



Clinical trial results:

A Phase 3, Randomized, Open-Label Study Evaluating the Efficacy of Axicabtagene Ciloleucel Versus Standard of Care Therapy in Subjects with Relapsed/Refractory Diffuse Large B Cell Lymphoma (ZUMA-7)

Summary

EudraCT number	2017-002261-22
Trial protocol	GB DE NL BE IT ES FR SE AT
Global end of trial date	25 November 2024

Results information

Result version number	v1 (current)
This version publication date	27 November 2025
First version publication date	27 November 2025

Trial information

Trial identification

Sponsor protocol code	KTE-C19-107
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03391466
WHO universal trial number (UTN)	-
Other trial identifiers	IND Number: 016278

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, CA, United States, 94404
Public contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com
Scientific contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 November 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 March 2021
Global end of trial reached?	Yes
Global end of trial date	25 November 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The goal of this clinical study is to assess whether axicabtagene ciloleucel therapy improves the clinical outcome compared with standard of care second-line therapy in participants with relapsed/refractory diffuse large B-cell lymphoma (DLBCL).

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 January 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 250
Country: Number of subjects enrolled	Netherlands: 25
Country: Number of subjects enrolled	Canada: 20
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Israel: 6
Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Switzerland: 1

Worldwide total number of subjects	359
EEA total number of subjects	66

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	251
From 65 to 84 years	108
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in the United States, Canada, Israel, European countries, the United Kingdom, and Australia.

Pre-assignment

Screening details:

437 participants were screened.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Axicabtagene Ciloleucel

Arm description:

Participants received cyclophosphamide 500 mg/m²/day intravenous (IV) infusion and fludarabine 30 mg/m²/day IV infusion conditioning chemotherapy for 3 days followed by axicabtagene ciloleucel administered as a single IV infusion at a target dose of 2×10^6 anti-cluster of differentiation antigen (CD) 19 chimeric antigen receptor (CAR) transduced autologous T cells/kg on Day 0.

Arm type	Experimental
Investigational medicinal product name	Axicabtagene Ciloleucel
Investigational medicinal product code	KTE-C19
Other name	Yescarta ®
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered intravenously

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

Dosage and administration details:

Administered intravenously

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

Dosage and administration details:

Administered intravenously

Arm title	Standard of Care Therapy
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Arm description:

Participants received 2 or 3, 21-day cycles of second-line chemotherapy regimen:

R-ICE:rituximab 375mg/m² before chemotherapy, ifosfamide 5g/m² 24 hours continuous infusion (CI) on Day2+mesna, carboplatin area under curve (AUC)5 Day 2, maximum dose 800mg, etoposide 100mg/m²/day on Days 1-3;

R-ESHAP:rituximab 375mg/m² Day 1, etoposide 40mg/m²/day IV on Days 1-4, methylprednisolone

500mg/day IV on Days 1-4 or 5, cisplatin at 25mg/m²/day CI Days 1-4, cytarabine 2g/m² on Day5; R-GDP:rituximab 375mg/m² Day1 (or Day8), gemcitabine 1g/m² on Days 1 and 8, dexamethasone 40mg on Days 1-4, cisplatin 75mg/m² Day 1 or carboplatin AUC=5; or R-DHAP:rituximab 375mg/m² before chemotherapy, dexamethasone 40mg/day on Days 1-4, high dose cytarabine 2g/m² every 12 hours for 2 doses on Day 2 following platinum, cisplatin 100mg/m² 24 hours CI on Day 1 or oxaliplatin 100mg/m². Participants who responded to second-line chemotherapy got high dose therapy and autologous stem cell transplant.

Arm type	Active comparator
Investigational medicinal product name	Platinum-containing Salvage Chemotherapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Platinum-containing salvage chemotherapy (Rituximab-ifosfamide, carboplatin, etoposide (R-ICE), Rituximab-dexamethasone, cytarabine, cisplatin, oxaliplatin (R-DHAP), Rituximab-etoposide, methylprednisolone, cisplatin, cytarabine(R-ESHAP), or Rituximab-gemcitabine, dexamethasone, cisplatin/carboplatin (R-GDP) as selected by treating investigator).

Number of subjects in period 1	Axicabtagene Ciloleucel	Standard of Care Therapy
Started	180	179
Completed	2	67
Not completed	178	112
Rollover to Long-term Follow-up Study Criteria	80	-
Death	84	91
Reason Not Specified	2	2
Subject Withdrawal of Consent from Further Follow-	3	13
Investigator Decision	-	1
Lost to follow-up	9	5

Baseline characteristics

Reporting groups

Reporting group title	Axicabtagene Ciloleucel
Reporting group description:	
Participants received cyclophosphamide 500 mg/m ² /day intravenous (IV) infusion and fludarabine 30 mg/m ² /day IV infusion conditioning chemotherapy for 3 days followed by axicabtagene ciloleucel administered as a single IV infusion at a target dose of 2 x 10 ⁶ anti-cluster of differentiation antigen (CD) 19 chimeric antigen receptor (CAR) transduced autologous T cells/kg on Day 0.	
Reporting group title	Standard of Care Therapy
Reporting group description:	
Participants received 2 or 3, 21-day cycles of second-line chemotherapy regimen:	
R-ICE:rituximab 375mg/m ² before chemotherapy, ifosfamide 5g/m ² 24 hours continuous infusion (CI) on Day2+mesna, carboplatin area under curve (AUC)5 Day 2, maximum dose 800mg, etoposide 100mg/m ² /day on Days 1-3;	
R-ESHAP:rituximab 375mg/m ² Day 1, etoposide 40mg/m ² /day IV on Days 1-4, methylprednisolone 500mg/day IV on Days 1-4 or 5, cisplatin at 25mg/m ² /day CI Days 1-4, cytarabine 2g/m ² on Day5;	
R-GDP:rituximab 375mg/m ² Day1 (or Day8), gemcitabine 1g/m ² on Days 1 and 8, dexamethasone 40mg on Days 1-4, cisplatin 75mg/m ² Day 1 or carboplatin AUC=5; or	
R-DHAP:rituximab 375mg/m ² before chemotherapy, dexamethasone 40mg/day on Days 1-4, high dose cytarabine 2g/m ² every 12 hours for 2 doses on Day 2 following platinum, cisplatin 100mg/m ² 24 hours CI on Day 1 or oxaliplatin 100mg/m ² .	
Participants who responded to second-line chemotherapy got high dose therapy and autologous stem cell transplant.	

Reporting group values	Axicabtagene Ciloleucel	Standard of Care Therapy	Total
Number of subjects	180	179	359
Age categorical			
Units: Subjects			
Between 18 and 65 years	129	121	250
>=65 years	51	58	109
Age continuous			
Units: years			
arithmetic mean	57.1	57.4	-
standard deviation	± 12.0	± 12.2	-
Gender categorical			
Units: Subjects			
Female	70	52	122
Male	110	127	237
Ethnicity			
Units: Subjects			
Hispanic or Latino	10	8	18
Not Hispanic or Latino	167	169	336
Unknown or Not Reported	3	2	5
Race			
Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	12	10	22
Native Hawaiian or Other Pacific Islander	2	1	3
Black or African American	11	7	18
White	145	152	297
More than one race	10	8	18

Unknown or Not Reported	0	0	0
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End points

End points reporting groups

Reporting group title	Axicabtagene Ciloleucel
Reporting group description: Participants received cyclophosphamide 500 mg/m ² /day intravenous (IV) infusion and fludarabine 30 mg/m ² /day IV infusion conditioning chemotherapy for 3 days followed by axicabtagene ciloleucel administered as a single IV infusion at a target dose of 2×10^6 anti-cluster of differentiation antigen (CD) 19 chimeric antigen receptor (CAR) transduced autologous T cells/kg on Day 0.	
Reporting group title	Standard of Care Therapy
Reporting group description: Participants received 2 or 3, 21-day cycles of second-line chemotherapy regimen: R-ICE:rituximab 375mg/m ² before chemotherapy, ifosfamide 5g/m ² 24 hours continuous infusion (CI) on Day2+mesna, carboplatin area under curve (AUC)5 Day 2, maximum dose 800mg, etoposide 100mg/m ² /day on Days 1-3; R-ESHAP:rituximab 375mg/m ² Day 1, etoposide 40mg/m ² /day IV on Days 1-4, methylprednisolone 500mg/day IV on Days 1-4 or 5, cisplatin at 25mg/m ² /day CI Days 1-4, cytarabine 2g/m ² on Day5; R-GDP:rituximab 375mg/m ² Day1 (or Day8), gemcitabine 1g/m ² on Days 1 and 8, dexamethasone 40mg on Days 1-4, cisplatin 75mg/m ² Day 1 or carboplatin AUC=5; or R-DHAP:rituximab 375mg/m ² before chemotherapy, dexamethasone 40mg/day on Days 1-4, high dose cytarabine 2g/m ² every 12 hours for 2 doses on Day 2 following platinum, cisplatin 100mg/m ² 24 hours CI on Day 1 or oxaliplatin 100mg/m ² . Participants who responded to second-line chemotherapy got high dose therapy and autologous stem cell transplant.	

Primary: Event Free Survival (EFS) Per Blinded Central Assessment

End point title	Event Free Survival (EFS) Per Blinded Central Assessment
End point description: EFS: Time from randomization to disease progression (PD), best response of stable disease (SD) up to Day 150, start of new anti-lymphoma therapy including stem cell transplant, or death from any cause. PD=Score 4 (uptake moderately > liver) or 5 (uptake markedly > liver and/or new lesions) with increased uptake from baseline; New fluorodeoxyglucose (FDG)-avid foci consistent with lymphoma rather than another etiology or in bone marrow; Individual node/lesion abnormal with longest diameter > 1.5 cm, $\geq 50\%$ increase from nadir; Splenic length increase > 50% of prior increase beyond baseline or ≥ 2 cm increase if no prior splenomegaly; New/recurrent splenomegaly, progression of non-measurable lesions, new lesion, or new/recurrent bone marrow involvement. KM estimates was used for analysis. Participants in Full Analysis Set were analyzed.	
End point type	Primary
End point timeframe: From randomization date up to a median follow-up: 24.9 months	

End point values	Axicabtagene Ciloleucel	Standard of Care Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180	179		
Units: months				
median (confidence interval 95%)	8.3 (4.5 to 15.8)	2.0 (1.6 to 2.8)		

Statistical analyses

Statistical analysis title	EFS - Axicabtagene Ciloleucel vs SOCT
Comparison groups	Axicabtagene Ciloleucel v Standard of Care Therapy
Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	< 0.0001 ^[2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.398
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.308
upper limit	0.514

Notes:

[1] - One-sided p-value based on log-rank test stratified by response to first-line therapy and second-line age-adjusted International Prognostic Index (IPI) as data collected on case report forms.

[2] - Stratified (randomization stratification factors) log-rank test.

Hazard ratio (95% confidence interval (CI)), stratified using randomization stratification factors

Secondary: Objective Response Rate (ORR) Per Blinded Central Assessment

End point title	Objective Response Rate (ORR) Per Blinded Central Assessment
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End point description:

ORR: % of participants with CR (Complete Metabolic Response (CMR); Complete Radiologic Response (CRR)) or PR (partial metabolic response (PMR); partial radiologic response (PRR)). CMR: Positron emission tomography (PET) 5-point scale scores: 1-No uptake above background; 2-Uptake ≤ mediastinum; 3-Uptake > mediastinum but ≤ liver, with/without residual mass; no new lesions, no FDG-avid disease in bone marrow. CRR: Target nodes/nodal masses regressed ≤ 1.5 cm in longest diameter, no extralymphatic sites, no non-measured lesions, normal organ size, no new sites, normal bone marrow morphology. PMR: Scores 4 (uptake moderately > liver), 5 (uptake markedly > liver, new lesions) with reduced uptake from baseline and residual mass, no new lesions. Responding at interim/residual disease at end of treatment. PRR: ≥ 50% decrease in sum of diameters of up to 6 target measurable lesions, no increase in non-measured lesions, spleen length decreased > 50% if previously enlarged, no new lesion sites. Analysis set: FAS.

End point type	Secondary
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End point timeframe:

From randomization date up to a median follow-up: 24.9 months

End point values	Axicabtagene Ciloleucel	Standard of Care Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180	179		
Units: percentage of participants				
number (confidence interval 95%)	83 (77.1 to 88.5)	50 (42.7 to 57.8)		

Statistical analyses

Statistical analysis title	ORR - Axicabtagene Ciloleucel vs SOCT
Comparison groups	Axicabtagene Ciloleucel v Standard of Care Therapy
Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	< 0.0001 ^[4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in ORR
Point estimate	33.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	23.2
upper limit	42.1

Notes:

[3] - One-sided p-value based on Cochran-Mantel-Haenszel (CMH) test, one-sided tailed test, stratified by response to first-line therapy and second-line age-adjusted International Prognostic Index (IPI) as data collected on case report forms.

[4] - Stratified (randomization factor) CMH test.

95% CI for the difference in ORR was from Wilson's score method with continuity correction.

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
Overall survival is defined as the time from randomization to death from any cause. Kaplan-Meier (KM) estimates were used for analysis. Participants in the Full Analysis Set were analyzed. '9999' means data not available due to insufficient number of events.	
End point type	Secondary
End point timeframe:	
Up to 74.9 months	

End point values	Axicabtagene Ciloleucel	Standard of Care Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180	179		
Units: months				
median (confidence interval 95%)	9999 (28.3 to 9999)	35.1 (18.5 to 9999)		

Statistical analyses

Statistical analysis title	OS - Axicabtagene Ciloleucel vs SOCT
Comparison groups	Axicabtagene Ciloleucel v Standard of Care Therapy

Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	= 0.027 ^[6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.007

Notes:

[5] - Stratified Cox regression models were used to estimate hazard ratio and 2-sided CIs for axicabtagene ciloleucel relative to standard of care therapy. The Breslow method was used to handle the ties for the Cox regression models.

[6] - Stratified (randomization factor) log-rank test.

Secondary: Duration of Response (DOR) Per Blinded Central Assessments

End point title	Duration of Response (DOR) Per Blinded Central Assessments
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End point description:

DOR was defined only for participants who experience an objective response after axicabtagene ciloleucel infusion and was the time from the first objective response per Lugano classification to disease progression or death from any cause. Objective response was defined in outcome measure 2 and disease progression was defined in outcome measure 1. KM estimates were used for analysis. Participants in the Full Analysis Set with objective response were analyzed. Participants not meeting the criteria by the analysis data cut-off date were censored at their last evaluable disease assessment date prior to the data cut-off date or new lymphoma therapy start date (including stem cell transplant in the axicabtagene ciloleucel arm or retreatment of axicabtagene ciloleucel), whichever was earlier. '9999' means data not available due to insufficient number of events.

End point type	Secondary
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End point timeframe:

From the date of first confirmed objective response (CR or PR) to disease progression or death regardless of cause (Up to 37.8 months)

End point values	Axicabtagene Ciloleucel	Standard of Care Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	90		
Units: months				
median (confidence interval 95%)	26.9 (13.6 to 9999)	8.9 (5.7 to 9999)		

Statistical analyses

Statistical analysis title	DOR - Axicabtagene Ciloleucel vs SOCT
Comparison groups	Axicabtagene Ciloleucel v Standard of Care Therapy

Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority ^[7]
P-value	= 0.0695 ^[8]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.736
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.488
upper limit	1.108

Notes:

[7] - One-sided p-value based on log-rank test stratified by response to first-line therapy and second-line age-adjusted IPI as data collected on case report forms.

[8] - Stratified (randomization stratification factors) log-rank test.

Stratified Cox regression models were used to estimate hazard ratio and 2-sided 95% CIs for axicabtagene ciloleucel relative to standard of care.

Secondary: Modified Event Free Survival (mEFS) Per Blinded Central Assessment

End point title	Modified Event Free Survival (mEFS) Per Blinded Central Assessment
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End point description:

Modified event free survival is defined the same way as EFS, except that a best response of SD up to and including Day 150 assessment post randomization was not considered an event. KM estimates were used for analysis. Participants in the Full Analysis Set were analyzed.

End point type	Secondary
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End point timeframe:

From randomization date up to a median follow-up: 24.9 months

End point values	Axicabtagene Ciloleucel	Standard of Care Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180	179		
Units: months				
median (confidence interval 95%)	10.3 (5.0 to 21.5)	2.0 (1.6 to 2.8)		

Statistical analyses

Statistical analysis title	mEFS - Axicabtagene Ciloleucel vs SOCT
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Statistical analysis description:

Stratified Cox regression models were used to estimate hazard ratio and 2-sided 95% CIs for axicabtagene ciloleucel relative to standard of care therapy. The Breslow method was used to handle the ties for the Cox regression models.

Comparison groups	Axicabtagene Ciloleucel v Standard of Care Therapy
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Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[9]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.376
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	0.487

Notes:

[9] - Stratified (randomization stratification factors) log-rank test. One-sided p-value based on log-rank test stratified by response to first-line therapy and second-line age-adjusted IPI as data collected on case report forms.

Secondary: EFS Per Investigator Disease Assessments

End point title	EFS Per Investigator Disease Assessments
End point description:	
EFS was defined as the time from randomization to the earliest date of disease progression per the Lugano Classification, best response of stable disease (SD) up to and including Day 150, commencement of new lymphoma therapy, or death from any cause. Disease progression is defined in outcome measure 1. Participants in the Full Analysis Set were analyzed.	
End point type	Secondary
End point timeframe:	
From randomization date up to a median follow-up: 47.2 months	

End point values	Axicabtagene Ciloleucel	Standard of Care Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180	179		
Units: months				
median (confidence interval 95%)	10.8 (5.0 to 25.5)	2.3 (1.7 to 3.1)		

Statistical analyses

Statistical analysis title	EFS - Axicabtagene Ciloleucel vs SOCT
Statistical analysis description:	
Stratified Cox regression models were used to estimate hazard ratio and 2-sided 95% CIs for axicabtagene ciloleucel relative to standard of care therapy. The Breslow method was used to handle the ties for the Cox regression models.	
Comparison groups	Axicabtagene Ciloleucel v Standard of Care Therapy

Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.422
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.327
upper limit	0.545

Secondary: Progression-Free Survival (PFS) Per Investigator Disease Assessments

End point title	Progression-Free Survival (PFS) Per Investigator Disease Assessments
End point description:	
PFS is defined as the time from the randomization date to the date of disease progression per Lugano classification or death from any cause. Disease progression is defined in outcome measure 1. KM estimates was used for analysis. Participants in the Full Analysis Set were analyzed.	
End point type	Secondary
End point timeframe:	
From randomization date up to a median follow-up: 47.2 months	

End point values	Axicabtagene Ciloleucel	Standard of Care Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180	179		
Units: months				
median (confidence interval 95%)	14.7 (5.4 to 43.5)	3.7 (2.9 to 5.3)		

Statistical analyses

Statistical analysis title	PFS - Axicabtagene Ciloleucel vs SOCT
Statistical analysis description:	
Stratified Cox regression models were used to estimate hazard ratio and 2-sided 95% CIs for axicabtagene ciloleucel relative to standard of care therapy. The Breslow method was used to handle the ties for the Cox regression models.	
Comparison groups	Axicabtagene Ciloleucel v Standard of Care Therapy
Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.506

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.383
upper limit	0.669

Secondary: Modified Event Free Survival (mEFS) Per Investigator Assessment

End point title	Modified Event Free Survival (mEFS) Per Investigator Assessment
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End point description:

mEFS is defined the same way as EFS, except that a best response of SD up to and including Day 150 assessment post randomization was not considered an event. KM estimates were used for analysis. Participants in the Full Analysis Set were analyzed.

End point type	Secondary
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End point timeframe:

From randomization date up to a median follow-up: 47.2 months

End point values	Axicabtagene Ciloleucel	Standard of Care Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180	179		
Units: month				
median (confidence interval 95%)	12.6 (5.0 to 29.1)	2.3 (1.7 to 3.1)		

Statistical analyses

Statistical analysis title	mEFS - Axicabtagene Ciloleucel vs SOCT
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Statistical analysis description:

Stratified Cox regression models were used to estimate hazard ratio and 2-sided 95% CIs for axicabtagene ciloleucel relative to standard of care therapy. The Breslow method was used to handle the ties for the Cox regression models.

Comparison groups	Axicabtagene Ciloleucel v Standard of Care Therapy
Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.412
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.318
upper limit	0.532

Secondary: Change From Baseline in Global Health Status Scores

End point title	Change From Baseline in Global Health Status Scores
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End point description:

Global health status was measured using European Organization for Research and Treatment of Cancer (EORTC) Quality Life Questionnaire (QLQ) C-30. This health related quality of life (HRQoL) questionnaire was comprised of 15 questions on functional scales, 13 questions on symptom scales and 2 on global health status scale. Global Health Status used a 7 point Likert-type scale of 1 (Very poor) to 7 (Excellent). All scores were transformed to 0-100. Higher scores for Global Health Status indicated better HRQoL. Participants in Quality of Life (QoL) Analysis Set with data available at given timepoint were analyzed. The QoL Analysis Set was defined as the subset of participants in the Full Analysis Set who have a baseline and Day 150 post-randomization QoL assessment.

End point type	Secondary
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End point timeframe:

Baseline, Days 50, 100, and 150; Months 9, 12, 15, 18, 21 and 24

End point values	Axicabtagene Ciloleucel	Standard of Care Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	130		
Units: Score on scale				
arithmetic mean (standard deviation)				
Baseline (n=165, 130)	68.6 (± 19.9)	70.1 (± 23.1)		
Change from Baseline at Study Day 50 (163, 124)	-7.4 (± 20.2)	-8.5 (± 22.7)		
Change from Baseline at Study Day 100 (n=146, 62)	1.3 (± 19.6)	-15.3 (± 22.7)		
Change from Baseline at Study Day 150 (n=110, 56)	5.9 (± 24.9)	-4.2 (± 23.7)		
Change from Baseline at Study Month 9 (88, 40)	8.0 (± 22.7)	3.5 (± 23.7)		
Change from Baseline at Study Month 12 (79, 33)	8.6 (± 24.9)	9.1 (± 20.2)		
Change from Baseline at Study Month 15 (n=67, 26)	9.0 (± 22.3)	9.9 (± 18.9)		
Change from Baseline at Study Month 18 (n=71, 23)	10.2 (± 20.9)	6.5 (± 21.3)		
Change from Baseline at Study Month 21 (n=45, 20)	10.0 (± 21.5)	15.0 (± 19.6)		
Change from Baseline at Study Month 24 (n=32, 12)	8.6 (± 21.0)	13.2 (± 17.2)		

Statistical analyses

Statistical analysis title	Global Health Status Scores - At Day 100
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Statistical analysis description:

Difference in mean change of scores from Baseline at Day 100.

Comparison groups	Axicabtagene Ciloleucel v Standard of Care Therapy
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Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[10]
Method	Mixed Model with Repeated Measures
Parameter estimate	Mixed Model with Repeated Measures
Point estimate	18.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.3
upper limit	23.9

Notes:

[10] - False Discovery Rate Methodology

Statistical analysis title	Global Health Status Scores - At Day 150
Statistical analysis description:	
Difference in mean change of scores from Baseline at Day 150.	
Comparison groups	Axicabtagene Ciloleucel v Standard of Care Therapy
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0124 ^[11]
Method	Mixed Model with Repeated Measures
Parameter estimate	Mixed Model with Repeated Measures
Point estimate	9.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.6
upper limit	17

Notes:

[11] - False Discovery Rate Methodology.

Statistical analysis title	Global Health Status Scores - At Month 9
Statistical analysis description:	
Difference in mean change of scores from Baseline at Month 9.	
Comparison groups	Axicabtagene Ciloleucel v Standard of Care Therapy
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2655 ^[12]
Method	Mixed Model with Repeated Measures
Parameter estimate	Mixed Model with Repeated Measures
Point estimate	4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	12

Notes:

[12] - False Discovery Rate Methodology

Secondary: Change From Baseline in EORTC QLQ-C30 Physical Functioning Score

End point title	Change From Baseline in EORTC QLQ-C30 Physical Functioning Score
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End point description:

The EORTC QLQ-C30 was composed of global health status/QoL scale; five functional domains (physical, role, emotional, cognitive, and social); three symptom domains (fatigue, nausea and vomiting, and pain); and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties).

The Physical Functioning domain included 5 questions in which participants were asked to rate their overall health and overall quality of life as it relates to physical functioning during the past week on a scale from 1 (very poor) to 7 (excellent). The 5 scores were transformed to a scale from 0 to 100, where a high score indicated better QoL. A positive change from baseline indicates better QoL. Participants in QoL Analysis Set with data available at given timepoint were analyzed.

End point type	Secondary
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End point timeframe:

Baseline, Days 50, 100, 150, Months 9, 12, 15, 18, 21 and 24

End point values	Axicabtagene Ciloleucel	Standard of Care Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	131		
Units: Score on scale				
arithmetic mean (standard deviation)				
Score at Baseline (n=164, 131)	83.5 (± 17.7)	85.3 (± 18.9)		
Change from Baseline at Study Day 50 (n=162, 126)	-12.9 (± 21.7)	-8.3 (± 17.5)		
Change from Baseline at Study Day 100 (n=146, 64)	-1.8 (± 17.8)	-15.0 (± 19.1)		
Change from Baseline at Study Day 150 (n=109, 56)	1.3 (± 18.9)	-5.2 (± 21.3)		
Change from Baseline at Study Month 9 (n=88, 40)	4.1 (± 17.1)	-2.4 (± 23.5)		
Change from Baseline at Study Month 12 (n=79, 33)	3.4 (± 20.8)	0.4 (± 20.3)		
Change from Baseline at Study Month 15 (n=67, 26)	3.9 (± 19.3)	1.6 (± 16.1)		
Change from Baseline at Study Month 18 (n=71, 23)	5.0 (± 15.1)	3.2 (± 17.9)		
Change from Baseline at Study Month 21 (n=45, 20)	6.0 (± 16.1)	4.3 (± 21.4)		
Change from Baseline at Study Month 24 (n=32, 12)	3.7 (± 16.5)	5.6 (± 8.0)		

Statistical analyses

Statistical analysis title	EORTC QLQ-C30 Score - At Day 100
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Statistical analysis description:

Difference in mean change of scores from Baseline at Day 100.

Comparison groups	Standard of Care Therapy v Axicabtagene Ciloleucel
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Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[13]
Method	Mixed Model with Repeated Measures
Parameter estimate	Mixed Model with Repeated Measures
Point estimate	13.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	8
upper limit	18.2

Notes:

[13] - False Discovery Rate Methodology.

Statistical analysis title	EORTC QLQ-C30 Score - At Day 150
Statistical analysis description:	
Difference in mean change of scores from Baseline at Day 150.	
Comparison groups	Axicabtagene Ciloleucel v Standard of Care Therapy
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1253 ^[14]
Method	Mixed Model with Repeated Measures
Parameter estimate	Mixed Model with Repeated Measures
Point estimate	5.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	11

Notes:

[14] - False Discovery Rate Methodology.

Secondary: Changes From Baseline in the European Quality of Life Five Dimensions Five Levels Scale Index Score

End point title	Changes From Baseline in the European Quality of Life Five Dimensions Five Levels Scale Index Score
End point description:	
<p>The Euro-QOL Five Dimensions Five Levels (EQ-5D-5L) questionnaire was a generic measure of health status that provided a simple descriptive profile and a single index value. The EQ-5D-5L comprised 2 components: a questionnaire covering 5 dimensions and a tariff of values based upon direct valuations of health stated using a visual analog scale (VAS). The total score for EQ-5D-5L index was presented on a range from 0 to 1 where higher scores indicated better outcome. A positive change from Baseline indicates improvement. Participants in QoL Analysis Set with data available at given timepoint were analyzed.</p>	
End point type	Secondary
End point timeframe:	
Baseline, Days 50, 100, 150; Months 9, 12, 15, 18, 21 and 24	

End point values	Axicabtagene Ciloleucel	Standard of Care Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	131		
Units: Score on scale				
arithmetic mean (standard deviation)				
Score at Baseline (n=165, 131)	0.803 (± 0.210)	0.799 (± 0.250)		
Change from Baseline at Study Day 50 (n=163, 123)	-0.049 (± 0.205)	-0.003 (± 0.198)		
Change from Baseline at Study Day 100 (n=146, 65)	0.012 (± 0.191)	-0.068 (± 0.246)		
Change from Baseline at Study Day 150 (n=109, 56)	0.050 (± 0.212)	0.014 (± 0.208)		
Change from Baseline at Study Month 9 (n=88, 39)	0.064 (± 0.190)	0.015 (± 0.197)		
Change from Baseline at Study Month 12 (n=79, 32)	0.072 (± 0.241)	0.051 (± 0.200)		
Change from Baseline at Study Month 15 (n=67, 26)	0.051 (± 0.209)	0.080 (± 0.125)		
Change from Baseline at Study Month 18 (n=71, 22)	0.094 (± 0.180)	0.072 (± 0.188)		
Change from Baseline at Study Month 21 (n=45, 20)	0.089 (± 0.235)	0.110 (± 0.177)		
Change from Baseline at Study Month 24 (n=33, 12)	0.051 (± 0.239)	0.117 (± 0.138)		

Statistical analyses

Statistical analysis title	EQ-5D-5L - At Day 100
Statistical analysis description: Difference in mean change of scores from Baseline at Day 100.	
Comparison groups	Axicabtagene Ciloleucel v Standard of Care Therapy
Number of subjects included in analysis	296
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0112 ^[15]
Method	Mixed Model with Repeated Measures
Parameter estimate	Mixed Model with Repeated Measures
Point estimate	0.081
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.024
upper limit	0.138

Notes:

[15] - False Discovery Rate Methodology.

Statistical analysis title	EQ-5D-5L - At Day 150
Statistical analysis description: Difference in mean change of scores from Baseline at Day 150.	
Comparison groups	Axicabtagene Ciloleucel v Standard of Care Therapy

Number of subjects included in analysis	296
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3703 ^[16]
Method	Mixed Model with Repeated Measures
Parameter estimate	Mixed Model with Repeated Measures
Point estimate	0.028
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.034
upper limit	0.091

Notes:

[16] - False Discovery Rate Methodology.

Secondary: Change From Baseline in EQ-5D-5L VAS Scale Score

End point title	Change From Baseline in EQ-5D-5L VAS Scale Score
End point description:	
The EQ-5D-5L VAS is a 20-cm VAS for recording self-rated current HRQoL state and is used to describe the participants' health status on the day of the assessment. The EQ-5D-5L VAS score is recorded by each participant for his or her current HRQoL state and scored 0 ("the worst health you can imagine") to 100 ("the best health you can imagine"). The value 100 indicates improvement. Participants in QoL Analysis Set with data available at given timepoint were analyzed.	
End point type	Secondary
End point timeframe:	
Baseline, Days 50, 100, 150; Months 9, 12, 15, 18, 21 and 24	

End point values	Axicabtagene Ciloleucel	Standard of Care Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	129		
Units: Score on scale				
arithmetic mean (standard deviation)				
Score at Baseline (n=165, 129)	72.4 (± 18.7)	74.4 (± 20.1)		
Change from Baseline at Study Day 50 (n=163, 124)	-1.9 (± 18.7)	-4.4 (± 16.7)		
Change from Baseline at Study Day 100 (n=145, 64)	4.0 (± 18.4)	-8.2 (± 19.8)		
Change from Baseline at Study Day 150 (n=110, 54)	9.1 (± 19.4)	-2.2 (± 22.2)		
Change from Baseline at Study Month 9 (n=88, 39)	11.4 (± 19.9)	4.4 (± 19.0)		
Change from Baseline at Study Month 12 (n= 80, 31)	10.1 (± 19.9)	6.6 (± 17.8)		
Change from Baseline at Study Month 15 (n=67, 26)	10.7 (± 20.7)	8.2 (± 13.7)		
Change from Baseline at Study Month 18 (n=70, 23)	15.1 (± 17.1)	9.3 (± 13.6)		
Change from Baseline at Study Month 21 (n=45, 20)	14.0 (± 17.2)	10.1 (± 14.3)		
Change from Baseline at Study Month 24 (n=33, 12)	10.9 (± 18.8)	12.2 (± 15.3)		

Statistical analyses

Statistical analysis title	EQ-5D-5L VAS - At Day 100
Statistical analysis description: Difference in mean change of scores from Baseline at Day 100.	
Comparison groups	Standard of Care Therapy v Axicabtagene Ciloleucel
Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[17]
Method	Mixed Model with Repeated Measures
Parameter estimate	Mixed Model with Repeated Measures
Point estimate	13.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.5
upper limit	18.8

Notes:

[17] - False Discovery Rate Methodology

Statistical analysis title	EQ-5D-5L VAS - At Day 150
Statistical analysis description: Difference in mean change of scores from Baseline at Day 150.	
Comparison groups	Axicabtagene Ciloleucel v Standard of Care Therapy
Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004 ^[18]
Method	Mixed Model with Repeated Measures
Parameter estimate	Mixed Model with Repeated Measures
Point estimate	11.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.4
upper limit	17.1

Notes:

[18] - False Discovery Rate Methodology

Statistical analysis title	EQ-5D-5L VAS - At Month 9
Statistical analysis description: Difference in mean change of scores from Baseline at Month 9.	
Comparison groups	Axicabtagene Ciloleucel v Standard of Care Therapy

Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2549 ^[19]
Method	Mixed Model with Repeated Measures
Parameter estimate	Mixed Model with Repeated Measures
Point estimate	3.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	10

Notes:

[19] - False Discovery Rate Methodology

Secondary: Number of Participants With Post-dose Anti-Axicabtagene Ciloleucel Antibodies

End point title	Number of Participants With Post-dose Anti-Axicabtagene Ciloleucel Antibodies ^[20]
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End point description:

Participants in the Safety Analysis Set (SAS) were analyzed. The Safety Analysis Set was defined as the subset of all randomized participants who received at least 1 dose of axicabtagene ciloleucel as protocol therapy or SOC chemotherapy as protocol therapy.

End point type	Secondary
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End point timeframe:

From first dose of axicabtagene up to a median follow-up: 24 months

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 applicable only for Axicabtagene Ciloleucel arm.

End point values	Axicabtagene Ciloleucel			
Subject group type	Reporting group			
Number of subjects analysed	170			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Experiencing Treatment-emergent Adverse Events (TEAEs)

End point title	Percentage of Participants Experiencing Treatment-emergent Adverse Events (TEAEs)
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End point description:

A TEAE was defined as any AE that begins on or after the first dose of study treatment (axicabtagene ciloleucel infusion or SOC), excluding bridging therapy. Participants in the Safety Analysis Set were analyzed.

End point type	Secondary
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End point timeframe:
From first dose up to to 61.8 months

End point values	Axicabtagene Ciloleucel	Standard of Care Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	168		
Units: percentage of participants				
number (not applicable)	100.0	100.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Increase in Laboratory Values Reported as Grade 3 or Higher

End point title	Percentage of Participants With Increase in Laboratory Values Reported as Grade 3 or Higher
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End point description:

Grading categories were determined by Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Grade 1: mild, Grade 2: moderate, Grade 3: severe or medically significant, Grade 4: life-threatening. Participants in the Safety Analysis Set were analyzed. Percentages were rounded-off.

End point type	Secondary
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End point timeframe:

From first dose up to to 61.8 months

End point values	Axicabtagene Ciloleucel	Standard of Care Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	168		
Units: percentage of participants				
number (not applicable)				
Hemoglobin (mmol/L)	0	0		
Leukocytes (10 ⁹ /L)	0	1		
Lymphocytes (10 ⁹ /L)	0	0		
Alanine Aminotransferase (U/L)	6	4		
Alkaline Phosphatase (U/L)	1	1		
Aspartate Aminotransferase (U/L)	6	2		
Bilirubin (umol/L)	2	1		
Calcium (mmol/L)	2	1		
Creatinine (umol/L)	4	1		
Glucose (mmol/L)	14	5		
Magnesium (mmol/L)	2	0		
Potassium (mmol/L)	0	1		
Sodium (mmol/L)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Decrease in Laboratory Values Reported as Grade 3 or Higher

End point title	Percentage of Participants With Decrease in Laboratory Values Reported as Grade 3 or Higher
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End point description:

Grading categories were determined by Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Grade 1: mild, Grade 2: moderate, Grade 3: severe or medically significant, Grade 4: life-threatening. Participants in the Safety Analysis Set were analyzed. Percentages were rounded-off.

End point type	Secondary
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End point timeframe:

From first dose up to to 61.8 months

End point values	Axicabtagene Ciloleucel	Standard of Care Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	168		
Units: percentage of participants				
number (not applicable)				
Hemoglobin (mmol/L)	41	44		
Leukocytes (10 ⁹ /L)	95	56		
Lymphocytes (10 ⁹ /L)	99	68		
Neutrophils (10 ⁹ /L)	94	51		
Platelets (10 ⁹ /L)	26	63		
Albumin (g/L)	4	1		
Calcium (mmol/L)	8	2		
Glucose (mmol/L)	0	0		
Magnesium (mmol/L)	2	3		
Phosphate (mmol/L)	5	5		
Potassium (mmol/L)	6	7		
Sodium (mmol/L)	12	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Death and Adverse events (AEs): Up to 74.9 months

Adverse event reporting additional description:

All-Cause Mortality: FAS = all randomized participants.

AEs: SAS = all randomized participants who received at least 1 dose of axicabtagene ciloleucel or SOCT.

Safety Retreatment Analysis Set = participants retreated with axicabtagene ciloleucel.

Death and AE data reported separately for axicabtagene ciloleucel initial and re-treatment.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	27.1
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Reporting groups

Reporting group title	Axicabtagene Ciloleucel
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Reporting group description:

Participants received cyclophosphamide 500 mg/m²/day intravenous (IV) infusion and fludarabine 30 mg/m²/day IV infusion conditioning chemotherapy for 3 days followed by axicabtagene ciloleucel administered as a single IV infusion at a target dose of 2 x 10⁶ anti-cluster of differentiation antigen (CD) 19 chimeric antigen receptor (CAR) transduced autologous T cells/kg on Day 0.

Reporting group title	Retreatment Axicabtagene Ciloleucel
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Reporting group description:

Participants who achieved a partial response or complete response and subsequently experienced disease progression received a second course of conditioning chemotherapy (cyclophosphamide 500 mg/m²/day IV infusion and fludarabine 30 mg/m²/day IV infusion) for 3 days followed by axicabtagene ciloleucel administered as a single IV infusion at a target dose of 2 x 10⁶ anti-CD 19 CAR transduced autologous T cells/kg.

Reporting group title	Standard of Care Therapy
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Reporting group description:

Participants received 2 or 3, 21-day cycles of second-line chemotherapy regimen:

R-ICE: rituximab 375mg/m² before chemotherapy, ifosfamide 5g/m² 24 hours continuous infusion (CI) on Day2+mesna, carboplatin area under curve (AUC)5 Day 2, maximum dose 800mg, etoposide 100mg/m²/day on Days 1-3;

R-ESHAP: rituximab 375mg/m² Day 1, etoposide 40mg/m²/day IV on Days 1-4, methylprednisolone 500mg/day IV on Days 1-4 or 5, cisplatin at 25mg/m²/day CI Days 1-4, cytarabine 2g/m² on Day5; R-GDP: rituximab 375mg/m² Day1 (or Day8), gemcitabine 1g/m² on Days 1 and 8, dexamethasone 40mg on Days 1-4, cisplatin 75mg/m² Day 1 or carboplatin AUC=5; or

R-DHAP: rituximab 375mg/m² before chemotherapy, dexamethasone 40mg/day on Days 1-4, high dose cytarabine 2g/m² every 12 hours for 2 doses on Day 2 following platinum, cisplatin 100mg/m² 24 hours CI on Day 1 or oxaliplatin 100mg/m².

Participants who responded to second-line chemotherapy got high dose therapy and autologous stem cell transplant

Serious adverse events	Axicabtagene Ciloleucel	Retreatment Axicabtagene Ciloleucel	Standard of Care Therapy
Total subjects affected by serious adverse events			
subjects affected / exposed	96 / 170 (56.47%)	2 / 10 (20.00%)	78 / 168 (46.43%)
number of deaths (all causes)	81	3	101
number of deaths resulting from adverse events		0	

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
B-cell lymphoma			
subjects affected / exposed	7 / 170 (4.12%)	0 / 10 (0.00%)	5 / 168 (2.98%)
occurrences causally related to treatment / all	0 / 7	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 7	0 / 0	0 / 4
Myelodysplastic syndrome			
subjects affected / exposed	2 / 170 (1.18%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myeloid leukaemia			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma pancreas			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ductal adenocarcinoma of pancreas			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular carcinoma			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Large granular lymphocytosis subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Metastatic malignant melanoma subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Plasma cell myeloma subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spindle cell sarcoma subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal squamous cell carcinoma subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Orthostatic hypotension subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension subjects affected / exposed	15 / 170 (8.82%)	1 / 10 (10.00%)	3 / 168 (1.79%)
occurrences causally related to treatment / all	15 / 16	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism			

subjects affected / exposed	2 / 170 (1.18%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angiopathy			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Haematopoietic stem cell ~ mobilisation			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 170 (1.76%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	27 / 170 (15.88%)	0 / 10 (0.00%)	8 / 168 (4.76%)
occurrences causally related to treatment / all	34 / 41	0 / 0	4 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	2 / 170 (1.18%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Influenza like illness			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucosal inflammation			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Incarcerated hernia			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Tachypnoea			
subjects affected / exposed	2 / 170 (1.18%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	3 / 170 (1.76%)	0 / 10 (0.00%)	2 / 168 (1.19%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	3 / 170 (1.76%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	2 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	2 / 168 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1

Acute respiratory failure			
subjects affected / exposed	2 / 170 (1.18%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary ~ disease			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung opacity			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	7 / 170 (4.12%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	5 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	3 / 170 (1.76%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Agitation			
subjects affected / exposed	2 / 170 (1.18%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradyphrenia			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Neutrophil count decreased			
subjects affected / exposed	3 / 170 (1.76%)	1 / 10 (10.00%)	3 / 168 (1.79%)
occurrences causally related to treatment / all	3 / 3	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	5 / 168 (2.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood fibrinogen decreased			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Troponin I increased			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 170 (1.18%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood stem cell harvest failure			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vascular access complication subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Pericardial effusion subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation subjects affected / exposed	5 / 170 (2.94%)	0 / 10 (0.00%)	2 / 168 (1.19%)
occurrences causally related to treatment / all	5 / 5	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus tachycardia subjects affected / exposed	2 / 170 (1.18%)	0 / 10 (0.00%)	2 / 168 (1.19%)
occurrences causally related to treatment / all	2 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Tachycardia subjects affected / exposed	2 / 170 (1.18%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiomyopathy			

subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heart failure with reduced ejection ~ fraction			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Tremor			
subjects affected / exposed	5 / 170 (2.94%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	5 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	17 / 170 (10.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	17 / 17	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aphasia			
subjects affected / exposed	9 / 170 (5.29%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	9 / 9	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	4 / 170 (2.35%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	3 / 5	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			

subjects affected / exposed	5 / 170 (2.94%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	5 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	3 / 168 (1.79%)
occurrences causally related to treatment / all	0 / 1	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoaesthesia			
subjects affected / exposed	2 / 170 (1.18%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ataxia			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cognitive disorder			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressed level of consciousness			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysarthria			

subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspraxia			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial paralysis			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Guillain-Barre syndrome			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lethargy			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Memory impairment			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	2 / 170 (1.18%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			

subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	6 / 170 (3.53%)	0 / 10 (0.00%)	22 / 168 (13.10%)
occurrences causally related to treatment / all	5 / 9	0 / 0	20 / 23
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	5 / 170 (2.94%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	9 / 14	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coagulopathy			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	2 / 170 (1.18%)	0 / 10 (0.00%)	3 / 168 (1.79%)
occurrences causally related to treatment / all	0 / 2	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Vision blurred			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 170 (1.76%)	0 / 10 (0.00%)	2 / 168 (1.19%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	2 / 168 (1.19%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterovesical fistula			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Food poisoning			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer perforation			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal fistula			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral disorder			

subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 170 (2.35%)	0 / 10 (0.00%)	8 / 168 (4.76%)
occurrences causally related to treatment / all	1 / 4	0 / 0	7 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Faecaluria			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	4 / 170 (2.35%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	2 / 168 (1.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flank pain			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	16 / 170 (9.41%)	0 / 10 (0.00%)	4 / 168 (2.38%)
occurrences causally related to treatment / all	8 / 26	0 / 0	3 / 5
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	5 / 170 (2.94%)	0 / 10 (0.00%)	4 / 168 (2.38%)
occurrences causally related to treatment / all	1 / 5	0 / 0	3 / 5
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Covid-19			
subjects affected / exposed	7 / 170 (4.12%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 9	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0

Urinary tract infection			
subjects affected / exposed	3 / 170 (1.76%)	1 / 10 (10.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Covid-19 pneumonia			
subjects affected / exposed	3 / 170 (1.76%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	2 / 170 (1.18%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	2 / 170 (1.18%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	2 / 170 (1.18%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			

subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	2 / 168 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis infective			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus infection			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metapneumovirus infection			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fungal cystitis			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Furuncle			

subjects affected / exposed	0 / 170 (0.00%)	1 / 10 (10.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis B reactivation			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parainfluenzae virus infection			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic abscess			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumococcal sepsis			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia legionella			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia staphylococcal			

subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonal sepsis			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhinovirus infection			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salmonella bacteraemia			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Progressive multifocal ~ leukoencephalopathy			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	3 / 168 (1.79%)
occurrences causally related to treatment / all	1 / 1	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	2 / 170 (1.18%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	2 / 168 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomagnesaemia			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	3 / 168 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Axicabtagene Ciloleucel	Retreatment Axicabtagene Ciloleucel	Standard of Care Therapy
Total subjects affected by non-serious adverse events subjects affected / exposed	170 / 170 (100.00%)	10 / 10 (100.00%)	166 / 168 (98.81%)
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 170 (0.59%)	1 / 10 (10.00%)	1 / 168 (0.60%)
occurrences (all)	1	1	1
Hypertension			
subjects affected / exposed	15 / 170 (8.82%)	0 / 10 (0.00%)	15 / 168 (8.93%)
occurrences (all)	19	0	16
Hypotension			
subjects affected / exposed	66 / 170 (38.82%)	3 / 10 (30.00%)	23 / 168 (13.69%)
occurrences (all)	82	3	30
General disorders and administration site conditions			
Pain			
subjects affected / exposed	0 / 170 (0.00%)	1 / 10 (10.00%)	1 / 168 (0.60%)
occurrences (all)	0	1	1
Mucosal inflammation			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	15 / 168 (8.93%)
occurrences (all)	1	0	16
Malaise			
subjects affected / exposed	15 / 170 (8.82%)	1 / 10 (10.00%)	9 / 168 (5.36%)
occurrences (all)	15	1	12
Asthenia			
subjects affected / exposed	13 / 170 (7.65%)	0 / 10 (0.00%)	15 / 168 (8.93%)
occurrences (all)	14	0	19
Oedema peripheral			
subjects affected / exposed	20 / 170 (11.76%)	0 / 10 (0.00%)	28 / 168 (16.67%)
occurrences (all)	21	0	31
Chills			
subjects affected / exposed	46 / 170 (27.06%)	0 / 10 (0.00%)	14 / 168 (8.33%)
occurrences (all)	51	0	17
Fatigue			
subjects affected / exposed	69 / 170 (40.59%)	2 / 10 (20.00%)	87 / 168 (51.79%)
occurrences (all)	79	2	118

Pyrexia subjects affected / exposed occurrences (all)	149 / 170 (87.65%) 183	9 / 10 (90.00%) 10	40 / 168 (23.81%) 62
Immune system disorders Hypogammaglobulinaemia subjects affected / exposed occurrences (all)	19 / 170 (11.18%) 19	0 / 10 (0.00%) 0	1 / 168 (0.60%) 1
Respiratory, thoracic and mediastinal disorders Pulmonary embolism subjects affected / exposed occurrences (all)	2 / 170 (1.18%) 2	1 / 10 (10.00%) 1	2 / 168 (1.19%) 2
Oropharyngeal pain subjects affected / exposed occurrences (all)	11 / 170 (6.47%) 11	0 / 10 (0.00%) 0	14 / 168 (8.33%) 14
Hiccups subjects affected / exposed occurrences (all)	5 / 170 (2.94%) 5	0 / 10 (0.00%) 0	21 / 168 (12.50%) 23
Dyspnoea subjects affected / exposed occurrences (all)	12 / 170 (7.06%) 16	1 / 10 (10.00%) 1	20 / 168 (11.90%) 27
Hypoxia subjects affected / exposed occurrences (all)	34 / 170 (20.00%) 36	0 / 10 (0.00%) 0	13 / 168 (7.74%) 14
Cough subjects affected / exposed occurrences (all)	42 / 170 (24.71%) 47	0 / 10 (0.00%) 0	18 / 168 (10.71%) 20
Atelectasis subjects affected / exposed occurrences (all)	1 / 170 (0.59%) 1	1 / 10 (10.00%) 1	0 / 168 (0.00%) 0
Pleural effusion subjects affected / exposed occurrences (all)	10 / 170 (5.88%) 10	0 / 10 (0.00%) 0	3 / 168 (1.79%) 3
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	11 / 170 (6.47%) 11	2 / 10 (20.00%) 2	14 / 168 (8.33%) 14

Confusional state			
subjects affected / exposed	34 / 170 (20.00%)	0 / 10 (0.00%)	4 / 168 (2.38%)
occurrences (all)	37	0	4
Insomnia			
subjects affected / exposed	21 / 170 (12.35%)	0 / 10 (0.00%)	26 / 168 (15.48%)
occurrences (all)	22	0	29
Investigations			
Neutrophil count decreased			
subjects affected / exposed	51 / 170 (30.00%)	5 / 10 (50.00%)	45 / 168 (26.79%)
occurrences (all)	104	11	65
Platelet count decreased			
subjects affected / exposed	30 / 170 (17.65%)	1 / 10 (10.00%)	64 / 168 (38.10%)
occurrences (all)	45	1	120
White blood cell count decreased			
subjects affected / exposed	46 / 170 (27.06%)	4 / 10 (40.00%)	37 / 168 (22.02%)
occurrences (all)	81	7	68
Lymphocyte count decreased			
subjects affected / exposed	31 / 170 (18.24%)	3 / 10 (30.00%)	21 / 168 (12.50%)
occurrences (all)	52	4	54
Alanine aminotransferase increased			
subjects affected / exposed	31 / 170 (18.24%)	2 / 10 (20.00%)	16 / 168 (9.52%)
occurrences (all)	37	2	26
Aspartate aminotransferase increased			
subjects affected / exposed	24 / 170 (14.12%)	1 / 10 (10.00%)	15 / 168 (8.93%)
occurrences (all)	33	1	21
Blood creatinine increased			
subjects affected / exposed	10 / 170 (5.88%)	0 / 10 (0.00%)	15 / 168 (8.93%)
occurrences (all)	10	0	27
Blood alkaline phosphatase increased			
subjects affected / exposed	10 / 170 (5.88%)	0 / 10 (0.00%)	14 / 168 (8.33%)
occurrences (all)	13	0	19
C-reactive protein increased			
subjects affected / exposed	15 / 170 (8.82%)	0 / 10 (0.00%)	4 / 168 (2.38%)
occurrences (all)	15	0	4
Weight decreased			

subjects affected / exposed	11 / 170 (6.47%)	1 / 10 (10.00%)	6 / 168 (3.57%)
occurrences (all)	17	1	7
Serum ferritin increased			
subjects affected / exposed	15 / 170 (8.82%)	0 / 10 (0.00%)	0 / 168 (0.00%)
occurrences (all)	20	0	0
Weight increased			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	12 / 168 (7.14%)
occurrences (all)	1	0	15
Blood bilirubin increased			
subjects affected / exposed	5 / 170 (2.94%)	1 / 10 (10.00%)	2 / 168 (1.19%)
occurrences (all)	7	1	3
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 170 (0.59%)	0 / 10 (0.00%)	12 / 168 (7.14%)
occurrences (all)	1	0	13
Cardiac disorders			
Tachycardia			
subjects affected / exposed	13 / 170 (7.65%)	0 / 10 (0.00%)	10 / 168 (5.95%)
occurrences (all)	13	0	12
Sinus tachycardia			
subjects affected / exposed	58 / 170 (34.12%)	4 / 10 (40.00%)	16 / 168 (9.52%)
occurrences (all)	69	5	22
Nervous system disorders			
Hyperaesthesia			
subjects affected / exposed	0 / 170 (0.00%)	1 / 10 (10.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	10 / 168 (5.95%)
occurrences (all)	0	0	10
Somnolence			
subjects affected / exposed	14 / 170 (8.24%)	0 / 10 (0.00%)	2 / 168 (1.19%)
occurrences (all)	14	0	2
Dysgeusia			
subjects affected / exposed	4 / 170 (2.35%)	0 / 10 (0.00%)	14 / 168 (8.33%)
occurrences (all)	4	0	15
Encephalopathy			

subjects affected / exposed	18 / 170 (10.59%)	0 / 10 (0.00%)	1 / 168 (0.60%)
occurrences (all)	21	0	1
Paraesthesia			
subjects affected / exposed	7 / 170 (4.12%)	1 / 10 (10.00%)	14 / 168 (8.33%)
occurrences (all)	7	1	16
Aphasia			
subjects affected / exposed	31 / 170 (18.24%)	1 / 10 (10.00%)	0 / 168 (0.00%)
occurrences (all)	33	1	0
Tremor			
subjects affected / exposed	41 / 170 (24.12%)	1 / 10 (10.00%)	1 / 168 (0.60%)
occurrences (all)	44	1	1
Dizziness			
subjects affected / exposed	36 / 170 (21.18%)	0 / 10 (0.00%)	21 / 168 (12.50%)
occurrences (all)	37	0	27
Headache			
subjects affected / exposed	69 / 170 (40.59%)	6 / 10 (60.00%)	43 / 168 (25.60%)
occurrences (all)	89	9	60
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	71 / 170 (41.76%)	4 / 10 (40.00%)	90 / 168 (53.57%)
occurrences (all)	115	6	177
Thrombocytopenia			
subjects affected / exposed	22 / 170 (12.94%)	0 / 10 (0.00%)	40 / 168 (23.81%)
occurrences (all)	36	0	84
Neutropenia			
subjects affected / exposed	75 / 170 (44.12%)	2 / 10 (20.00%)	28 / 168 (16.67%)
occurrences (all)	120	3	54
Leukopenia			
subjects affected / exposed	9 / 170 (5.29%)	0 / 10 (0.00%)	6 / 168 (3.57%)
occurrences (all)	11	0	7
Febrile neutropenia			
subjects affected / exposed	0 / 170 (0.00%)	0 / 10 (0.00%)	24 / 168 (14.29%)
occurrences (all)	0	0	28
Ear and labyrinth disorders			
Tinnitus			

subjects affected / exposed occurrences (all)	0 / 170 (0.00%) 0	0 / 10 (0.00%) 0	11 / 168 (6.55%) 11
Gastrointestinal disorders			
Stomatitis			
subjects affected / exposed	4 / 170 (2.35%)	0 / 10 (0.00%)	29 / 168 (17.26%)
occurrences (all)	6	0	31
Abdominal pain			
subjects affected / exposed	22 / 170 (12.94%)	1 / 10 (10.00%)	23 / 168 (13.69%)
occurrences (all)	25	1	27
Constipation			
subjects affected / exposed	34 / 170 (20.00%)	3 / 10 (30.00%)	58 / 168 (34.52%)
occurrences (all)	38	3	73
Diarrhoea			
subjects affected / exposed	71 / 170 (41.76%)	2 / 10 (20.00%)	66 / 168 (39.29%)
occurrences (all)	77	3	88
Nausea			
subjects affected / exposed	68 / 170 (40.00%)	4 / 10 (40.00%)	116 / 168 (69.05%)
occurrences (all)	91	4	208
Vomiting			
subjects affected / exposed	33 / 170 (19.41%)	3 / 10 (30.00%)	55 / 168 (32.74%)
occurrences (all)	41	3	84
Toothache			
subjects affected / exposed	1 / 170 (0.59%)	1 / 10 (10.00%)	3 / 168 (1.79%)
occurrences (all)	1	1	3
Dyspepsia			
subjects affected / exposed	5 / 170 (2.94%)	0 / 10 (0.00%)	14 / 168 (8.33%)
occurrences (all)	5	0	16
Dry mouth			
subjects affected / exposed	16 / 170 (9.41%)	0 / 10 (0.00%)	8 / 168 (4.76%)
occurrences (all)	16	0	8
Abdominal distension			
subjects affected / exposed	4 / 170 (2.35%)	0 / 10 (0.00%)	11 / 168 (6.55%)
occurrences (all)	4	0	11
Hepatobiliary disorders			
Hypertransaminasaemia			

subjects affected / exposed occurrences (all)	11 / 170 (6.47%) 11	0 / 10 (0.00%) 0	1 / 168 (0.60%) 1
Skin and subcutaneous tissue disorders			
Night sweats			
subjects affected / exposed	4 / 170 (2.35%)	1 / 10 (10.00%)	4 / 168 (2.38%)
occurrences (all)	4	1	4
Erythema			
subjects affected / exposed	10 / 170 (5.88%)	0 / 10 (0.00%)	3 / 168 (1.79%)
occurrences (all)	10	0	3
Alopecia			
subjects affected / exposed	3 / 170 (1.76%)	0 / 10 (0.00%)	10 / 168 (5.95%)
occurrences (all)	3	0	10
Pruritus			
subjects affected / exposed	7 / 170 (4.12%)	1 / 10 (10.00%)	9 / 168 (5.36%)
occurrences (all)	7	1	10
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	12 / 170 (7.06%)	0 / 10 (0.00%)	5 / 168 (2.98%)
occurrences (all)	12	0	5
Acute kidney injury			
subjects affected / exposed	12 / 170 (7.06%)	0 / 10 (0.00%)	16 / 168 (9.52%)
occurrences (all)	16	0	20
Micturition urgency			
subjects affected / exposed	4 / 170 (2.35%)	1 / 10 (10.00%)	1 / 168 (0.60%)
occurrences (all)	4	1	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	15 / 170 (8.82%)	1 / 10 (10.00%)	23 / 168 (13.69%)
occurrences (all)	15	1	26
Arthralgia			
subjects affected / exposed	20 / 170 (11.76%)	1 / 10 (10.00%)	14 / 168 (8.33%)
occurrences (all)	22	1	14
Muscular weakness			
subjects affected / exposed	18 / 170 (10.59%)	1 / 10 (10.00%)	11 / 168 (6.55%)
occurrences (all)	20	1	11
Myalgia			

subjects affected / exposed occurrences (all)	14 / 170 (8.24%) 15	2 / 10 (20.00%) 2	7 / 168 (4.17%) 7
Pain in extremity subjects affected / exposed occurrences (all)	14 / 170 (8.24%) 14	0 / 10 (0.00%) 0	9 / 168 (5.36%) 10
Bone pain subjects affected / exposed occurrences (all)	7 / 170 (4.12%) 7	0 / 10 (0.00%) 0	14 / 168 (8.33%) 14
Infections and infestations			
Oral candidiasis subjects affected / exposed occurrences (all)	14 / 170 (8.24%) 14	0 / 10 (0.00%) 0	5 / 168 (2.98%) 5
Upper respiratory tract infection subjects affected / exposed occurrences (all)	9 / 170 (5.29%) 10	0 / 10 (0.00%) 0	5 / 168 (2.98%) 5
Pneumonia subjects affected / exposed occurrences (all)	2 / 170 (1.18%) 2	1 / 10 (10.00%) 1	5 / 168 (2.98%) 5
Furuncle subjects affected / exposed occurrences (all)	0 / 170 (0.00%) 0	1 / 10 (10.00%) 1	0 / 168 (0.00%) 0
Pseudomonas infection subjects affected / exposed occurrences (all)	0 / 170 (0.00%) 0	1 / 10 (10.00%) 1	0 / 168 (0.00%) 0
Metabolism and nutrition disorders			
Hypokalaemia subjects affected / exposed occurrences (all)	44 / 170 (25.88%) 60	1 / 10 (10.00%) 1	47 / 168 (27.98%) 82
Decreased appetite subjects affected / exposed occurrences (all)	42 / 170 (24.71%) 49	1 / 10 (10.00%) 1	41 / 168 (24.40%) 50
Hypophosphataemia subjects affected / exposed occurrences (all)	45 / 170 (26.47%) 58	2 / 10 (20.00%) 3	29 / 168 (17.26%) 43
Hypomagnesaemia			

subjects affected / exposed	20 / 170 (11.76%)	1 / 10 (10.00%)	34 / 168 (20.24%)
occurrences (all)	26	1	49
Hyperglycaemia			
subjects affected / exposed	27 / 170 (15.88%)	1 / 10 (10.00%)	17 / 168 (10.12%)
occurrences (all)	47	2	44
Hypocalcaemia			
subjects affected / exposed	27 / 170 (15.88%)	1 / 10 (10.00%)	17 / 168 (10.12%)
occurrences (all)	38	1	26
Hypoalbuminaemia			
subjects affected / exposed	22 / 170 (12.94%)	2 / 10 (20.00%)	12 / 168 (7.14%)
occurrences (all)	33	2	21
Hyponatraemia			
subjects affected / exposed	19 / 170 (11.18%)	3 / 10 (30.00%)	7 / 168 (4.17%)
occurrences (all)	20	3	9
Dehydration			
subjects affected / exposed	3 / 170 (1.76%)	1 / 10 (10.00%)	7 / 168 (4.17%)
occurrences (all)	5	1	7
Hyperkalaemia			
subjects affected / exposed	4 / 170 (2.35%)	1 / 10 (10.00%)	3 / 168 (1.79%)
occurrences (all)	4	1	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 November 2017	<ul style="list-style-type: none">- Moved details of EFS/censoring to the Statistical Considerations section of the protocol.- Added modified EFS based on blinded central review and on investigator disease assessments.- Updated language that participants being treated with axicabtagene ciloleucel were under an observation period for at least 7 days after axicabtagene ciloleucel infusion to monitor for and manage any adverse events and not hospitalized.- Clarified inclusion criteria 102 to include participants with refractory disease with partial response after at least 6 cycles as best response to first-line therapy have biopsy-proven residual disease or disease progression ≤ 12 months from initiation of therapy.- Added language to clarify that participants have all organ systems meet inclusion criteria set forth in criterion 110, except for bone marrow function that was impacted by conditioning chemotherapy.- Added language that axicabtagene ciloleucel was intended to be definitive therapy and not a bridge to ASCT.- Clarified when primary analysis of EFS were conducted.- Further clarified that an additional sensitivity analysis for EFS was performed for participants in the axicabtagene ciloleucel arm who undergo ASCT while in an axicabtagene ciloleucel induced response.
16 January 2018	<ul style="list-style-type: none">- The stratification factors of 'relapse ≤ 6 months of initiating first line therapy' and 'relapse > 6 and ≤ 12 months of initiating first line therapy' have been broadened to 'relapse ≤ 6 months of first line therapy' and 'relapse > 6 and ≤ 12 months of first line therapy'.- Clarified the required duration of participant observation after axicabtagene ciloleucel infusion to be aligned with country-specific requirements.- Clarified the required duration of participant observation after axicabtagene ciloleucel infusion to be aligned with country-specific requirements.- The following have been added: PMBCL: Primary mediastinal B-cell lymphoma; TBI: Total body irradiation; WBC: White blood cell- Updated to include the results of the Phase 3 ORCHARRD trial as additional rationale for updated definition of early relapsed disease.- The stratification factors of 'relapse ≤ 6 months of initiating first line therapy' and relapse > 6 and ≤ 12 months of initiating first line therapy' have been broadened to relapse ≤ 6 months of first line therapy' and relapse > 6 and ≤ 12 months of first line therapy'.- Study duration for participants randomized to axicabtagene ciloleucel corrected from 5 years to 15 years (a typographical error, the duration for these participants was 15 years throughout the rest of the protocol)- Definition of Large B-cell lymphoma updated to WHO 2016, including the following types (in bold) defined by WHO 2016, DLBCL not otherwise specified (ABC/GCB); HGBL with or without MYC and BCL2 and/or BCL6 rearrangement; DLBCL arising from FL; T cell/histiocyte rich large B-cell lymphoma; DLBCL associated with chronic inflammation; Primary cutaneous DLBCL, leg type; Epstein-Barr virus (EBV) + DLBCL- The timeframe for partial response of 'best response after at least 6 cycles and biopsy-proven residual disease or disease progression ≤ 12 months from initiation of therapy' has been broadened to '≤ 12 months of first line therapy'.

19 March 2019	<ul style="list-style-type: none"> - Updated the protocol amendment number and date to Amendment #4 19 March 2019 - Clarified for participants weighing > 100 kg, a maximum flat dose of axicabtagene ciloleucel at 2×10^8 anti CD19 CAR T cells administered. - Clarified the collection of targeted SAEs for SOC vs. axi-cel (5 or 15 years) participants - Clarified the preferred term for reporting death due to disease progression, "B-cell lymphoma" - Fixed grammatical, typographical and formatting errors
25 June 2020	<ul style="list-style-type: none"> - The primary EFS analysis event trigger was revised from 270 to approximately 250 EFS events while increasing the required duration of follow-up from 150 days to 9 months. Please see below for detailed rationale. - Additionally, the protocol was updated to align with the revised pregnancy and lactation reporting language in the current version of the axicabtagene ciloleucel Investigator's Brochure. - New/amended text contained in the Protocol Amendment 5 is presented below in bold font.
14 April 2023	<ul style="list-style-type: none"> - Retreatment eligibility criteria updated to reflect the maximum time after the initial axicabtagene ciloleucel infusion a participant could be retreated. - Safety reporting email updated to: Safety_FC@gilead.com. Clarification added regarding any relevant information on ongoing SAEs post the database closure, which must be submitted to Kite within 24 hours after the investigator's knowledge of the event. - Anti-CD19 CAR T levels measured in peripheral blood were summarized with descriptive statistics. - Country specific requirements added from separate documents for harmonization of the protocol to prepare for the EU CTR transition. - Addition of an appendix providing guidelines around pandemic risk assessments and mitigation plan.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/25113753>

<http://www.ncbi.nlm.nih.gov/pubmed/26980727>

<http://www.ncbi.nlm.nih.gov/pubmed/35839452>

<http://www.ncbi.nlm.nih.gov/pubmed/36646322>

<http://www.ncbi.nlm.nih.gov/pubmed/34891224>

<http://www.ncbi.nlm.nih.gov/pubmed/36999993>

<http://www.ncbi.nlm.nih.gov/pubmed/37272527>

<http://www.ncbi.nlm.nih.gov/pubmed/39240498>

<http://www.ncbi.nlm.nih.gov/pubmed/37983485>

<http://www.ncbi.nlm.nih.gov/pubmed/38315832>

<http://www.ncbi.nlm.nih.gov/pubmed/38233586>

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<http://www.ncbi.nlm.nih.gov/pubmed/38504387>

<http://www.ncbi.nlm.nih.gov/pubmed/40083872>