 95%)	100 (63 to 100)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Percentage of Participants Whose Disease Was PET Negative After 2 Cycles of Protocol Therapy Per IRF Assessment

End point title	Phase 1: Percentage of Participants Whose Disease Was PET Negative After 2 Cycles of Protocol Therapy Per IRF Assessment ^[29]
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End point description:

The Deauville score according to IRF assessment of response was used to evaluate the results of PET scans. PET negative after Cycle 2 was defined as an IRF Deauville score of (1 or 2 or 3). This outcome measure was planned to be assessed only for participants treated in Phase 1 arm. Response-evaluable population included participants who received at least one dose of study drug, have measurable disease at baseline, and have at least one post-baseline disease assessment based on an independent review facility.

End point type	Secondary
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End point timeframe:

From first dose of study drug up to Cycle 2 (Each Cycle length=28 days)

Notes:

[29] - 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 endpoint was planned to be reported in Phase 1 only.

End point values	Phase 1: Brentuximab Vedotin 48 mg/m ² + AVD			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: percentage of participants				
number (confidence interval 95%)	88 (47 to 100)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Percentage of Participants Whose Disease Was PET Positive After 6 Cycles of Protocol Therapy Per IRF Assessment

End point title	Phase 1: Percentage of Participants Whose Disease Was PET Positive After 6 Cycles of Protocol Therapy Per IRF Assessment ^[30]
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End point description:

The Deauville score according to IRF assessment of response was used to evaluate the results of PET scans. PET positive after Cycle 6 defined as an IRF Deauville score of (4 or 5). This outcome measure was planned to be assessed only for participants treated in Phase 1 arm. This outcome measure was

planned to be assessed only for participants treated in Phase 1 arm.

End point type	Secondary
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End point timeframe:

From first dose of study drug up to Cycle 6 (Each Cycle length=28 days)

Notes:

[30] - 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 endpoint was planned to be reported in Phase 1 only.

End point values	Phase 1: Brentuximab Vedotin 48 mg/m ² + AVD			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: percentage of participants				
number (confidence interval 95%)	13 (1 to 53)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Percentage of Participants Who Were Antitherapeutic Antibody (ATA) Positive, Persistently Positive or Transiently Positive, and Neutralizing Antitherapeutic Antibody (nATA) Positive

End point title	Phase 1: Percentage of Participants Who Were Antitherapeutic Antibody (ATA) Positive, Persistently Positive or Transiently Positive, and Neutralizing Antitherapeutic Antibody (nATA) Positive ^[31]
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End point description:

ATA positive was defined as participants who have a positive ATA in any postbaseline sample. Transiently ATA positive was defined as participants who have positive ATA in 1 or 2 postbaseline samples. Persistently ATA positive was defined as participants who have positive ATA in more than 2 postbaseline timepoints. Transiently ATA positive was defined as participants who have positive ATA in 1 or 2 postbaseline samples. nATA positive was defined as participants who have at least one positive nATA in any postbaseline ATA positive sample. Here, percentage of participants who were transiently or persistently ATA positive are considered as ATA positive. This outcome measure is planned to be assessed only for participants treated in Phase 1 arm. Immunogenicity population included participants who received at least 1 dose of study drug and had the baseline immunogenicity sample and at least 1 postbaseline immunogenicity sample assessment.

End point type	Secondary
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End point timeframe:

Up to 7 months

Notes:

[31] - 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 endpoint was planned to be reported in Phase 1 only.

End point values	Phase 1: Brentuximab Vedotin 48 mg/m ² + AVD			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: percentage of participants				
number (not applicable)				
Transiently ATA Positive	13			
Persistently ATA Positive	0			
nATA Positive	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Progression-free Survival (PFS)

End point title	Phase 2: Progression-free Survival (PFS) ^[32]
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End point description:

PFS (IRF):time from 1st dose until disease progression per IRF/death due to any cause,whichever occurred first. Endpoint was planned to be assessed for all participant treated at recommended dose in Phase 2.As per SAP,Phase 2 data was summarized and reported in 2 arms:Phases 2 and Phase 1+ Phase 2. Median and 95% CI was not estimable as most of the participants were censored. The safety/efficacy population included participants who received at least 1 dose of any drug in the A+AVD regimen.

End point type	Secondary
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End point timeframe:

Up to 24 months

Notes:

[32] - 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 endpoint was planned to be reported in Phase 2 only.

End point values	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	51	59		
Units: months				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Event-free Survival (EFS)

End point title	Phase 2: Event-free Survival (EFS) ^[33]
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End point description:

EFS: Time from first dose until any treatment failure: PD per IRF including progression events during follow-up period, failing to complete 6 cycles of treatment due to any reason or death due to any cause, whichever occurred first. EFS per IRF were censored on last adequate disease assessment date per IRF if none of above events occur during study. This endpoint was planned to be assessed for all participants treated at recommended dose in Phase 2. As prespecified in SAP, data for Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. The safety/efficacy population included participants who received at least 1 dose of any drug in the A+AVD regimen. For participants who do not have an objective PD and did not die at the last follow-up, EFS has been censored on the date of last adequate disease assessment.

End point type	Secondary
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End point timeframe:

Up to 24 months

Notes:

[33] - 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 endpoint was planned to be reported in Phase 2 only.

End point values	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	51	59		
Units: months				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Overall Survival (OS)

End point title	Phase 2: Overall Survival (OS) ^[34]
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End point description:

Overall survival was defined as time from first dose until death. In the absence of confirmation of death, survival time was censored at the last date the participant was known to be alive, including study closure. This outcome measure was planned to be assessed only for all participants treated at the recommended dose in Phase 2. As prespecified in SAP, data for Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. The safety/efficacy population included participants who received at least 1 dose of any drug in the A+AVD regimen. The safety/efficacy population included participants who received at least 1 dose of any drug in the A+AVD regimen.

End point type	Secondary
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End point timeframe:

Up to 24 months

Notes:

[34] - 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 endpoint was planned to be reported in Phase 2 only.

End point values	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	51	59		
Units: months				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Duration of Response (DOR)

End point title	Phase 2: Duration of Response (DOR) ^[35]
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End point description:

DOR per IRF in participants with a response (CR or PR per IRF) was defined as the time from start of the first objective tumor response (CR or PR per IRF) to the first subsequent PD or death due to any cause, whichever occurred first. This endpoint was planned to be assessed only for all participants treated at the recommended dose Phase 2. As prespecified in SAP, data for Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. Response Evaluable Population=Participants who received at least one dose of study drug, have measurable disease at baseline, and have at least one post-baseline disease assessment (assessments based on investigator assessments or assessments based on an independent review facility). For participants who do not have an objective PD and did not die at the last follow-up, DOR has been censored on the date of last adequate disease assessment.

End point type	Secondary
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End point timeframe:

Up to 24 months

Notes:

[35] - 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 endpoint was planned to be reported in Phase 2 only.

End point values	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	51	59		
Units: months				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Percentage of Participants Receiving Irradiation for HL

Following Study Treatment

End point title	Phase 2: Percentage of Participants Receiving Irradiation for HL Following Study Treatment ^[36]
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End point description:

This outcome measure was planned to be assessed only for all participants treated at the recommended dose in Phase 2. As prespecified in SAP, data for Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. The safety/efficacy population included participants who received at least 1 dose of any drug in the A+AVD regimen.

End point type	Secondary
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End point timeframe:

Up to 24 months

Notes:

[36] - 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 endpoint was planned to be reported in Phase 2 only.

End point values	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	51	59		
Units: percentage of participants				
number (confidence interval 95%)	25 (14 to 40)	25 (14 to 37)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Percentage of Participants Who Experienced AEs From the First Dose of Protocol Therapy Through 30 Days After Administration of the Last Dose of Protocol Therapy

End point title	Phase 2: Percentage of Participants Who Experienced AEs From the First Dose of Protocol Therapy Through 30 Days After Administration of the Last Dose of Protocol Therapy ^[37]
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End point description:

This outcome measure was planned to be assessed only for all participants treated at the recommended dose in Phase 2. As prespecified in SAP, data for Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. The safety population included participants who had received at least 1 dose of any study drug (A+AVD regimen).

End point type	Secondary
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End point timeframe:

From first dose in Cycle 1 Day 1 until 30 days after the last dose of study drug in Cycle 6 Day 15 (up to Cycle 7 Day 15) (Cycle length=28 days)

Notes:

[37] - 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 endpoint was planned to be reported in Phase 2 only.

End point values	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	51	59		
Units: percentage of participants				
number (not applicable)	100	100		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Percentage of Participants Who Experienced SAEs From the First Dose of Protocol Therapy Through 30 Days After Administration of the Last Dose of Protocol Therapy

End point title	Phase 2: Percentage of Participants Who Experienced SAEs From the First Dose of Protocol Therapy Through 30 Days After Administration of the Last Dose of Protocol Therapy ^[38]
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End point description:

This outcome measure was planned to be assessed only for all participants treated at the recommended dose in Phase 2. As prespecified in SAP, data for Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. The safety population included participants who had received at least 1 dose of any study drug (A+AVD regimen).

End point type	Secondary
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End point timeframe:

From first dose in Cycle 1 Day 1 until 30 days after the last dose of study drug in Cycle 6 Day 15 (up to Cycle 7 Day 15) (Cycle length=28 days)

Notes:

[38] - 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 endpoint was planned to be reported in Phase 2 only.

End point values	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	51	59		
Units: percentage of participants				
number (not applicable)	45	41		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Percentage of Participants Who Were ATA Positive, Persistently Positive, or Transiently Positive, and nATA Positive

End point title	Phase 2: Percentage of Participants Who Were ATA Positive,
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End point description:

ATA positive: participants who have a positive ATA in any postbaseline sample. Transiently ATA positive: participants who have positive ATA in 1 or 2 postbaseline samples. Persistently ATA positive was defined as participants who have positive ATA in more than 2 postbaseline timepoints. Transiently ATA positive: participants who have positive ATA in 1 or 2 postbaseline samples. nATA positive: participants who have at least one positive nATA in any postbaseline ATA positive sample. Here, percentage of participants who were transiently or persistently ATA positive are considered as ATA positive. This endpoint was planned to be assessed only for all participants treated at recommended dose in Phase 2. As prespecified in SAP, Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. Immunogenicity population: participants who received at least 1 dose of study drug and had the baseline immunogenicity sample and at least 1 postbaseline immunogenicity sample assessment.

End point type	Secondary
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End point timeframe:

From first dose until 30 days after the last dose of study drug (up to 7 months)

Notes:

[39] - 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 endpoint was planned to be reported in Phase 2 only.

End point values	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1 + 2: Brentuximab Vedotin 48 mg/m ² + AVD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	51	59		
Units: percentage of participants				
number (not applicable)				
Transiently ATA Positive	6	7		
Persistently ATA Positive	0	0		
nATA Positive	4	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Mean Serum Cmax of Brentuximab Vedotin and TAb

End point title	Phase 2: Mean Serum Cmax of Brentuximab Vedotin and
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End point description:

This outcome measure was planned to be assessed only for all participants treated at the recommended dose in Phase 2. As prespecified in SAP, data for Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. The PK population included participants with sufficient data to enable calculation of at least 1 PK parameter, with data available for analyses. 'n' = Number analyzed is number of participants with data available for analysis at the given time point.

End point type	Secondary
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End point timeframe:

Days 1 and 15 of Cycles 1 and 3 pre-infusion and up to 30 minutes after the end of infusion (Cycle length=28 days)

Notes:

[40] - 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 endpoint was planned to be reported in Phase 2 only.

End point values	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	50 ^[41]	57 ^[42]		
Units: µg/mL				
arithmetic mean (standard deviation)				
Cmax of Brentuximab Vedotin at Cycle 1 Day 1	23.1 (± 5.54)	23.0 (± 5.21)		
Cmax of Brentuximab Vedotin at Cycle 1 Day 15	25.3 (± 5.12)	24.9 (± 4.97)		
Cmax of Brentuximab Vedotin at Cycle 3 Day 1	27.4 (± 6.14)	27.3 (± 5.82)		
Cmax of Brentuximab Vedotin at Cycle 3 Day 15	25.4 (± 4.03)	25.8 (± 4.81)		
Cmax of TAb Vedotin at Cycle 1 Day 1	22.1 (± 5.34)	22.4 (± 5.23)		
Cmax of TAb Vedotin at Cycle 1 Day 15	26.5 (± 9.02)	26.4 (± 8.52)		
Cmax of TAb Vedotin at Cycle 3 Day 1	29.5 (± 8.89)	29.5 (± 8.44)		
Cmax of TAb Vedotin at Cycle 3 Day 15	32.2 (± 11.0)	31.4 (± 10.4)		

Notes:

[41] - n=50, 34, 47, 25, 48, 34, 46, 25

[42] - n=57,40, 55, 32, 55, 40, 52, 31

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Mean Plasma Cmax of MMAE

End point title	Phase 2: Mean Plasma Cmax of MMAE ^[43]
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End point description:

This outcome measure was planned to be assessed only for all participants treated at the recommended dose in Phase 2. As prespecified in SAP, data for Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. The PK population included participants with sufficient data to enable calculation of at least 1 PK parameter, with data available for analyses. 'n' = Number analyzed is number of participants with data available for analysis at the given time point.

End point type	Secondary
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End point timeframe:

Days 1 and 15 of Cycles 1 and 3 pre-infusion and up to 30 minutes after the end of infusion (Cycle length=28 days)

Notes:

[43] - 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 endpoint was planned to be reported in Phase 2 only.

End point values	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	46 ^[44]	54 ^[45]		
Units: ng/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 1	5.49 (± 2.62)	5.49 (± 2.80)		
Cycle 1 Day 15	2.95 (± 1.66)	2.81 (± 1.57)		

Cycle 3 Day 1	1.75 (± 0.643)	1.69 (± 0.635)		
Cycle 3 Day 15	1.74 (± 0.599)	1.61 (± 0.597)		

Notes:

[44] - n=46,31,45,24

[45] - n=54,37,53,31

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Mean Serum AUC0-15d of Brentuximab Vedotin and TAb

End point title	Phase 2: Mean Serum AUC0-15d of Brentuximab Vedotin and TAb ^[46]
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End point description:

This outcome measure was planned to be assessed only for all participants treated at the recommended dose in Phase 2. As prespecified in SAP, data for Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. The PK population included participants with sufficient data to enable calculation of at least 1 PK parameter, with data available for analyses. 'n'= Number analyzed is number of participants with data available for analysis at the given time point.

End point type	Secondary
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End point timeframe:

Days 1 and 15 of Cycles 1 and 3 pre-infusion and up to 30 minutes after the end of infusion (Cycle length=28 days)

Notes:

[46] - 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 endpoint was planned to be reported in Phase 2 only.

End point values	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	50 ^[47]	57 ^[48]		
Units: day*µg/mL				
arithmetic mean (standard deviation)				
AUC0-15d of Brentuximab Vedotin at Cycle 1 Day 1	49.7 (± 17.2)	48.8 (± 16.3)		
AUC0-15d of Brentuximab Vedotin at Cycle 1 Day 15	54.9 (± 22.2)	54.0 (± 20.6)		
AUC0-15d of Brentuximab Vedotin at Cycle 3 Day 1	62.6 (± 16.9)	63.9 (± 18.6)		
AUC0-15d of Brentuximab Vedotin at Cycle 3 Day 15	60.6 (± 11.1)	61.4 (± 11.5)		
AUC0-15d of TAb at Cycle 1 Day 1	77.2 (± 18.6)	77.6 (± 18.0)		
AUC0-15d of TAb at Cycle 1 Day 15	97.3 (± 28.7)	98.1 (± 27.0)		
AUC0-15d of TAb at Cycle 3 Day 1	119 (± 30.6)	120 (± 29.1)		
AUC0-15d of TAb at Cycle 3 Day 15	124 (± 21.6)	125 (± 24.1)		

Notes:

[47] - n=50, 34, 47, 24, 48, 33, 46, 23

[48] - n=57,40, 54, 30, 55, 39, 52, 29

Statistical analyses

Secondary: Phase 2: Mean Plasma AUC0-15 of MMAE

End point title	Phase 2: Mean Plasma AUC0-15 of MMAE ^[49]
End point description: This outcome measure was planned to be assessed only for all participants treated at the recommended dose in Phase 2. As prespecified in SAP, data for Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. The PK population included participants with sufficient data to enable calculation of at least 1 PK parameter, with data available for analyses. 'n'= Number analyzed is number of participants with data available for analysis at the given time point.	
End point type	Secondary
End point timeframe: Days 1 and 15 of Cycles 1 and 3 pre-infusion and up to 30 minutes after the end of infusion (Cycle length=28 days)	
Notes: [49] - 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 endpoint was planned to be reported in Phase 2 only.	

End point values	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	41 ^[50]	48 ^[51]		
Units: day*ng/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 1	31.2 (± 16.2)	31.0 (± 16.8)		
Cycle 1 Day 15	18.4 (± 11.9)	17.9 (± 11.4)		
Cycle 3 Day 1	11.5 (± 5.16)	11.1 (± 4.93)		
Cycle 3 Day 15	12.3 (± 6.12)	11.3 (± 5.90)		

Notes:

[50] - n=40, 28, 41, 16

[51] - n=47, 31, 48, 20

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Median Tmax of Brentuximab Vedotin and TAb in Serum

End point title	Phase 2: Median Tmax of Brentuximab Vedotin and TAb in Serum ^[52]
End point description: This outcome measure was planned to be assessed only for all participants treated at the recommended dose in Phase 2. As prespecified in SAP, data for Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. The PK population included participants with sufficient data to enable calculation of at least 1 PK parameter, with data available for analyses. 'n'= Number analyzed is number of participants with data available for analysis at the given time point.	
End point type	Secondary
End point timeframe: Days 1 and 15 of Cycles 1 and 3 pre-infusion and up to 30 minutes after the end of infusion (Cycle length=28 days)	

Notes:

[52] - 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 endpoint was planned to be reported in Phase 2 only.

End point values	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	50 ^[53]	57 ^[54]		
Units: hour				
median (full range (min-max))				
Tmax of Brentuximab Vedotin at Cycle 1 Day 1	1.03 (0.530 to 164)	1.00 (0.530 to 164)		
Tmax of Brentuximab Vedotin at Cycle 1 Day 15	1.00 (0.500 to 22.7)	1.00 (0.500 to 22.7)		
Tmax of Brentuximab Vedotin at Cycle 3 Day 1	1.00 (0.00 to 23.0)	1.00 (0.00 to 23.0)		
Tmax of Brentuximab Vedotin at Cycle 3 Day 15	1.00 (0.520 to 1.50)	1.00 (0.520 to 1.50)		
Tmax of TAb at Cycle 1 Day 1	1.01 (0.530 to 20.8)	1.00 (0.530 to 20.8)		
Tmax of TAb at Cycle 1 Day 15	1.00 (0.500 to 334)	1.00 (0.500 to 334)		
Tmax of TAb at Cycle 3 Day 1	1.00 (0.00 to 23.3)	1.00 (0.00 to 23.3)		
Tmax of TAb at Cycle 3 Day 15	1.00 (0.520 to 1.50)	1.00 (0.520 to 1.50)		

Notes:

[53] - n=50, 34, 47, 25, 48, 34, 46, 25

[54] - n=57,40, 55, 32, 55, 40, 52, 31

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Median Tmax of MMAE in Plasma

End point title	Phase 2: Median Tmax of MMAE in Plasma ^[55]
End point description:	
This outcome measure was planned to be assessed only for all participants treated at the recommended dose in Phase 2. As prespecified in SAP, data for Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. The PK population included participants with sufficient data to enable calculation of at least 1 PK parameter, with data available for analyses. "n"= Number analyzed is number of participants with data available for analysis at the given time point.	
End point type	Secondary
End point timeframe:	
Days 1 and 15 of Cycles 1 and 3 pre-infusion and up to 30 minutes after the end of infusion (Cycle length=28 days)	

Notes:

[55] - 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 endpoint was planned to be reported in Phase 2 only.

End point values	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	46 ^[56]	54 ^[57]		
Units: hour				
median (full range (min-max))				
Cycle 1 Day 1	44.1 (19.7 to 72.0)	44.4 (19.7 to 72.0)		
Cycle 1 Day 15	42.9 (20.0 to 72.0)	42.9 (20.0 to 72.0)		
Cycle 3 Day 1	44.9 (20.3 to 71.7)	45.3 (20.3 to 71.7)		
Cycle 3 Day 15	45.4 (20.0 to 71.7)	46.0 (20.0 to 71.7)		

Notes:

[56] - n=46,31,45,34

[57] - n=54,37,53,31

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Percentage of Participants Who Experienced Peripheral Neuropathy, Regardless of Seriousness, From the First Dose of Protocol Therapy

End point title	Phase 2: Percentage of Participants Who Experienced Peripheral Neuropathy, Regardless of Seriousness, From the First Dose of Protocol Therapy ^[58]
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End point description:

Peripheral Neuropathy (PN) was defined by the peripheral neuropathy standardized MedDRA query (SMQ) broad search. This outcome measure was planned to be assessed only for all participants treated at the recommended dose in Phase 2. As prespecified in SAP, data for Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. The safety population included participants who received at least 1 dose of any drug in the A+AVD regimen.

End point type	Secondary
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End point timeframe:

Up to 24 months

Notes:

[58] - 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 endpoint was planned to be reported in Phase 2 only.

End point values	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	51	59		
Units: percentage of participants				
number (not applicable)	20	19		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Time to Onset and Resolution for All Peripheral Neuropathy Events

End point title	Phase 2: Time to Onset and Resolution for All Peripheral Neuropathy Events ^[59]
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End point description:

Time to onset of first event was defined as time from first dose of study drug to onset of first treatment-emergent PN event. Time to resolution was calculated as the time from onset date to the date of resolution PN (SMQ) event. Participants with multiple resolved events were counted once at the longest time to resolution. Resolution was defined as an event outcome of resolved or resolved with sequelae. This outcome measure was planned to be assessed only for all participants treated at the recommended dose in Phase 2. As prespecified in SAP, data for Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. The safety population included participants who received at least 1 dose of any drug in the A+AVD regimen. Overall number analyzed signifies participants who had peripheral neuropathy were analyzed for this outcome measure, 'n' = number analyzed are participants with evaluable for the specific category.

End point type	Secondary
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End point timeframe:

Up to 24 months

Notes:

[59] - 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 endpoint was planned to be reported in Phase 2 only.

End point values	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	12 ^[60]	14 ^[61]		
Units: weeks				
median (full range (min-max))				
Time to Onset	5.93 (0.9 to 19.9)	5.93 (0.9 to 19.9)		
Time to Resolution	1.57 (0.3 to 100.3)	1.57 (0.3 to 100.3)		

Notes:

[60] - n=12,11

[61] - n=14,13

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Immune Reconstitution-Change From Baseline Immunoglobulin G Levels at End of Treatment (EOT)

End point title	Phase 2: Immune Reconstitution-Change From Baseline Immunoglobulin G Levels at End of Treatment (EOT) ^[62]
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End point description:

This outcome measure was planned to be assessed only for all participants treated at the recommended dose in Phase 2. As prespecified in SAP, data for Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. Immune Reconstitution Population included participants who received at least 1 dose of study drug and had a sufficient immune reconstitution blood sampling to allow for immune reconstitution evaluation. 'n'= Number analyzed= number of participants with data available for

analysis at the given time point.

End point type	Secondary
End point timeframe:	
Baseline and End of Treatment (Month 7)	

Notes:

[62] - 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 endpoint was planned to be reported in Phase 2 only.

End point values	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	50 ^[63]	58 ^[64]		
Units: g/L				
arithmetic mean (standard deviation)				
Baseline	16.518 (± 5.5306)	16.217 (± 5.2175)		
Change from Baseline at EOT	-4.822 (± 4.8964)	-4.675 (± 4.7204)		

Notes:

[63] - n=50,50

[64] - n=58,57

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Percentage of Participants With Low and High ATA Titer Values

End point title	Phase 1: Percentage of Participants With Low and High ATA Titer Values ^[65]
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End point description:

High and low ATA titer was defined for the ATA positive (transiently or persistently positive) participants only. High ATA titer was defined as participants who have at least one postbaseline ATA titer > 25. Low ATA titer was defined as participants whose postbaseline ATA titer are all ≤ 25. This outcome measure is planned to be assessed only for participants treated in Phase 1 arm. As prespecified in SAP, data for Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. Immunogenicity population included participants who received at least 1 dose of study drug and had the baseline immunogenicity sample and at least 1 postbaseline immunogenicity sample assessment.

Immunogenicity population included participants who received at least 1 dose of study drug and had the baseline immunogenicity sample and at least 1 postbaseline immunogenicity sample assessment.

End point type	Secondary
End point timeframe:	
Up to 6 months	

Notes:

[65] - 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 endpoint was planned to be reported in Phase 1 only.

End point values	Phase 1: Brentuximab Vedotin 48 mg/m ² + AVD			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: percentage of participants				
number (not applicable)				
ATA Titer low	13			
ATA Titer High	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Percentage of Participants With Low and High ATA Titer Values

End point title	Phase 2: Percentage of Participants With Low and High ATA Titer Values ^[66]
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End point description:

High and low ATA titer was defined for the ATA positive (transiently or persistently positive) participants only. High ATA titer was defined as participants who have at least one postbaseline ATA titer >25. Low ATA titer was defined as participants whose postbaseline ATA titer are all ≤25. This outcome measure was planned to be assessed only for all participants treated at the recommended dose in Phase 2. As prespecified in SAP, data for Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. Immunogenicity population included participants who received at least 1 dose of study drug and had the baseline immunogenicity sample and at least 1 postbaseline immunogenicity sample assessment.

End point type	Secondary
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End point timeframe:

Up to 6 months

Notes:

[66] - 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 endpoint was planned to be reported in Phase 2 only.

End point values	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	51	59		
Units: percentage of participants				
number (not applicable)				
ATA Titer Low	6	7		
ATA Titer High	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1 and 2: Mean Cmax of Brentuximab Vedotin in ATA Positive and ATA Negative Participants

End point title	Phase 1 and 2: Mean Cmax of Brentuximab Vedotin in ATA Positive and ATA Negative Participants
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End point description:

This outcome measure is planned to be assessed only for participants treated in Phase 1 arm. As prespecified in SAP, data for Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. No sufficient number of participants with positive ATA status was available, thus the impact of ATA status on the pharmacokinetic parameters could not be assessed. Hence data is not available for this outcome measure.

End point type	Secondary
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End point timeframe:

Cycle 1 and 3: Days 1 and 15 pre-infusion and up to 30 minutes after the end of infusion (Cycle length=28 days)

End point values	Phase 1: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	0 ^[67]	0 ^[68]	0 ^[69]	
Units: ng/mL				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[67] - Data not available for this endpoint, no sufficient number of participants with positive ATA status.

[68] - Data not available for this endpoint, no sufficient number of participants with positive ATA status.

[69] - Data not available for this endpoint, no sufficient number of participants with positive ATA status.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1 and 2: Mean AUC 0-15 of Brentuximab Vedotin in ATA Positive and ATA Negative Participants

End point title	Phase 1 and 2: Mean AUC 0-15 of Brentuximab Vedotin in ATA Positive and ATA Negative Participants
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End point description:

This outcome measure is planned to be assessed only for participants treated in Phase 1 arm. As prespecified in SAP, data for Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. No sufficient number of participants with positive ATA status was available, thus the impact of ATA status on the pharmacokinetic parameters could not be assessed. Hence data is not available for this outcome measure.

End point type	Secondary
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End point timeframe:

Cycle 1 and 3: Days 1 and 15 pre-infusion and up to 30 minutes after the end of infusion (Cycle length=28 days)

End point values	Phase 1: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	0 ^[70]	0 ^[71]	0 ^[72]	
Units: day*ng/mL				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[70] - Data not available for this endpoint, no sufficient number of participants with positive ATA status.

[71] - Data not available for this endpoint, no sufficient number of participants with positive ATA status.

[72] - Data not available for this endpoint, no sufficient number of participants with positive ATA status.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Percentage of Participants Achieving CR Per IRF Assessment Per IWG Criteria in ATA Positive and ATA Negative Participants

End point title	Phase 1: Percentage of Participants Achieving CR Per IRF Assessment Per IWG Criteria in ATA Positive and ATA Negative Participants ^[73]
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End point description:

CR was defined as the disappearance of all evidence of disease as assessed by IRF as per IWG Criteria. The data is reported per ATA status as categories. This outcome measure is planned to be assessed only for participants treated in Phase 1 arm. Immunogenicity population included participants who received at least 1 dose of study drug and had the baseline immunogenicity sample and at least 1 postbaseline immunogenicity sample assessment.

End point type	Secondary
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End point timeframe:

Up to 24 months

Notes:

[73] - 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 endpoint was planned to be reported in Phase 1 only.

End point values	Phase 1: Brentuximab Vedotin 48 mg/m ² + AVD			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: percentage of participants				
number (confidence interval 95%)				
ATA Negative who Achieved CR	86 (42 to 100)			
Transiently ATA Positive who Achieved CR	100 (3 to 100)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Number of ATA Positive and ATA Negative Participants With AEs and SAEs

End point title	Phase 1: Number of ATA Positive and ATA Negative Participants With AEs and SAEs ^[74]
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End point description:

This outcome measure is planned to be assessed only for participants treated in Phase 1 arm. The Safety Population included participants who received at least 1 dose of any drug in the A+AVD regimen, with data available for analyses.

End point type	Secondary
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End point timeframe:

Up to 24 months

Notes:

[74] - 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 endpoint was planned to be reported in Phase 1 only.

End point values	Phase 1: Brentuximab Vedotin 48 mg/m ² + AVD			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: participants				
number (not applicable)				
ATA Negative: AEs	7			
ATA Positive: AEs	1			
ATA Negative: SAEs	0			
ATA Positive: SAEs	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Mean Cmax of Brentuximab Vedotin in ATA Positive and ATA Negative Participants

End point title	Phase 2: Mean Cmax of Brentuximab Vedotin in ATA Positive and ATA Negative Participants ^[75]
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End point description:

This outcome measure was planned to be assessed only for all participants treated at the recommended dose in Phase 2. As prespecified in SAP, data for Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. No sufficient number of participants with positive ATA status was available, thus the impact of ATA status on the pharmacokinetic parameters could not be assessed. Hence data is not available for this outcome measure.

End point type	Secondary
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End point timeframe:

Cycle 1-6: Days 1 and 15 pre-infusion and up to 30 minutes after the end of infusion (Cycle length=28 days)

Notes:

[75] - 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 endpoint was planned to be reported in Phase 2 only.

End point values	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	0 ^[76]	0 ^[77]		
Units: ng/mL				
arithmetic mean (standard deviation)	()	()		

Notes:

[76] - Data not available for this endpoint, no sufficient number of participants with positive ATA status.

[77] - Data not available for this endpoint, no sufficient number of participants with positive ATA status.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Mean AUC 0-15 of Brentuximab Vedotin in ATA Positive and ATA Negative Participants

End point title	Phase 2: Mean AUC 0-15 of Brentuximab Vedotin in ATA Positive and ATA Negative Participants ^[78]
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End point description:

This outcome measure was planned to be assessed only for all participants treated at the recommended dose in Phase 2. As prespecified in SAP, data for Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. No sufficient number of participants with positive ATA status was available, thus the impact of ATA status on the pharmacokinetic parameters could not be assessed. Hence data is not available for this outcome measure.

End point type	Secondary
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End point timeframe:

Cycle 1-6: Days 1 and 15 pre-infusion and up to 30 minutes after the end of infusion (Cycle length=28 days)

Notes:

[78] - 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 endpoint was planned to be reported in Phase 2 only.

End point values	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	0 ^[79]	0 ^[80]		
Units: day*ng/mL				
arithmetic mean (standard deviation)	()	()		

Notes:

[79] - Data not available for this endpoint, no sufficient number of participants with positive ATA status.

[80] - Data not available for this endpoint, no sufficient number of participants with positive ATA status.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Percentage of Participants Achieving CR Per IRF Assessment Per IWG Criteria in ATA Positive and ATA Negative Participants

End point title	Phase 2: Percentage of Participants Achieving CR Per IRF
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End point description:

CR is defined as the disappearance of all evidence of disease as assessed by IRF as per IWG Criteria. This outcome measure was planned to be assessed only for all participants treated at the recommended dose in Phase 2. As prespecified in SAP, data for Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. Immunogenicity Population included participants who received at least 1 dose of study drug and had the baseline immunogenicity sample and at least 1 postbaseline immunogenicity sample assessment. 'n'= Number analyzed is the number of participants analyzed for the specified category.

End point type	Secondary
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End point timeframe:

Up to 24 months

Notes:

[81] - 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 endpoint was planned to be reported in Phase 2 only.

End point values	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	51 ^[82]	59 ^[83]		
Units: percentage of participants				
number (confidence interval 95%)				
ATA Negative	75 (60 to 86)	76 (63 to 87)		
Transiently ATA Positive	67 (9 to 99)	75 (19 to 99)		

Notes:

[82] - n=48,3

[83] - n=55,4

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Number of ATA Positive and ATA Negative Participants With AEs and SAEs

End point title	Phase 2: Number of ATA Positive and ATA Negative Participants With AEs and SAEs ^[84]
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End point description:

This outcome measure was planned to be assessed only for all participants treated at the recommended dose in Phase 2. As prespecified in SAP, data for Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. The Safety Population included participants who received at least 1 dose of any drug in the A+AVD regimen.

End point type	Secondary
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End point timeframe:

Up to 24 months

Notes:

[84] - 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 endpoint was planned to be reported in Phase 2 only.

End point values	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	51	59		
Units: participants				
number (not applicable)				
ATA Negative: AEs	48	55		
ATA Positive: AEs	3	4		
ATA Negative: SAEs	21	21		
ATA Positive: SAEs	2	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Immune Reconstitution-Change From Baseline in Immunoglobulin M at the End of Treatment (EOT)

End point title	Phase 2: Immune Reconstitution-Change From Baseline in Immunoglobulin M at the End of Treatment (EOT) ^[85]
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End point description:

This outcome measure was planned to be assessed only for all participants treated at the recommended dose in Phase 2. As prespecified in SAP, data for Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. Immune Reconstitution Population included participants who received at least 1 dose of study drug and had a sufficient immune reconstitution blood sampling to allow for immune reconstitution evaluation, with data available for analyses. 'n' = Number analyzed is number of participants with data available for analysis at the given time point.

End point type	Secondary
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End point timeframe:

Baseline, EOT [Month 7]

Notes:

[85] - 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 endpoint was planned to be reported in Phase 2 only.

End point values	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	48 ^[86]	56 ^[87]		
Units: g/L				
arithmetic mean (standard deviation)				
Baseline	1.275 (± 0.5065)	1.261 (± 0.4824)		
Change at EOT (Month 7)	1.261 (± 0.4824)	-0.375 (± 0.5766)		

Notes:

[86] - n=48,46

[87] - n=56,53

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Immune Reconstitution-Change From Baseline in Immunoglobulin A at EOT

End point title	Phase 2: Immune Reconstitution-Change From Baseline in Immunoglobulin A at EOT ^[88]
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End point description:

This outcome measure was planned to be assessed only for all participants treated at the recommended dose in Phase 2. As prespecified in SAP, data for Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. Immune Reconstitution Population included participants who received at least 1 dose of study drug and had a sufficient immune reconstitution blood sampling to allow for immune reconstitution evaluation. Overall number analyzed are the participants with data available for analyses. 'n' = Number analyzed= number of participants with data available for analysis at the given time point.

End point type	Secondary
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End point timeframe:

Baseline, EOT [Month 7]

Notes:

[88] - 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 endpoint was planned to be reported in Phase 2 only.

End point values	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	48 ^[89]	57 ^[90]		
Units: g/L				
arithmetic mean (standard deviation)				
Baseline	2.708 (± 1.2379)	2.671 (± 1.1879)		
Change from Baseline at EOT	-0.195 (± 1.0479)	-0.125 (± 1.0844)		

Notes:

[89] - n=48,47

[90] - n=57,54

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Immune Reconstitution-Change From Baseline in Tetanus at EOT

End point title	Phase 2: Immune Reconstitution-Change From Baseline in Tetanus at EOT ^[91]
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End point description:

This outcome measure was planned to be assessed only for all participants treated at the recommended dose in Phase 2. As prespecified in SAP, data for Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. Immune Reconstitution Population included participants who received at least 1 dose of study drug and had a sufficient immune reconstitution blood sampling to allow for immune reconstitution evaluation. Overall number analyzed are the number of participants with data available for analyses. Number analyzed =number of participants with data available for analysis at the given time point.

End point type	Secondary
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End point timeframe:

Baseline, EOT [Month 7]

Notes:

[91] - 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 endpoint was planned to be reported in Phase 2 only.

End point values	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	48 ^[92]	56 ^[93]		
Units: (IU)/mL				
arithmetic mean (standard deviation)				
Baseline	1.636 (± 2.5600)	1.935 (± 3.0358)		
Change from Baseline at EOT	-0.648 (± 1.3412)	-0.914 (± 2.2679)		

Notes:

[92] - n=48,42

[93] - n=56,49

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Immune Reconstitution-Change From Baseline in Haemophilus Influenzae B Antibody, IgG at EOT

End point title	Phase 2: Immune Reconstitution-Change From Baseline in Haemophilus Influenzae B Antibody, IgG at EOT ^[94]
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End point description:

This outcome measure was planned to be assessed only for all participants treated at the recommended dose in Phase 2. As prespecified in SAP, data for Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. Immune Reconstitution Population included participants who received at least 1 dose of study drug and had a sufficient immune reconstitution blood sampling to allow for immune reconstitution evaluation. Overall number analyzed are the number of participants with data available for analyses. Number analyzed= number of participants with data available for analysis at the given time point.

End point type	Secondary
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End point timeframe:

Baseline, EOT [Month 7]

Notes:

[94] - 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 endpoint was planned to be reported in Phase 2 only.

End point values	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	50 ^[95]	58 ^[96]		
Units: µg/mL				

arithmetic mean (standard deviation)				
Baseline	10.39 (± 27.017)	9.50 (± 25.167)		
Change from Baseline at EOT	-7.00 (± 24.258)	-6.03 (± 23.160)		

Notes:

[95] - n=50,49

[96] - n=58,55

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Immune Reconstitution-Change From Baseline Poliovirus Antibodies at EOT

End point title	Phase 2: Immune Reconstitution-Change From Baseline Poliovirus Antibodies at EOT ^[97]
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End point description:

This outcome measure was planned to be assessed only for all participants treated at the recommended dose in Phase 2. As prespecified in SAP, data for Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. Immune Reconstitution Population included participants who received at least 1 dose of study drug and had a sufficient immune reconstitution blood sampling to allow for immune reconstitution evaluation. Overall number analyzed are the number of participants with data available for analyses. 'n' = Number analyzed= number of participants with data available for analysis at the given time point.

End point type	Secondary
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End point timeframe:

Baseline, EOT [Month 7]

Notes:

[97] - 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 endpoint was planned to be reported in Phase 2 only.

End point values	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	50 ^[98]	58 ^[99]		
Units: ratio				
arithmetic mean (standard deviation)				
Baseline: Type I	0.02447 (± 0.027568)	0.02373 (± 0.028092)		
EOT: Type I	0.00913 (± 0.022423)	0.00845 (± 0.023091)		
Baseline: Type III	0.03641 (± 0.036709)	0.03432 (± 0.036653)		
EOT: Type III	0.01141 (± 0.029889)	0.01013 (± 0.028461)		

Notes:

[98] - n=50,50,50,50

[99] - n=58,56,58,56

Statistical analyses

Secondary: Phase 2: Immune Reconstitution-Change From Baseline in Poliovirus Antibodies Ratio at EOT

End point title	Phase 2: Immune Reconstitution-Change From Baseline in Poliovirus Antibodies Ratio at EOT ^[100]
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End point description:

This outcome measure was planned to be assessed only for all participants treated at the recommended dose in Phase 2. As prespecified in SAP, data for Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. Immune Reconstitution Population included participants who received at least 1 dose of study drug and had a sufficient immune reconstitution blood sampling to allow for immune reconstitution evaluation. Overall number analyzed are the number of participants with data available for analyses. 'n' = Number analyzed= number of participants with data available for analysis at the given time point.

End point type	Secondary
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End point timeframe:

Baseline, EOT [Month 7]

Notes:

[100] - 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 endpoint was planned to be reported in Phase 2 only.

End point values	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	48 ^[101]	56 ^[102]		
Units: mg/dl				
arithmetic mean (standard deviation)				
Baseline	2086.6 (± 615.62)	2045.1 (± 583.04)		
Change from Baseline at EOT	-582.3 (± 565.52)	-556.3 (± 553.97)		

Notes:

[101] - n=48,46

[102] - n=56,56

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Immune Reconstitution-Change From Baseline in Peripheral Blood CD34+A at EOT

End point title	Phase 2: Immune Reconstitution-Change From Baseline in Peripheral Blood CD34+A at EOT ^[103]
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End point description:

This outcome measure was planned to be assessed only for all participants treated at the recommended dose in Phase 2. As prespecified in SAP, data for Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. Immune Reconstitution Population included participants who received at least 1 dose of study drug and had a sufficient immune reconstitution blood sampling to allow for immune reconstitution evaluation. Overall number analyzed are the number of participants with data available for analyses. 'n' = Number analyzed= number of participants with data available for analysis at the given time point.

End point type	Secondary
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End point timeframe:

Baseline, EOT [Month 7]

Notes:

[103] - 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 endpoint was planned to be reported in Phase 2 only.

End point values	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	38 ^[104]	44 ^[105]		
Units: µL				
arithmetic mean (standard deviation)				
Baseline	4.182 (± 4.1227)	3.917 (± 3.8917)		
Change from Baseline at EOT	-1.512 (± 4.7075)	-1.456 (± 4.3472)		

Notes:

[104] - n=38,29

[105] - n=44,34

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Immune Reconstitution-Change From Baseline in Total Lymphocyte Count at EOT

End point title	Phase 2: Immune Reconstitution-Change From Baseline in Total Lymphocyte Count at EOT ^[106]
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End point description:

This outcome measure was planned to be assessed only for all participants treated at the recommended dose in Phase 2. As prespecified in SAP, data for Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. Immune Reconstitution Population included participants who received at least 1 dose of study drug and had a sufficient immune reconstitution blood sampling to allow for immune reconstitution evaluation.

End point type	Secondary
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End point timeframe:

Baseline, EOT [Month 7]

Notes:

[106] - 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 endpoint was planned to be reported in Phase 2 only.

End point values	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	49 ^[107]	57 ^[108]		
Units: 10 ⁹ lymphocytes/L				
arithmetic mean (standard deviation)				

Baseline	1.8022 (± 0.95206)	1.7408 (± 0.91394)		
Change from Baseline at EOT	0.6736 (± 3.77611)	0.5965 (± 3.50121)		

Notes:

[107] - n=49,48

[108] - n=57,56

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Immune Reconstitution-Change From Baseline in the Percentage of CD4+ (CD4+CD45RA-CD197- and CD4+CD45RA+CD197+) and CD8+ (CD8+CD45RA-CD197- and CD8+CD45RA-CD197+) Subset of Cells at EOT

End point title	Phase 2: Immune Reconstitution-Change From Baseline in the Percentage of CD4+ (CD4+CD45RA-CD197- and CD4+CD45RA+CD197+) and CD8+ (CD8+CD45RA-CD197- and CD8+CD45RA-CD197+) Subset of Cells at EOT ^[109]
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End point description:

This outcome measure was planned to be assessed only for all participants treated at the recommended dose in Phase 2. As prespecified in SAP, data for Phase 2 was summarized and reported in two arms: Phase 2 and Phase 1 + Phase 2. Immune Reconstitution Population included participants who received at least 1 dose of study drug and had a sufficient immune reconstitution blood sampling to allow for immune reconstitution evaluation. Overall number analyzed are the number of participants with data available for analyses. 'n' = Number analyzed= number of participants with data available for analysis at the given time point.

End point type	Secondary
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End point timeframe:

Baseline, EOT [Month 7]

Notes:

[109] - 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 endpoint was planned to be reported in Phase 2 only.

End point values	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1+ 2: Brentuximab Vedotin 48 mg/m ² + AVD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	32 ^[110]	39 ^[111]		
Units: percentage of CD4+ and CD8+ subset cells				
arithmetic mean (standard deviation)				
Baseline: CD4+CD45RA-CD197-	28.0 (± 12.76)	29.0 (± 13.42)		
Change from Baseline at EOT: CD4+CD45RA-CD197-	-5.0 (± 17.72)	-5.1 (± 16.44)		
Baseline: CD4+CD45RA-CD197+	23.7 (± 14.33)	22.3 (± 13.86)		
Change from Baseline at EOT: CD4+CD45RA-CD197+	13.0 (± 14.14)	12.6 (± 13.21)		
Baseline: CD4+CD45RA+CD197-	2.9 (± 3.41)	3.1 (± 3.22)		
Change from Baseline at EOT: CD4+CD45RA+CD197-	-0.7 (± 2.25)	-0.7 (± 2.41)		
Baseline: CD4+CD45RA+CD197+	46.2 (± 14.44)	46.3 (± 14.89)		
Change from Baseline at EOT: CD4+CD45RA+CD197+	-7.2 (± 11.60)	-6.8 (± 11.04)		
Baseline: CD8+CD45RA-CD197-	39.9 (± 19.32)	40.6 (± 20.00)		

Change from Baseline at EOT: CD8+CD45RA-CD197-	-11.5 (± 13.85)	-11.0 (± 14.33)		
Baseline: CD8+CD45RA-CD197+	2.4 (± 1.81)	2.3 (± 1.76)		
Change from Baseline at EOT: CD8+CD45RA-CD197+	1.6 (± 2.52)	2.1 (± 3.08)		
Baseline: CD8+CD45RA+CD197-	25.9 (± 15.43)	25.8 (± 14.60)		
Change from Baseline at EOT: CD8+CD45RA+CD197-	-6.0 (± 11.27)	-6.5 (± 11.83)		
Baseline: CD8+CD45RA+CD197+	31.3 (± 18.00)	30.8 (± 18.53)		
Change from Baseline at EOT: CD8+CD45RA+CD197+	15.7 (± 11.48)	15.4 (± 12.15)		

Notes:

[110] - n=39,29,29,23,39,29,39,29,39,29,35,26,39,29,39,29

[111] - n=32,23,32,29, 32,23,32, 23,32, 23, 28,20,32,23,32,23

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to 30 days post last dose (Up to approximately 4 years)

Adverse event reporting additional description:

The Safety Population included participants who received at least 1 dose of any drug in the A+AVD regimen. Data is reported in 2 arms: Phase 1 includes participants who received at least one dose of study drug in Phase 1 and continued to Phase 2 to receive the same drug; Phase 2 included participants who were enrolled directly in Phase 2.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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Reporting groups

Reporting group title	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD
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Reporting group description:

Brentuximab vedotin 48 mg/m² (A), intravenous infusion, once on Days 1 and 15 of each 28-day cycle approximately 1 hour after administration of doxorubicin 25 mg/m², vinblastine 6 mg/m², and dacarbazine 375 mg/m² (AVD), intravenous infusion, once on Days 1 and 15 of each 28-day cycle for up to 6 cycles.

Reporting group title	Phase 1: Brentuximab Vedotin 48 mg/m ² + AVD
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Reporting group description:

Brentuximab vedotin 48 mg/m² (A), intravenous infusion, once on Days 1 and 15 of each 28-day cycle approximately 1 hour after administration of doxorubicin 25 mg/m², vinblastine 6 mg/m², and dacarbazine 375 mg/m² (AVD), intravenous infusion, once on Days 1 and 15 of each 28-day cycle for up to 6 cycles. Participants who received at least one dose of study in Phase 1 and continued to receive the study drug in Phase 2 were included in this arm group.

Serious adverse events	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1: Brentuximab Vedotin 48 mg/m ² + AVD	
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 51 (45.10%)	1 / 8 (12.50%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	1 / 51 (1.96%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	1 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	1 / 51 (1.96%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vascular disorders			
Venous thrombosis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Intracardiac thrombus			
subjects affected / exposed	1 / 51 (1.96%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Peripheral motor neuropathy			
subjects affected / exposed	1 / 51 (1.96%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	1 / 51 (1.96%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	9 / 51 (17.65%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	9 / 17	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	3 / 51 (5.88%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	2 / 51 (3.92%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	1 / 51 (1.96%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	3 / 51 (5.88%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 51 (3.92%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	2 / 51 (3.92%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 51 (1.96%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 51 (3.92%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 51 (1.96%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			

subjects affected / exposed	1 / 51 (1.96%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 51 (1.96%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 51 (1.96%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 51 (1.96%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 51 (1.96%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 51 (1.96%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	2 / 51 (3.92%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bacteraemia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 51 (1.96%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 51 (1.96%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lip infection			
subjects affected / exposed	1 / 51 (1.96%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 51 (1.96%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 51 (1.96%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Phase 2: Brentuximab Vedotin 48 mg/m ² + AVD	Phase 1: Brentuximab Vedotin 48 mg/m ² + AVD	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	51 / 51 (100.00%)	8 / 8 (100.00%)	
Vascular disorders			
Hyperaemia			
subjects affected / exposed	0 / 51 (0.00%)	2 / 8 (25.00%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	20 / 51 (39.22%)	4 / 8 (50.00%)	
occurrences (all)	27	5	
Fatigue			
subjects affected / exposed	9 / 51 (17.65%)	3 / 8 (37.50%)	
occurrences (all)	12	6	
Asthenia			
subjects affected / exposed	3 / 51 (5.88%)	5 / 8 (62.50%)	
occurrences (all)	6	7	
Catheter site pain			
subjects affected / exposed	3 / 51 (5.88%)	1 / 8 (12.50%)	
occurrences (all)	3	1	
Pain			
subjects affected / exposed	6 / 51 (11.76%)	0 / 8 (0.00%)	
occurrences (all)	7	0	
Chills			
subjects affected / exposed	2 / 51 (3.92%)	1 / 8 (12.50%)	
occurrences (all)	3	1	
Influenza like illness			
subjects affected / exposed	3 / 51 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	4	0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 51 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Reproductive system and breast			

disorders			
Pelvic pain			
subjects affected / exposed	0 / 51 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	10 / 51 (19.61%)	3 / 8 (37.50%)	
occurrences (all)	11	3	
Cough			
subjects affected / exposed	8 / 51 (15.69%)	1 / 8 (12.50%)	
occurrences (all)	9	1	
Nasal congestion			
subjects affected / exposed	5 / 51 (9.80%)	2 / 8 (25.00%)	
occurrences (all)	5	4	
Rhinitis allergic			
subjects affected / exposed	3 / 51 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	4	0	
Pharyngeal erythema			
subjects affected / exposed	1 / 51 (1.96%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Laryngeal pain			
subjects affected / exposed	0 / 51 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Dyspnoea			
subjects affected / exposed	5 / 51 (9.80%)	0 / 8 (0.00%)	
occurrences (all)	6	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	6 / 51 (11.76%)	1 / 8 (12.50%)	
occurrences (all)	8	1	
Insomnia			
subjects affected / exposed	3 / 51 (5.88%)	1 / 8 (12.50%)	
occurrences (all)	3	2	
Investigations			
White blood cell count decreased			

subjects affected / exposed	20 / 51 (39.22%)	5 / 8 (62.50%)	
occurrences (all)	94	21	
Neutrophil count decreased			
subjects affected / exposed	18 / 51 (35.29%)	4 / 8 (50.00%)	
occurrences (all)	78	18	
Weight decreased			
subjects affected / exposed	12 / 51 (23.53%)	1 / 8 (12.50%)	
occurrences (all)	23	1	
Lymphocyte count decreased			
subjects affected / exposed	7 / 51 (13.73%)	0 / 8 (0.00%)	
occurrences (all)	32	0	
Polymerase chain reaction positive			
subjects affected / exposed	3 / 51 (5.88%)	1 / 8 (12.50%)	
occurrences (all)	6	1	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 51 (1.96%)	2 / 8 (25.00%)	
occurrences (all)	1	2	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 51 (1.96%)	1 / 8 (12.50%)	
occurrences (all)	1	7	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 51 (1.96%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Injury, poisoning and procedural complications			
Nail avulsion			
subjects affected / exposed	0 / 51 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	5 / 51 (9.80%)	0 / 8 (0.00%)	
occurrences (all)	6	0	
Palpitations			
subjects affected / exposed	0 / 51 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Nervous system disorders			

Headache			
subjects affected / exposed	14 / 51 (27.45%)	5 / 8 (62.50%)	
occurrences (all)	20	7	
Dizziness			
subjects affected / exposed	6 / 51 (11.76%)	1 / 8 (12.50%)	
occurrences (all)	7	1	
Peripheral sensory neuropathy			
subjects affected / exposed	3 / 51 (5.88%)	2 / 8 (25.00%)	
occurrences (all)	4	4	
Paraesthesia			
subjects affected / exposed	3 / 51 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	3	0	
Peripheral motor neuropathy			
subjects affected / exposed	3 / 51 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	3	0	
Dysgeusia			
subjects affected / exposed	1 / 51 (1.96%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	20 / 51 (39.22%)	8 / 8 (100.00%)	
occurrences (all)	170	40	
Anaemia			
subjects affected / exposed	12 / 51 (23.53%)	1 / 8 (12.50%)	
occurrences (all)	27	1	
Leukopenia			
subjects affected / exposed	5 / 51 (9.80%)	1 / 8 (12.50%)	
occurrences (all)	7	2	
Thrombocytopenia			
subjects affected / exposed	1 / 51 (1.96%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Eye disorders			
Conjunctival hyperaemia			
subjects affected / exposed	1 / 51 (1.96%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Eyelid oedema			

subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	1 / 8 (12.50%) 1	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	42 / 51 (82.35%)	8 / 8 (100.00%)	
occurrences (all)	139	65	
Nausea			
subjects affected / exposed	36 / 51 (70.59%)	8 / 8 (100.00%)	
occurrences (all)	107	24	
Stomatitis			
subjects affected / exposed	21 / 51 (41.18%)	4 / 8 (50.00%)	
occurrences (all)	24	6	
Abdominal pain			
subjects affected / exposed	21 / 51 (41.18%)	2 / 8 (25.00%)	
occurrences (all)	40	2	
Constipation			
subjects affected / exposed	17 / 51 (33.33%)	4 / 8 (50.00%)	
occurrences (all)	31	6	
Diarrhoea			
subjects affected / exposed	10 / 51 (19.61%)	4 / 8 (50.00%)	
occurrences (all)	20	5	
Abdominal pain upper			
subjects affected / exposed	7 / 51 (13.73%)	8 / 8 (100.00%)	
occurrences (all)	7	5	
Oral pain			
subjects affected / exposed	7 / 51 (13.73%)	1 / 8 (12.50%)	
occurrences (all)	7	1	
Odynophagia			
subjects affected / exposed	3 / 51 (5.88%)	2 / 8 (25.00%)	
occurrences (all)	4	2	
Dyspepsia			
subjects affected / exposed	2 / 51 (3.92%)	1 / 8 (12.50%)	
occurrences (all)	2	1	
Toothache			
subjects affected / exposed	3 / 51 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	3	0	

Mouth ulceration subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1	1 / 8 (12.50%) 1	
Hepatobiliary disorders Hepatotoxicity subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	1 / 8 (12.50%) 1	
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	11 / 51 (21.57%) 13	0 / 8 (0.00%) 0	
Pruritus subjects affected / exposed occurrences (all)	7 / 51 (13.73%) 8	0 / 8 (0.00%) 0	
Rash maculo-papular subjects affected / exposed occurrences (all)	4 / 51 (7.84%) 6	2 / 8 (25.00%) 2	
Dermatitis contact subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 3	1 / 8 (12.50%) 1	
Dry skin subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 2	1 / 8 (12.50%) 1	
Erythema subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1	2 / 8 (25.00%) 2	
Papule subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 2	1 / 8 (12.50%) 1	
Rash subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 3	0 / 8 (0.00%) 0	
Urticaria subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 3	0 / 8 (0.00%) 0	
Dermatitis acneiform			

subjects affected / exposed	1 / 51 (1.96%)	1 / 8 (12.50%)	
occurrences (all)	2	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	12 / 51 (23.53%)	2 / 8 (25.00%)	
occurrences (all)	16	6	
Arthralgia			
subjects affected / exposed	8 / 51 (15.69%)	1 / 8 (12.50%)	
occurrences (all)	12	1	
Bone pain			
subjects affected / exposed	8 / 51 (15.69%)	0 / 8 (0.00%)	
occurrences (all)	19	0	
Pain in extremity			
subjects affected / exposed	6 / 51 (11.76%)	2 / 8 (25.00%)	
occurrences (all)	6	3	
Myalgia			
subjects affected / exposed	5 / 51 (9.80%)	1 / 8 (12.50%)	
occurrences (all)	5	1	
Pain in jaw			
subjects affected / exposed	6 / 51 (11.76%)	0 / 8 (0.00%)	
occurrences (all)	7	0	
Groin pain			
subjects affected / exposed	2 / 51 (3.92%)	1 / 8 (12.50%)	
occurrences (all)	3	1	
Muscular weakness			
subjects affected / exposed	3 / 51 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal pain			
subjects affected / exposed	1 / 51 (1.96%)	2 / 8 (25.00%)	
occurrences (all)	1	2	
Spinal pain			
subjects affected / exposed	1 / 51 (1.96%)	2 / 8 (25.00%)	
occurrences (all)	1	2	
Infections and infestations			

Rhinitis			
subjects affected / exposed	7 / 51 (13.73%)	3 / 8 (37.50%)	
occurrences (all)	9	4	
Upper respiratory tract infection			
subjects affected / exposed	5 / 51 (9.80%)	1 / 8 (12.50%)	
occurrences (all)	5	1	
Conjunctivitis			
subjects affected / exposed	4 / 51 (7.84%)	2 / 8 (25.00%)	
occurrences (all)	4	6	
Oral herpes			
subjects affected / exposed	4 / 51 (7.84%)	1 / 8 (12.50%)	
occurrences (all)	4	1	
Influenza			
subjects affected / exposed	1 / 51 (1.96%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Pharyngitis			
subjects affected / exposed	3 / 51 (5.88%)	1 / 8 (12.50%)	
occurrences (all)	3	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	12 / 51 (23.53%)	2 / 8 (25.00%)	
occurrences (all)	21	2	
Dehydration			
subjects affected / exposed	5 / 51 (9.80%)	0 / 8 (0.00%)	
occurrences (all)	5	0	
Acidosis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Hyperuricaemia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Hypoalbuminaemia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 December 2019	The following changes were implemented as per Amendment 3: 1. Optional long-term follow-up procedures are added 2. Protocol signatory updates 3. Adjusted the total number of participating sites.
11 June 2021	The following changes were implemented as per Amendment 4: 1. Modifications in study conduct instituted in response to the COVID-19 pandemic. 2. Clarification of time points for analysis and reporting of study results. 3. Additional guidance pertaining to the long-term follow-up procedures. 4. Updated sponsor name.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported