Clinical trial results:
A Phase II, single arm, multicenter, open-label trial to determine the safety and efficacy of tisagenlecleucel in pediatric patients with relapsed or refractory mature B-cell non-Hodgkin lymphoma (BIANCA)

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.nov for complete trial results

Summary

EudraCT number	2017-005019-15
Trial protocol	ES FR DE SE DK NO AT GB NL FI IT
Global end of trial date	26 April 2023
Results information	
Result version number	v1 (current)
This version publication date	10 November 2023
First version publication date	10 November 2023

Trial information

Trial identification	
Sponsor protocol code	CCTL019C2202
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03610724
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Novartis Pharma, AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111, novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111, novartis.email@novartis.com

Notes:

Paediatric regulatory details	
Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001654-PIP02-17

Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 April 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 April 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the efficacy of tisagenlecleucel therapy as measured by ORR and determined by local investigator assessments in subjects with aggressive r/r B-cell NHL.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 February 2019
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	Australia: 2
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Japan: 4
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Norway: 2
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	United Kingdom: 4

Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	33
EEA total number of subjects	14

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	11
Adolescents (12-17 years)	18
Adults (18-64 years)	4
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted in twenty-four centers across 14 countries. Although 34 participants met the eligibility criteria and apheresis was accepted by the manufacturing facility, only 33 were infused in the study.

Pre-assignment

Screening details:

Consent, Screening, Pre-treatment, Treatment and Follow-up. In the Pretreatment phase, the subject may have undergone optional bridging therapy or lymphodepleting chemotherapy.
Full Analysis Set: 33
Efficacy Analysis Set (EAS): 28; 4 patients with Complete Response prior to infusion & 1 without a scan prior to infusion excluded from EAS.

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	Tisagenlecleucel

Arm description:

These participants were infused once with CAR-positive viable T cells.

Arm type	Experimental
Investigational medicinal product name	Tisagenlecleucel
Investigational medicinal product code	CTL019
Other name	
Pharmaceutical forms	Blood fraction modifier
Routes of administration	Intravenous use

Dosage and administration details:

Tisagenlecleucel was administered once as an intravenous infusion, at a dose of either 0.2 to 5 x 106 CAR-positive viable T cells per kg body weight for subjects ≤ 50 kg or 0.1 to 2.5 x 108 CARpositive viable T cells for subjects > 50 kg

Investigational medicinal product name	lymphodepleting chemotherapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

lymphodepletion with recommended Fludarabine (30 mg/m2 IV daily for 4 days) and cyclophosphamide (500 mg/m2 IV
daily for 2 days starting with the first dose of fludarabine) (unless contra-indicated for subject)

Investigational medicinal product name	Bridging Therapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Pre-treatment phase could also include bridging therapy of investigator’s choice

Number of subjects in period 1	Tisagenlecleucel
Started	33
Met Eligibilty criteria and were infused	33
Met Eligibilty criteria, not infused*	1
Completed treatment & primary f/u phase	14
Discont. treatment & primary f/u phase	19
Completed	14
Not completed	19
Adverse event, serious fatal	17
Physician decision	1
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Tisagenlecleucel
Reporting group description:	
These participants were infused once with CAR-positive viable T cells.	

Reporting group values	Tisagenlecleucel	Total	
Number of subjects	33	33	
Age categorical Units: Subjects			
Children (2-11 years)	11	11	
Adolescents (12-17 years)	18	18	
Adults (18-64 years)	4	4	
Age Continuous Units: years			
median	12.8		
standard deviation	± 4.98	-	
Sex: Female, Male Units: Participants			
Female	10	10	
Male	23	23	
Race/Ethnicity, Customized Units: Subjects			
White	28	28	
Black or African American	1	1	
Asian	2	2	
Missing	2	2	

End points

End points reporting groups

Reporting group title	Tisagenlecleucel

Reporting group description:

These participants were infused once with CAR-positive viable T cells.

Primary: Overall response rate (ORR) as determined by local investigator

End point title	Overall response rate (ORR) as determined by local investigator[1]

End point description:

The overall response rate (ORR) is defined as the percentage of subjects with a best overall disease response of complete response (CR) or partial response (PR), where the best overall disease response is defined as the best disease response recorded from tisagenlecleucel infusion until progressive disease or start of new anticancer therapy, whichever comes first.

End point type	Primary

End point timeframe:

any time post-tisagenlecleucel infusion until progressive disease, start of new anticancer therapy, discontinuation or end of study (2 years after last patient first visit), 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: No statistical analysis was done.

End point values	Tisagenlecleucel			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: Percentage of participants				
number (confidence interval 95%)	32.1 (15.9 to 52.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Event free survival (EFS)

End point title	Event free survival (EFS)

End point description:

Event free survival (EFS) is defined as the time from date of first tisagenlecleucel infusion to the earliest date of death from any cause, disease progression as determined by local investigator assessments, or starting new anticancer therapy for underlying cancer, excluding hematopoietic stem cell transplant (HSCT).

End point type	Secondary

End point timeframe:

Through study completion, up to 4 years

End point values	Tisagenlecleucel			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: months				
median (confidence interval 95%)	2.1 (1.1 to 2.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DOR)

End point title	Duration of response (DOR)

End point description:

Duration of response (DOR) is defined as the time from the date of first documented disease response (CR or PR) as determined by local investigator assessments to the date of first documented progression or death due to underlying cancer.

End point type	Secondary

End point timeframe:

Through study completion, up to 4 years

End point values	Tisagenlecleucel			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: months				
median (confidence interval 95%)	9 (1.0 to 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (PFS)

End point title	Progression free survival (PFS)

End point description:

Progression free survival (PFS) is defined as the time from the date of first tisagenlecleucel infusion to the date of first documented disease progression as determined by local investigator assessments or death due to any cause.

End point type	Secondary

End point timeframe:

Through study completion, up to 4 years

End point values	Tisagenlecleucel			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: months				
median (confidence interval 95%)	2.5 (1.1 to 2.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Relapse free survival (RFS)

End point title	Relapse free survival (RFS)

End point description:

Relapse free survival (RFS) is defined as the time from the date of first documented disease response (CR or PR) as determined by local investigator assessments to the date of first documented disease progression or death due to any cause.

End point type	Secondary

End point timeframe:

Through study completion, up to 4 years

End point values	Tisagenlecleucel			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: months				
median (confidence interval 95%)	9 (1.0 to 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

Overall survival (OS) is defined as the time from date of first tisagenlecleucel infusion to the date of death due to any cause.

End point type	Secondary

End point timeframe:

Through study completion, up to 4 years

End point values	Tisagenlecleucel			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: months				
median (confidence interval 95%)	10.4 (3.4 to 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cellular kinetics parameter: Tlast

End point title	Cellular kinetics parameter: Tlast

End point description:

The time of last observed quantifiable transgene level in peripheral blood. Pharmacokinetics of tisagenlecleucel were based on chimeric antigen receptor (CAR) transgene levels in peripheral blood as detected by qPCR, unless otherwise noted.

End point type	Secondary

End point timeframe:

Through study completion, up to 4 years

End point values	Tisagenlecleucel			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: days				
median (full range (min-max))	40.0 (13.0 to 1090)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cellular kinetics parameter: Tmax

End point title	Cellular kinetics parameter: Tmax

End point description:

The time to reach maximum (peak) transgene level (days) in peripheral blood or other body fluid after single dose administration. Pharmacokinetics of tisagenlecleucel were based on chimeric antigen receptor (CAR) transgene levels in peripheral blood as detected by qPCR, unless otherwise noted.

End point type	Secondary

End point timeframe:

Through study completion, up to 4 years

End point values	Tisagenlecleucel			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: days				
median (full range (min-max))	12.7 (1.90 to 21.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Levels of pre-existing and treatment induced humoral immunogenicity and cellular immunogenicity against tisagenlecleucel cellular kinetics, safety and efficacy

End point title	Levels of pre-existing and treatment induced humoral immunogenicity and cellular immunogenicity against tisagenlecleucel cellular kinetics, safety and efficacy

End point description:

The humoral immunogenicity assay measures the antibody titers specific to tisagenlecleucel prior to and following infusion by flow cytometry. A subject was only defined as positive for tisagenlecleucel treatment-induced or -boosted anti-mCAR19 antibodies when the anti-mCAR19 antibody median fluorescence intensity at any time post-infusion was at least 2.28-fold higher (for samples analyzed on or prior to 05-May-2021) or 2.38-fold higher (for samples analyzed on or after 06-May-2021) than pre-infusion levels for participants whose baseline status was positive (boosted) or if the baseline status was negative but any post-baseline interpretation was positive (induced).

End point type	Secondary

End point timeframe:

Until disease progression or through study completion, up to 4 years

End point values	Tisagenlecleucel			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: Percentage of participants				
number (not applicable)				
anti-tisagenlecleucel antibodies (+ve) at baseline	87.9			
anti-tisa antibodies (+ve) anytime post-baseline	97.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Cellular kinetics parameter: Clast

End point title	Cellular kinetics parameter: Clast

End point description:

The last observed quantifiable transgene level in peripheral blood. Pharmacokinetics of tisagenlecleucel were based on chimeric antigen receptor (CAR) transgene levels in peripheral blood as detected by qPCR, unless otherwise noted.

End point type	Secondary

End point timeframe:

Through study completion, up to 4 years

End point values	Tisagenlecleucel			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: copies/µg				
geometric mean (geometric coefficient of variation)	344 (± 350.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cellular kinetics parameter: AUC0-28d

End point title	Cellular kinetics parameter: AUC0-28d

End point description:

Area Under the Concentration-time Curve (AUs) from the time course of transgene levels in peripheral blood following tisagenlecleucel infusion (days*copies/µg), from day of infusion to day 28. D28 refers to the timepoint for definition of responder populations. Pharmacokinetics of tisagenlecleucel were based on chimeric antigen receptor (CAR) transgene levels in peripheral blood as detected by qPCR, unless otherwise noted.

End point type	Secondary

End point timeframe:

Through study completion, up to 4 years

End point values	Tisagenlecleucel			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: copies/µg*days				
geometric mean (geometric coefficient of variation)	53500 (± 154.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cellular kinetics parameter: Cmax

End point title	Cellular kinetics parameter: Cmax

End point description:

The maximum (peak) transgene level (copies/µg) observed in peripheral blood or other body fluid after single dose administration as measured by qPCR. Pharmacokinetics of tisagenlecleucel were based on chimeric antigen receptor (CAR) transgene levels in peripheral blood as detected by qPCR, unless otherwise noted. Pharmacokinetics of tisagenlecleucel were based on chimeric antigen receptor (CAR) transgene levels in peripheral blood as detected by qPCR, unless otherwise noted.

End point type	Secondary

End point timeframe:

Through study completion, up to 4 years

End point values	Tisagenlecleucel			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: copies/µg				
geometric mean (geometric coefficient of variation)	5140 (± 238.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who proceeded to stem cell transplant (SCT) after tisagenlecleucel infusion

End point title	Percentage of participants who proceeded to stem cell transplant (SCT) after tisagenlecleucel infusion

End point description:

These participants proceeded to transplant any time post-tisagenlecleucel therapy until end of study (EOS).

End point type	Secondary

End point timeframe:

Through study completion, up to 4 years

End point values	Tisagenlecleucel			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: Percentage of participants				
number (not applicable)	21.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Positive Predictive Value (PPV)

End point title	Maximum Positive Predictive Value (PPV)

End point description:

Retrospective assessment of potential cytokine release syndrome (CRS) predictive models considering also data from other CTL019 trials. The Positive Predictive Value (PVV) is the percentage of participants who actually had severe CRS out of all the cases where the prediction model predicts that severe CRS will occur. The maximum PPV is the highest value attained across all potential CRS predictive models.

End point type	Secondary

End point timeframe:

Through study completion, up to 4 years

End point values	Tisagenlecleucel			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: Percentage of participants				
number (not applicable)	36.0			

Statistical analyses

No statistical analyses for this end point

Post-hoc: All Collected Deaths

End point title	All Collected Deaths

End point description:

On-treatment deaths were collected during the pos-infusion period starting at the day of first infusion until the end of the study, up to 48 months. All deaths is the sum of pre-infusion and post-infusion deaths.

Note: 33 patients were infused with tisagenlecleucel. The one death prior to infusion is an additional patient who was enrolled but not infused and is not part of the 33 infused patients.

End point type	Post-hoc

End point timeframe:

Pre-treatment deaths: from enrollment to pre-infusion; On-treatment deaths: post-infusion up to 48 months

End point values	Tisagenlecleucel			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: Participants				
On-treatment deaths incl post-infusion deaths	17			
Deaths prior to infusion	1			
All Deaths	18			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs: collected during the post-infusion period, starting at the day of 1st infusion until the end of the study, up to max. duration of 48 months for each patient.
Deaths: collected at all points post-infusion until patients completed the study (LPLV).

Adverse event reporting additional description:

Any sign or symptom that occurs during the post-infusion period (starting at the day of first infusion of CTL019 until the end of the study) and safety follow-up. Deaths in the post treatment survival follow-up are not considered Adverse Events while still included in the All-Cause Mortality table.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Tisagenlecleucel - All patients

Reporting group description:

These participants were infused once with CAR-positive viable T cells.

Serious adverse events	Tisagenlecleucel - All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 33 (72.73%)		
number of deaths (all causes)	17		
number of deaths resulting from adverse events	0		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Condition aggravated			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Disease progression			

subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pyrexia				
subjects affected / exposed	7 / 33 (21.21%)			
occurrences causally related to treatment / all	4 / 7			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Cytokine release syndrome				
subjects affected / exposed	8 / 33 (24.24%)			
occurrences causally related to treatment / all	8 / 8			
deaths causally related to treatment / all	0 / 0			
Haemophagocytic lymphohistiocytosis				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Pneumothorax				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	3 / 33 (9.09%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Respiratory distress				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Investigations			
Ejection fraction decreased			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutrophil count decreased			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tachycardia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Seizure			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Peripheral sensorimotor neuropathy			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Motor dysfunction			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Aphasia			

subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Depressed level of consciousness			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		
Disturbance in attention			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hemiparesis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Memory impairment			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Dental caries				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestinal obstruction				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Proctitis				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	2 / 33 (6.06%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Musculoskeletal and connective tissue disorders				
Back pain				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Aspergillus infection				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pseudomonas infection				

subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Candida infection			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Urinary tract infection			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Vascular device infection			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Tisagenlecleucel - All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 33 (100.00%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Haematoma			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Hypertension			

subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Chills			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	4		
Fatigue			
subjects affected / exposed	5 / 33 (15.15%)		
occurrences (all)	5		
Generalised oedema			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Oedema peripheral			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Pain			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	14 / 33 (42.42%)		
occurrences (all)	25		
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	16 / 33 (48.48%)		
occurrences (all)	19		
Drug hypersensitivity			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Hypogammaglobulinaemia			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	4		
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	5 / 33 (15.15%) 5		
Epistaxis subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 4		
Pleural effusion subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2		
Tachypnoea subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2		
Depression subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2		
Insomnia subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	5 / 33 (15.15%) 8		
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 3		
Blood bilirubin increased subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 3		
Blood creatinine increased subjects affected / exposed occurrences (all)	5 / 33 (15.15%) 6		
Blood lactate dehydrogenase increased			

subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Lymphocyte count decreased			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	4		
Neutrophil count decreased			
subjects affected / exposed	10 / 33 (30.30%)		
occurrences (all)	19		
Platelet count decreased			
subjects affected / exposed	9 / 33 (27.27%)		
occurrences (all)	9		
SARS-CoV-2 test positive			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Serum ferritin increased			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Weight decreased			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	4		
White blood cell count decreased			
subjects affected / exposed	8 / 33 (24.24%)		
occurrences (all)	8		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Tachycardia			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	4		
Nervous system disorders			

Depressed level of consciousness				
subjects affected / exposed	2 / 33 (6.06%)			
occurrences (all)	2			
Dizziness				
subjects affected / exposed	2 / 33 (6.06%)			
occurrences (all)	3			
Headache				
subjects affected / exposed	8 / 33 (24.24%)			
occurrences (all)	11			
Neuralgia				
subjects affected / exposed	2 / 33 (6.06%)			
occurrences (all)	2			
Neuropathy peripheral				
subjects affected / exposed	2 / 33 (6.06%)			
occurrences (all)	2			
Paraesthesia				
subjects affected / exposed	3 / 33 (9.09%)			
occurrences (all)	3			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	11 / 33 (33.33%)			
occurrences (all)	18			
Bone marrow failure				
subjects affected / exposed	2 / 33 (6.06%)			
occurrences (all)	2			
Coagulopathy				
subjects affected / exposed	2 / 33 (6.06%)			
occurrences (all)	2			
Febrile neutropenia				
subjects affected / exposed	2 / 33 (6.06%)			
occurrences (all)	2			
Leukopenia				
subjects affected / exposed	5 / 33 (15.15%)			
occurrences (all)	7			
Lymphopenia				

subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Neutropenia			
subjects affected / exposed	7 / 33 (21.21%)		
occurrences (all)	11		
Thrombocytopenia			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	4		
Eye disorders			
Vision blurred			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Abdominal pain			
subjects affected / exposed	6 / 33 (18.18%)		
occurrences (all)	9		
Abdominal pain upper			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Constipation			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Lower gastrointestinal haemorrhage			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	9 / 33 (27.27%)		
occurrences (all)	13		
Small intestinal obstruction			

subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Stomatitis			
subjects affected / exposed	5 / 33 (15.15%)		
occurrences (all)	6		
Vomiting			
subjects affected / exposed	13 / 33 (39.39%)		
occurrences (all)	19		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Dry skin			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Pruritus			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Rash			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Neck pain			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Infections and infestations			

Myelitis subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	5 / 33 (15.15%) 6		
Hyperphosphataemia subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 3		
Hypomagnesaemia subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 4		
Hyponatraemia subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2		
Hypophosphataemia subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2		
Hypokalaemia subjects affected / exposed occurrences (all)	5 / 33 (15.15%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 January 2020	Update of inclusion criteria to allow patients between 18 and 25 years of age; Update inclusion criteria to allow Burkitt leukemia; Addition of a data monitoring committee for safety monitoring; Removed absolute lymphocyte count and absolute CD3+ T cell requirements from inclusion criteria

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.nov for complete trial results

Notes: