Clinical trial results:
A Phase 2 Multicenter Study Evaluating the Efficacy and Safety of Axicabtagene Ciloleucel as First-Line Therapy in Subjects with High-Risk Large B-Cell Lymphoma (ZUMA-12)

Summary

EudraCT number	2019-002291-13
Trial protocol	FR
Global end of trial date	12 October 2023

Results information

Result version number	v1
This version publication date	18 October 2024
First version publication date	18 October 2024

Trial information

Trial identification

Sponsor protocol code	KTE-C19-112

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03761056
WHO universal trial number (UTN)	-

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	12 October 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 May 2021
Global end of trial reached?	Yes
Global end of trial date	12 October 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to estimate the efficacy of axicabtagene ciloleucel in participants with high-risk large B-cell lymphoma.

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	29 January 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	15 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	United States: 33
Worldwide total number of subjects	42
EEA total number of subjects	2

Notes:

Subjects enrolled per age group

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

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	26
From 65 to 84 years	15
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in the United States, France, and Australia.
Completed in below table denotes participants Completed study and enrolled to long-term follow-up (LTFU) protocol, another study (KT-US-982-5968; NCT# NCT05041309).

Pre-assignment

Screening details:

54 participants were screened.

Period 1

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

Arms

Arm title	Axicabtagene Ciloleucel

Arm description:

Participants received cyclophosphamide 500 mg/m^2/day intravenously (IV) and fludarabine 30 mg/m^2/day IV 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 (CD)19 chimeric antigen receptor (CAR) transduced autologous T cells/kg on Day 0. For participants weighing ≥ 100 kg, a maximum flat dose of axicabtagene ciloleucel at 2 x 10^8 anti-CD19 CAR T cells was administered. Participants who achieved partial response or complete response and subsequently experienced disease progression had an option to receive second course of conditioning chemotherapy therapy and axicabtagene ciloleucel. Participants received the same axicabtagene ciloleucel regimen as the original target dose anytime during the study (Up to 4 years).

Arm type	Experimental
Investigational medicinal product name	Axicabtagene Ciloleucel
Investigational medicinal product code	
Other name	Yescarta
Pharmaceutical forms	Injection/infusion
Routes of administration	Infusion

Dosage and administration details:

A single infusion of chimeric antigen receptor (CAR)-transduced autologous T cells.

Number of subjects in period 1	Axicabtagene Ciloleucel
Started	42
Completed	29
Not completed	13
Withdrawal of consent from further follow-up	2
Death	8
Investigator decision	1
Enrolled but never treated	2

Baseline characteristics

Reporting groups	
Reporting group title	Axicabtagene Ciloleucel
Reporting group description:	
Participants received cyclophosphamide 500 mg/m^2/day intravenously (IV) and fludarabine 30 mg/m^2/day IV 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 (CD)19 chimeric antigen receptor (CAR) transduced autologous T cells/kg on Day 0. For participants weighing ≥ 100 kg, a maximum flat dose of axicabtagene ciloleucel at 2 x 10^8 anti-CD19 CAR T cells was administered. Participants who achieved partial response or complete response and subsequently experienced disease progression had an option to receive second course of conditioning chemotherapy therapy and axicabtagene ciloleucel. Participants received the same axicabtagene ciloleucel regimen as the original target dose anytime during the study (Up to 4 years).	

Reporting group values	Axicabtagene Ciloleucel	Total	
Number of subjects	42	42	
Age categorical			
The Full Analysis Set was defined as all participants enrolled/leukapheresed.			
Units: Subjects			
Adults (18 – 64 Years)	26	26	
Geriatrics (65 – 84 Years)	15	15	
Geriatrics (85 Years and Over)	1	1	
Age continuous			
Units: years			
arithmetic mean	60		
standard deviation	± 13.5	-	
Gender categorical			
Units: Subjects			
Female	13	13	
Male	29	29	
Ethnicity			
Units: Subjects			
Hispanic or Latino	2	2	
Not Hispanic or Latino	38	38	
Unknown or Not Reported	2	2	
Race			
Units: Subjects			
American Indian or Alaska Native	1	1	
Asian	1	1	
Black or African American	1	1	
White	34	34	
Other or More Than One Race	5	5	

End points

End points reporting groups

Reporting group title	Axicabtagene Ciloleucel

Reporting group description:

Participants received cyclophosphamide 500 mg/m^2/day intravenously (IV) and fludarabine 30 mg/m^2/day IV 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 (CD)19 chimeric antigen receptor (CAR) transduced autologous T cells/kg on Day 0. For participants weighing ≥ 100 kg, a maximum flat dose of axicabtagene ciloleucel at 2 x 10^8 anti-CD19 CAR T cells was administered. Participants who achieved partial response or complete response and subsequently experienced disease progression had an option to receive second course of conditioning chemotherapy therapy and axicabtagene ciloleucel. Participants received the same axicabtagene ciloleucel regimen as the original target dose anytime during the study (Up to 4 years).

Primary: Complete Response (CR) Rate per the Lugano Classification as Determined by Study Investigators

End point title	Complete Response (CR) Rate per the Lugano Classification as Determined by Study Investigators[1]

End point description:

CR Rate is the percentage of participants with CR (complete metabolic response (CMR); complete radiological response (CRR)). CMR: positron emission tomography (PET) 5-point scale (5-PS) scores of 1 (no uptake above background), 2 (uptake ≤ mediastinum), 3 (uptake > mediastinum but ≤ liver) with/without a residual mass); no new lesions; and no evidence of fluorodeoxyglucose (FDG)-avid disease in bone marrow (BM). CRR: target nodes/nodal masses regressed to ≤ 1.5 cm in longest transverse diameter of lesion (LDi); no extralymphatic sites of disease; absent non-measured lesion (NMLs); organ enlargement regress to normal; no new sites; and bone marrow normal by morphology.

The Response Evaluable Analysis Set included participants who were enrolled and treated with axicabtagene ciloleucel at a dose of at least 1 x 10^6 anti-CD19 CAR T cells/kg, and centrally confirmed disease type (double-/triple- hit lymphomas) or International Prognostic Index (IPI) score ≥ 3.

End point type	Primary

End point timeframe:

Up to 4 years

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical analyses were not available for this endpoint. Only descriptive data provided were analysed. The CR rate targeted in this study was 60%.

End point values	Axicabtagene Ciloleucel			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: percentage of participants				
number (confidence interval 95%)	86 (71 to 95)			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR) per the Lugano Classification as

Determined by Study Investigators

End point title	Objective Response Rate (ORR) per the Lugano Classification as Determined by Study Investigators

End point description:

ORR: percentage of participants with CR (CMR;CRR) or PR (partial metabolic response (PMR); partial radiologic response (PRR)). CMR and CRR defined in OM 1. PMR: scores 4 (uptake moderately >liver),5 (uptake markedly >liver, new lesions) with reduced uptake compared with baseline and residual mass; no new lesions; responding disease at interim/residual disease at end of treatment (EOT). PRR: ≥50% decrease in sum of the product of perpendicular diameters (SPD) of up to 6 target measurable nodes and extra-nodal sites; absent/normal, regressed, but no increase of NMLs; spleen regressed by >50% in length beyond normal; no new sites.

Participants in the Response Evaluable Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Up to 4 years

End point values	Axicabtagene Ciloleucel			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: percentage of participants				
number (confidence interval 95%)	92 (78 to 98)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)

End point description:

PFS was defined as the time from axicabtagene ciloleucel infusion date to the date of disease progression per Lugano classification or death from any cause.

Participants in Response Evaluable Analysis Set were analyzed. Participants not meeting the criteria by analysis data cutoff date were censored at their last evaluable disease assessment date or new antilymphoma therapy start date (with stem cell transplant or retreatment of axicabtagene ciloleucel) whichever was earlier. PD is defined in endpoint 3. '9999' means data not available as participants were censored.

End point type	Secondary

End point timeframe:

Up to 4 years

End point values	Axicabtagene Ciloleucel			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: months				
median (full range (min-max))	9999 (9999 to 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is defined as the time from axicabtagene ciloleucel infusion to the date of death from any cause.

Participants in Response Evaluable Analysis Set were analyzed. Participants who did not die by the analysis data cutoff date were
censored at their last known alive date prior to the data cutoff date with the exception that participants known to be alive or
determined to have died after the data cutoff date were to be censored at the data cutoff date. '9999' means data not available due to low number of participants with events. KM estimates were used for analysis.

End point type	Secondary

End point timeframe:

Up to 4 years

End point values	Axicabtagene Ciloleucel			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: months				
median (full range (min-max))	9999 (9999 to 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) per the Lugano Classification

End point title	Duration of Response (DOR) per the Lugano Classification

End point description:

DOR applied to participants who had OR after axicabtagene ciloleucel infusion. DOR: Time from first OR to disease progression (PD) or death from any cause. OR was defined in endpoint 2. PD: a score 4 (uptake moderately >liver) or 5 (uptake markedly >liver and/or new lesions) with increase in intensity of uptake from baseline; new FDG-avid foci consistent with lymphoma at interim or end of treatment assessment; new FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection,

inflammation); new or recurrent FDG-avid foci in bone marrow.
Participants in Response Evaluable Analysis Set with OR were analyzed. Participants not meeting criteria by data cutoff date were censored at last evaluable disease assessment date/new anti-lymphoma therapy start (with stem cell transplant or retreatment of axicabtagene ciloleucel), whichever was earlier. KM estimates were used for analysis. '9999' means data not available due to low number of participants with events.

End point type	Secondary

End point timeframe:

Up to 4 years

End point values	Axicabtagene Ciloleucel			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: months				
median (full range (min-max))	9999 (9999 to 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Event-Free Survival (EFS)

End point title	Event-Free Survival (EFS)

End point description:

EFS was defined as the time from axicabtagene ciloleucel infusion date to earliest date of PD (Lugano classification), commencement of subsequent new anti-lymphoma therapy including stem cell transplant, or death from any cause. PD is defined in endpoint 3 (DOR).

Participants in Response Evaluable Analysis Set were analyzed. Participants not meeting the criteria by analysis data cutoff date were censored at their last evaluable disease assessment date. '9999' means data not available as participants were censored. KM estimates were used for analysis.

End point type	Secondary

End point timeframe:

Up to 4 years

End point values	Axicabtagene Ciloleucel			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: months				
median (full range (min-max))	9999 (9999 to 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Experiencing Laboratory Toxicity Grade Shifts to Grade 3 or Higher Resulting From Increased Parameter Value

End point title	Percentage of Participants Experiencing Laboratory Toxicity Grade Shifts to Grade 3 or Higher Resulting From Increased Parameter Value

End point description:

Grading categories were determined by Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Participants in Safety Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Up to 2 years

End point values	Axicabtagene Ciloleucel			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percentage of participants				
number (not applicable)				
Hemoglobin	3			
Alanine Aminotransferase	8			
Alkaline Aminotransferase	0			
Aspartate Aminotransferase	5			
Bilirubin	20			
Calcium	5			
Creatinine	5			
Glucose	15			
Magnesium	5			
Sodium	0			
Urate	18			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Treatment-Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (SAE)

End point title	Percentage of Participants With Treatment-Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (SAE)

End point description:

An AE was any untoward medical occurrence in a participant in a clinical trial participant, which did not necessarily have a causal relationship with the treatment. Treatment-emergent adverse events were defined as any adverse event with onset on or after the axicabtagene ciloleucel infusion. Serious adverse event was defined as an event that resulted in the following: death; life-threatening situation; in-patient hospitalization or prolongation of existing hospitalization; persistent or significant disability or incapacity; congenital anomaly or birth defect; and medically important event or reaction.

Safety Analysis Set included all participants treated with any dose of axicabtagene ciloleucel.

End point type	Secondary

End point timeframe:

Up to 2 years

End point values	Axicabtagene Ciloleucel			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percentage of participants				
number (not applicable)				
TEAEs	100			
Treatment-Emergent SAE	55			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Experiencing Laboratory Toxicity Grade Shifts to Grade 3 or Higher Resulting From Decreased Parameter Value

End point title	Percentage of Participants Experiencing Laboratory Toxicity Grade Shifts to Grade 3 or Higher Resulting From Decreased Parameter Value

End point description:

Grading categories were determined by CTCAE version 5.0.

Participants in Safety Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Up to 2 years

End point values	Axicabtagene Ciloleucel			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percentage of participants				
number (not applicable)				
Hemoglobin	43			
Leukocytes	93			
Lymphocytes	75			
Neutrophils	95			
Platelets	25			
Albumin	3			
Calcium	10			
Glucose	0			

Magnesium	3			
Potassium	5			
Sodium	23			

Statistical analyses

No statistical analyses for this end point

Secondary: Peak Serum Level of Granzyme B, Interferon-gamma (IFNg), Interleukin (IL)-2, IL-5, IL-6, IL-8

End point title	Peak Serum Level of Granzyme B, Interferon-gamma (IFNg), Interleukin (IL)-2, IL-5, IL-6, IL-8

End point description:

Peak is defined as the maximum post-baseline level of cytokine from baseline to Week 4.

Participants in Safety Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Up to Week 4

End point values	Axicabtagene Ciloleucel			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: pg/mL				
median (inter-quartile range (Q1-Q3))				
Granzyme B	28.5 (11.8 to 75.6)			
IFNg	409.4 (157.8 to 856.8)			
IL-2	16.4 (9.7 to 32.9)			
IL-5	6.3 (6.3 to 26.2)			
IL-6	35.1 (13.2 to 181.1)			
IL-8	63.0 (30.1 to 107.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Peak Level of Anti-CD19 CAR T Cells in Blood

End point title	Pharmacokinetics: Peak Level of Anti-CD19 CAR T Cells in Blood

End point description:

Peak was defined as the maximum number of CAR T cells in blood measured after infusion.

Participants in Safety Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Up to Month 24

End point values	Axicabtagene Ciloleucel			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: cells/μL				
median (inter-quartile range (Q1-Q3))	36.27 (20.51 to 133.96)			

Statistical analyses

No statistical analyses for this end point

Secondary: Relapse with Central Nervous Disease (CNS) Disease

End point title	Relapse with Central Nervous Disease (CNS) Disease

End point description:

Relapse with CNS disease was defined as the time from the axicabtagene ciloleucel infusion date to the earliest date of CNS involvement with lymphoma as determined by typical symptoms, cerebrospinal fluid (CSF) evaluation, and/or diagnostic imaging.

Participants in Response Evaluable Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

First infusion date of axicabtagene ciloleucel to data cutoff date of 19 Dec 2023 (Up to approximately 57.2 months)

End point values	Axicabtagene Ciloleucel			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: months				
median (full range (min-max))	0 (0 to 0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Peak Serum Level of C-Reactive Protein (CRP)

End point title	Peak Serum Level of C-Reactive Protein (CRP)

End point description:

Peak is defined as the maximum post-baseline level of cytokine from baseline to Week 4.

Participants in Safety Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Up to Week 4

End point values	Axicabtagene Ciloleucel			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: mg/L				
median (inter-quartile range (Q1-Q3))	208.4 (60.9 to 407.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Peak Serum Level of Ferritin

End point title	Peak Serum Level of Ferritin

End point description:

Peak is defined as the maximum post-baseline level of cytokine from baseline to Week 4.

Participants in Safety Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Up to Week 4

End point values	Axicabtagene Ciloleucel			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: ng/mL				
median (inter-quartile range (Q1-Q3))	749.1 (473.9 to 1874.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Peak Serum Level of Granzyme B, Interferon-gamma (IFNg), Interleukin (IL)-2, IL-5, IL-6, IL-8, CRP, and Ferritin

End point title	Time to Peak Serum Level of Granzyme B, Interferon-gamma (IFNg), Interleukin (IL)-2, IL-5, IL-6, IL-8, CRP, and Ferritin

End point description:

Time to peak is defined as the number of days from axicabtagene ciloleucel infusion to the date when the cytokine first reached the maximum post-baseline level.

Participants in Safety Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Up to Week 4

End point values	Axicabtagene Ciloleucel			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: days				
median (inter-quartile range (Q1-Q3))				
Granzyme B	8 (8 to 8)			
IFNg	4 (4 to 8)			
IL-2	4 (4 to 4)			
IL-5	1 (1 to 4)			
IL-6	8 (4 to 8)			
IL-8	8 (4 to 8)			
CRP	4 (4 to 8)			
Ferritin	8 (6 to 8)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality: Up to 4 years; Adverse events: Up to 2 years

Adverse event reporting additional description:

All-cause mortality: All Enrolled Analysis Set included all enrolled/leukapheresed participants.
Adverse Events: Axicabtagene Ciloleucel arm: Safety Analysis Set included all participants treated with any dose of study drug.
Retreatment arm: Safety Retreatment Analysis Set included all participants who underwent retreatment with study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Retreatment Axicabtagene Ciloleucel

Reporting group description:

Participants who achieved partial response or complete response and subsequently experienced disease progression had an option to receive second course of conditioning chemotherapy therapy and axicabtagene ciloleucel. Participants received the same axicabtagene ciloleucel regimen as the original target dose anytime during the study (Up to 4 years).

Reporting group title	Axicabtagene Ciloleucel

Reporting group description:

Participants received 500 mg/m^2 cyclophosphamide IV and 30 mg/m^2/day fludarabine IV 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-CD19 CAR T cells/kg on Day 0. For participants weighing ≥ 100 kg, a maximum flat dose of axicabtagene ciloleucel at 2 x 10^8 anti-CD19 CAR T cells was administered.

Serious adverse events	Retreatment Axicabtagene Ciloleucel	Axicabtagene Ciloleucel	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	22 / 40 (55.00%)	
number of deaths (all causes)	1	7	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
subjects affected / exposed	0 / 1 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stromal tumour			

subjects affected / exposed	0 / 1 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukaemia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal adenocarcinoma			
subjects affected / exposed	0 / 1 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 1 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 1 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 1 (0.00%)	3 / 40 (7.50%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 1 (0.00%)	2 / 40 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Autoimmune disorder			
subjects affected / exposed	0 / 1 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 1 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 1 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	0 / 1 (0.00%)	4 / 40 (10.00%)	
occurrences causally related to treatment / all	0 / 0	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 1 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 1 (100.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			

subjects affected / exposed	0 / 1 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Immune effector cell-associated ~ neurotoxicity syndrome			
subjects affected / exposed	0 / 1 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 1 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	0 / 1 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 1 (0.00%)	5 / 40 (12.50%)	
occurrences causally related to treatment / all	0 / 0	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Memory impairment			
subjects affected / exposed	0 / 1 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Neutropenia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 1 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 1 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 1 (0.00%)	2 / 40 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 1 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Covid-19			
subjects affected / exposed	0 / 1 (0.00%)	2 / 40 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Covid-19 pneumonia			
subjects affected / exposed	0 / 1 (0.00%)	2 / 40 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection ~ reactivation			

subjects affected / exposed	0 / 1 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 1 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	0 / 1 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital infection			
subjects affected / exposed	0 / 1 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 1 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Retreatment Axicabtagene Ciloleucel	Axicabtagene Ciloleucel	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	40 / 40 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 1 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	3	
Hypotension			
subjects affected / exposed	0 / 1 (0.00%)	14 / 40 (35.00%)	
occurrences (all)	0	18	
General disorders and administration site conditions			

Non-cardiac chest pain			
subjects affected / exposed	0 / 1 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Oedema peripheral			
subjects affected / exposed	0 / 1 (0.00%)	5 / 40 (12.50%)	
occurrences (all)	0	5	
Chills			
subjects affected / exposed	0 / 1 (0.00%)	11 / 40 (27.50%)	
occurrences (all)	0	12	
Fatigue			
subjects affected / exposed	0 / 1 (0.00%)	20 / 40 (50.00%)	
occurrences (all)	0	21	
Pyrexia			
subjects affected / exposed	0 / 1 (0.00%)	39 / 40 (97.50%)	
occurrences (all)	0	49	
Immune system disorders			
Hypogammaglobulinaemia			
subjects affected / exposed	0 / 1 (0.00%)	4 / 40 (10.00%)	
occurrences (all)	0	4	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 1 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 1 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	3	
Cough			
subjects affected / exposed	0 / 1 (0.00%)	5 / 40 (12.50%)	
occurrences (all)	0	5	
Hypoxia			
subjects affected / exposed	0 / 1 (0.00%)	11 / 40 (27.50%)	
occurrences (all)	0	13	
Pulmonary oedema			
subjects affected / exposed	0 / 1 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	

Pleural effusion			
subjects affected / exposed	0 / 1 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	3	
Nasal congestion			
subjects affected / exposed	0 / 1 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	3	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 1 (0.00%)	6 / 40 (15.00%)	
occurrences (all)	0	7	
Confusional state			
subjects affected / exposed	0 / 1 (0.00%)	11 / 40 (27.50%)	
occurrences (all)	0	11	
Agitation			
subjects affected / exposed	0 / 1 (0.00%)	4 / 40 (10.00%)	
occurrences (all)	0	8	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 1 (0.00%)	7 / 40 (17.50%)	
occurrences (all)	0	7	
Platelet count decreased			
subjects affected / exposed	0 / 1 (0.00%)	7 / 40 (17.50%)	
occurrences (all)	0	9	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 1 (0.00%)	5 / 40 (12.50%)	
occurrences (all)	0	7	
Lymphocyte count decreased			
subjects affected / exposed	0 / 1 (0.00%)	4 / 40 (10.00%)	
occurrences (all)	0	5	
Blood bilirubin increased			
subjects affected / exposed	0 / 1 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	4	
White blood cell count decreased			
subjects affected / exposed	1 / 1 (100.00%)	18 / 40 (45.00%)	
occurrences (all)	2	31	
Neutrophil count decreased			

subjects affected / exposed	1 / 1 (100.00%)	21 / 40 (52.50%)	
occurrences (all)	2	31	
Blood fibrinogen decreased			
subjects affected / exposed	0 / 1 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	7	
Cardiac disorders			
Ventricular arrhythmia			
subjects affected / exposed	0 / 1 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	3	
Sinus bradycardia			
subjects affected / exposed	0 / 1 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	4	
Sinus tachycardia			
subjects affected / exposed	0 / 1 (0.00%)	10 / 40 (25.00%)	
occurrences (all)	0	15	
Atrial fibrillation			
subjects affected / exposed	0 / 1 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	3	
Tachycardia			
subjects affected / exposed	0 / 1 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Nervous system disorders			
Memory impairment			
subjects affected / exposed	0 / 1 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	3	
Dizziness			
subjects affected / exposed	0 / 1 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Dysgraphia			
subjects affected / exposed	0 / 1 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	3	
Encephalopathy			
subjects affected / exposed	0 / 1 (0.00%)	8 / 40 (20.00%)	
occurrences (all)	0	12	
Tremor			

subjects affected / exposed	0 / 1 (0.00%)	10 / 40 (25.00%)	
occurrences (all)	0	10	
Headache			
subjects affected / exposed	0 / 1 (0.00%)	28 / 40 (70.00%)	
occurrences (all)	0	34	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 1 (0.00%)	5 / 40 (12.50%)	
occurrences (all)	0	6	
Anaemia			
subjects affected / exposed	0 / 1 (0.00%)	13 / 40 (32.50%)	
occurrences (all)	0	18	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 1 (0.00%)	8 / 40 (20.00%)	
occurrences (all)	0	10	
Constipation			
subjects affected / exposed	1 / 1 (100.00%)	8 / 40 (20.00%)	
occurrences (all)	1	8	
Nausea			
subjects affected / exposed	0 / 1 (0.00%)	21 / 40 (52.50%)	
occurrences (all)	0	28	
Diarrhoea			
subjects affected / exposed	1 / 1 (100.00%)	20 / 40 (50.00%)	
occurrences (all)	1	22	
Abdominal pain			
subjects affected / exposed	0 / 1 (0.00%)	4 / 40 (10.00%)	
occurrences (all)	0	4	
Dry mouth			
subjects affected / exposed	0 / 1 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	3	
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 1 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	0 / 1 (0.00%)	4 / 40 (10.00%)	
occurrences (all)	0	4	
Muscular weakness			
subjects affected / exposed	0 / 1 (0.00%)	6 / 40 (15.00%)	
occurrences (all)	0	9	
Infections and infestations			
Sinusitis			
subjects affected / exposed	0 / 1 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Covid-19			
subjects affected / exposed	0 / 1 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Urinary tract infection			
subjects affected / exposed	0 / 1 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	3	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 1 (0.00%)	11 / 40 (27.50%)	
occurrences (all)	0	12	
Decreased appetite			
subjects affected / exposed	0 / 1 (0.00%)	8 / 40 (20.00%)	
occurrences (all)	0	8	
Hypophosphataemia			
subjects affected / exposed	0 / 1 (0.00%)	7 / 40 (17.50%)	
occurrences (all)	0	7	
Hyponatraemia			
subjects affected / exposed	0 / 1 (0.00%)	5 / 40 (12.50%)	
occurrences (all)	0	9	
Hypocalcaemia			
subjects affected / exposed	0 / 1 (0.00%)	4 / 40 (10.00%)	
occurrences (all)	0	4	
Hypoalbuminaemia			
subjects affected / exposed	0 / 1 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	3	
Dehydration			

subjects affected / exposed	1 / 1 (100.00%)	1 / 40 (2.50%)	
occurrences (all)	1	1	
Hypomagnesaemia			
subjects affected / exposed	0 / 1 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 August 2019	• Clarified the indication language to include "LBCL with a high-intermediate-/high-risk IPI score of ≥ 3; all subjects must have positive PET after 2 cycles (PET2+) of chemoimmunotherapy." • Updated the DSMB meeting content, frequency, and the inclusion of an interim analysis. Changed language from reviewing SAE information and SUSARs on a "regular basis" to "semi-annual basis" throughout subject treatment in the study. • Clarified DLBCL subtypes based upon the 2016 revision of the WHO classification and added additional disease background information • Clarified language for neurological examination frequency from "every other day" to read as "a neurological examination should be done prior to axicabtagene ciloleucel infusion on treatment Day 0, then on Day 1, Day 3, Day 5, and Day 7 during the observation period, which must last a minimum of 7 days." • Added language allowing for PET-CT done as a screening procedure for disease assessment, as needed, and clarified that disease assessments will be evaluated per the Lugano classification • Changed acetaminophen dosage from "650 mg PO or equivalent" to "500 to 1000 mg taken orally or equivalent", changed diphenhydramine range to "12.5 to 25 mg administered either orally or intravenously or equivalent" • Added duration for enrolled subjects in the long-term follow-up for up to 15 years, if applicable • Updated several aspects of the summary of assessments, including: • Added new footnotes to the SOA for country-specific assessments, including pregnancy testing and serologic testing • Added a blood draw for minimum residual disease testing at Week 4, Month 3, and Month 6 • Added "stable disease" as a potential outcome for best response to treatment
25 March 2022	• A LTFU study was developed to allow for rollover of participants to complete the 15-year follow-up after infusion of axicabtagene ciloleucel on ZUMA-12. The protocol was amended to provide the opportunity for participants to roll over to the LTFU study for safety follow-up and reduced burden of study-specific assessments. • The AE and SAE reporting period was extended from 24 months to 15 years. A US Food and Drug Administration (FDA) mandate on the LTFU study required targeted AE/SAE reporting up to 15 years for all participants who received axicabtagene ciloleucel. The collection of targeted AE/SAEs was therefore extended in ZUMA-12 to prevent reporting gaps before participant transition to the LTFU study.
14 June 2022	• The introduction of a time limit for optional retreatment. If a participant is eligible and wishes to undergo retreatment, they must do so within 24 months after their initial axicabtagene ciloleucel infusion. • The option of investigational product retreatment has been removed from the LTFU study. Participants will not be able to undergo retreatment once they roll over from the ZUMA-12 study to the LTFU study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported