



Clinical trial results:

A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL).

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	2014-003060-20
Trial protocol	AT DE NO NL IT
Global end of trial date	22 December 2022

Results information

Result version number	v1 (current)
This version publication date	07 January 2024
First version publication date	07 January 2024

Trial information

Trial identification

Sponsor protocol code	CCTL019C2201
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02445248
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)	No
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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	22 December 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 December 2022
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 in the Main Cohort (i.e., patients treated with tisagenlecleucel manufactured at the Novartis manufacturing facility in Morris Plains, US) as defined as the overall response rate (ORR), which included complete response (CR) and partial response (PR) as determined by a central independent review committee (IRC).

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	29 July 2015
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: 15
Country: Number of subjects enrolled	Austria: 9
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Japan: 9
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Norway: 6
Country: Number of subjects enrolled	United States: 46
Worldwide total number of subjects	115
EEA total number of subjects	36

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)	89
From 65 to 84 years	26
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

115 participants were infused in this study: 99 in the Main Cohort and 16 in Cohort A.

Pre-assignment

Screening details:

After informed consent/assent was obtained, and prior to infusion, participants underwent a routine lymphodepleting therapy, 14 to 5 days before CTL019 infusion.

There were 27 centers across 10 countries for this trial.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Tisagenlecleucel - Main cohort

Arm description:

Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who received tisagenlecleucel manufactured at the Novartis manufacturing facility in Morris Plains, US.

Arm type	Experimental
Investigational medicinal product name	Lymphodepleting chemotherapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Fludarabine (25 mg/m² intravenously [i.v.] daily for 3 doses) and cyclophosphamide (250 mg/m² i.v. daily for 3 doses starting with the first dose of fludarabine).

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:

The target dose of CTL019 transduced cells for adult patients consisted of a single infusion of 5 x 10⁸ viable CTL019 transduced cells, which was administered via intravenous infusion. The acceptable dose range was 1 - 5x10⁸ viable CTL019 transduced cells.

Arm title	Tisagenlecleucel Cohort A
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Arm description:

Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who received tisagenlecleucel manufactured at the Fraunhofer Institut für Zelltherapie, Leipzig, Germany.

Arm type	Experimental
Investigational medicinal product name	Lymphodepleting chemotherapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Fludarabine (25 mg/m² intravenously [i.v.] daily for 3 doses) and cyclophosphamide (250 mg/m² i.

v. daily for 3 doses starting with the first dose of fludarabine).

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:

The target dose of CTL019 transduced cells for adult patients consisted of a single infusion of 5×10^8 viable CTL019 transduced cells, which was administered via intravenous infusion. The acceptable dose range was 1 - 5×10^8 viable CTL019 transduced cells.

Number of subjects in period 1	Tisagenlecleucel - Main cohort	Tisagenlecleucel Cohort A
Started	99	16
Completed	26	3
Not completed	73	13
Adverse event, serious fatal	45	12
Physician decision	5	-
Subject decision	8	-
Adverse event, non-fatal	1	-
Progressive disease	13	1
Lost to follow-up	1	-

Baseline characteristics

Reporting groups

Reporting group title	Tisagenlecleucel - Main cohort
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Reporting group description:

Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who received tisagenlecleucel manufactured at the Novartis manufacturing facility in Morris Plains, US.

Reporting group title	Tisagenlecleucel Cohort A
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Reporting group description:

Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who received tisagenlecleucel manufactured at the Fraunhofer Institut für Zelltherapie, Leipzig, Germany.

Reporting group values	Tisagenlecleucel - Main cohort	Tisagenlecleucel Cohort A	Total
Number of subjects	99	16	115
Age categorical			
Units: Subjects			
Adults (18-64 years)	75	14	89
From 65-84 years	24	2	26
Age Continuous			
Units: years			
arithmetic mean	54.3	51.1	
standard deviation	± 13.09	± 12.98	-
Sex: Female, Male			
Units: Participants			
Female	36	8	44
Male	63	8	71
Race/Ethnicity, Customized			
Units: Subjects			
White	83	15	98
Asian	10	0	10
Black	4	0	4
Other	2	1	3
ECOG performance status			
Units: Subjects			
ECOG status of 0	54	11	65
ECOG status of 1	45	5	50

End points

End points reporting groups

Reporting group title	Tisagenlecleucel - Main cohort
Reporting group description: Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who received tisagenlecleucel manufactured at the Novartis manufacturing facility in Morris Plains, US.	
Reporting group title	Tisagenlecleucel Cohort A
Reporting group description: Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who received tisagenlecleucel manufactured at the Fraunhofer Institut für Zelltherapie, Leipzig, Germany.	
Subject analysis set title	Tisagenlecleucel - Cohort A
Subject analysis set type	Sub-group analysis
Subject analysis set description: Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who received tisagenlecleucel manufactured at the Fraunhofer Institut für Zelltherapie, Leipzig, Germany.	
Subject analysis set title	Tisagenlecleucel - All Patients
Subject analysis set type	Full analysis
Subject analysis set description: Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who received tisagenlecleucel manufactured at the Novartis manufacturing facility in Morris Plains, US and at the Fraunhofer Institut für Zelltherapie, Leipzig, Germany.	
Subject analysis set title	Tisagenlecleucel - Cohort A
Subject analysis set type	Sub-group analysis
Subject analysis set description: Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who received tisagenlecleucel manufactured at the Fraunhofer Institut für Zelltherapie, Leipzig, Germany.	
Subject analysis set title	Tisagenlecleucel - All Patients
Subject analysis set type	Sub-group analysis
Subject analysis set description: Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who received tisagenlecleucel manufactured at the Novartis manufacturing facility in Morris Plains, US and at the Fraunhofer Institut für Zelltherapie, Leipzig, Germany.	
Subject analysis set title	Tisagenlecleucel - CR/PR
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants with complete response (CR)/partial response (PR) post-tisagenlecleucel infusion.	
Subject analysis set title	Tisagenlecleucel - SD/PD/UNK
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants with stable disease (SD), progressive disease (PD) and an unknown response (UNK) post-tisagenlecleucel infusion.	
Subject analysis set title	Tisagenlecleucel - CR/PR
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants with complete response (CR)/partial response (PR) post-tisagenlecleucel infusion.	
Subject analysis set title	Tisagenlecleucel - SD/PD/UNK
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants with stable disease (SD), progressive disease (PD) and an unknown response (UNK) post-tisagenlecleucel infusion.	
Subject analysis set title	Tisagenlecleucel - CR/PR
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with complete response (CR)/partial response (PR) post-tisagenlecleucel infusion.

Subject analysis set title	Tisagenlecleucel - SD/PD/UNK
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with stable disease (SD), progressive disease (PD) and an unknown response (UNK) post-tisagenlecleucel infusion.

Subject analysis set title	Tisagenlecleucel - CR
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with complete response post-tisagenlecleucel infusion.

Subject analysis set title	Tisagenlecleucel - PR
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with partial response (PR) post-tisagenlecleucel infusion.

Subject analysis set title	Tisagenlecleucel - SD
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with stable disease post-tisagenlecleucel infusion.

Subject analysis set title	Tisagenlecleucel - PD
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with progressive disease post-tisagenlecleucel infusion.

Subject analysis set title	Tisagenlecleucel - UNK
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with unknown response post-tisagenlecleucel infusion.

Subject analysis set title	Tisagenlecleucel - All Participants response
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with complete response, partial response, stable disease, progressive disease and unknown response post-tisagenlecleucel infusion.

Primary: Overall Response Rate (ORR) per Independent Review Committee (IRC) in Main cohort

End point title	Overall Response Rate (ORR) per Independent Review Committee (IRC) in Main cohort ^{[1][2]}
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End point description:

ORR, which includes complete response (CR) and partial response (PR) in the Main cohort as determined by IRC assessment. ORR is the percentage of participants with a best overall disease response of CR or PR, where the best overall disease response is defined as the best disease response recorded from CTL019 infusion until progressive disease or start of new anticancer therapy (including ASCT), whichever comes first.

End point type	Primary
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End point timeframe:

60 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis for this endpoint

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The primary objective was met in the interim analysis (data cut-off date of 20-Dec-2016: $p < 0.0001$ to reject H_0 : ORR \leq 20%) and was also reported in the primary analysis. Therefore, the hypothesis test for the primary efficacy analysis was not repeated for the next analyses. In addition, the EudraCT system requires that at least 2 comparison groups be used but this study has only 1 arm and

so a comparison cannot be done in the EudraCT system.

End point values	Tisagenlecleucel - Main cohort			
Subject group type	Reporting group			
Number of subjects analysed	99			
Units: Percentage of participants				
number (confidence interval 95%)	54.5 (44.2 to 64.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR) per Independent Review Committee (IRC) in Cohort A & in All Patients

End point title	Overall Response Rate (ORR) per Independent Review Committee (IRC) in Cohort A & in All Patients
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End point description:

ORR, which includes complete response (CR) and partial response (PR) in the Main cohort as determined by IRC assessment. ORR is the percentage of participants with a best overall disease response of CR or PR, where the best overall disease response is defined as the best disease response recorded from CTL019 infusion until progressive disease or start of new anticancer therapy (including ASCT), whichever comes first.

End point type	Secondary
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End point timeframe:

5 years

End point values	Tisagenlecleucel - Cohort A	Tisagenlecleucel - All Patients		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	115		
Units: Percentage of participants				
number (confidence interval 95%)	43.8 (19.8 to 70.1)	53.0 (43.5 to 62.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to response (TTR) as assessed by Independent Review Committee (Main Cohort & All Patients)

End point title	Time to response (TTR) as assessed by Independent Review Committee (Main Cohort & All Patients) ^[3]
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End point description:

TTR is the time between date of CTL019 infusion until first documented response (CR or PR).

End point type	Secondary
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End point timeframe:

60 months

Notes:

[3] - 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: No statistical analysis for this endpoint

End point values	Tisagenlecleucel - Main cohort	Tisagenlecleucel - All Patients		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	99	115		
Units: Months				
median (confidence interval 95%)	1.0 (0.9 to 1.0)	1.0 (0.9 to 1.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of overall response (DOR) per IRC

End point title	Duration of overall response (DOR) per IRC ^[4]
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End point description:

DOR is the time from achievement of CR or PR, whichever occurs first, to relapse or death due to diffuse large B-cell lymphoma (DLBCL).

End point type	Secondary
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End point timeframe:

60 months

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis for this endpoint

End point values	Tisagenlecleucel - Main cohort	Tisagenlecleucel - Cohort A	Tisagenlecleucel - All Patients	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	54	7	61	
Units: Months				
median (confidence interval 95%)	99 (10.0 to 999)	9 (1.2 to 99)	99 (10.0 to 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Event free survival (EFS) per Independent Review Committee

End point title	Event free survival (EFS) per Independent Review Committee ^[5]
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End point description:

EFS is the time from date of CTL019 infusion to the date of first documented disease progression or relapse, new treatment for lymphoma or death due to any cause.

End point type	Secondary
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End point timeframe:

60 months

Notes:

[5] - 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: No statistical analysis for this endpoint

End point values	Tisagenlecleucel I - Main cohort	Tisagenlecleucel I - Cohort A	Tisagenlecleucel I - All Patients	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	99	16	115	
Units: Months				
median (confidence interval 95%)	2.8 (2.2 to 3.5)	2.1 (1.0 to 3.1)	2.8 (2.1 to 3.1)	

Statistical analyses

Statistical analysis title	Stats for EFS
Comparison groups	Tisagenlecleucel - Main cohort v Tisagenlecleucel - Cohort A
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Median EFS
Point estimate	2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.1
upper limit	3.1

Secondary: Progression free survival (PFS) per Independent Review Committee

End point title	Progression free survival (PFS) per Independent Review Committee ^[6]
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End point description:

PFS is the time from date of CTL019 infusion to the date of first documented disease progression or death due to any cause.

End point type	Secondary
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End point timeframe:

60 months

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis for this endpoint

End point values	Tisagenlecleucel - Main cohort	Tisagenlecleucel - Cohort A	Tisagenlecleucel - All Patients	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	99	16	115	
Units: Months				
median (confidence interval 95%)	3.0 (2.4 to 6.2)	2.9 (1.0 to 99)	2.9 (2.3 to 5.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS) per Independent Review Committee

End point title	Overall survival (OS) per Independent Review Committee ^[7]
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End point description:

OS is the time from date of CTL019 infusion to the date of death due to any cause.

End point type	Secondary
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End point timeframe:

60 months

Notes:

[7] - 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: No statistical analysis for this endpoint

End point values	Tisagenlecleucel - Main cohort	Tisagenlecleucel - Cohort A	Tisagenlecleucel - All Patients	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	99	16	115	
Units: Months				
median (confidence interval 95%)	12.5 (7.2 to 34.2)	5.9 (3.1 to 19.2)	11.1 (6.6 to 23.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (Pk): AUC0-28d and AUC0-84d

End point title	Pharmacokinetics (Pk): AUC0-28d and AUC0-84d
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End point description:

The AUC from time zero to day 28 and 84 or other disease assessment days, in peripheral blood. AUC0-28d and AUC0-84d, based on the transgene level data by qPCR, were summarized by Month 3 response, per Independent Review Committee assessment.

End point type	Secondary
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End point timeframe:

0 - 28 days after infusion for AUC0-28d, 0 - 84 days after infusion for AUC0-84d

End point values	Tisagenlecleucel I - CR/PR	Tisagenlecleucel I - SD/PD/UNK		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	62		
Units: copies/ug*days				
geometric mean (geometric coefficient of variation)				
AUC0-28d	63000 (± 177.7)	52300 (± 321.4)		
AUC0-84d (n = 43, 29)	102000 (± 171.7)	92900 (± 165.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (Pk): Tmax

End point title	Pharmacokinetics (Pk): Tmax
End point description:	
Tmax is the time to reach maximum (peak) peripheral blood or other body fluid drug concentration after single dose administration (days). Tmax, based on the transgene level data by qPCR, was summarized by Month 3 response, per Independent Review Committee assessment.	
End point type	Secondary
End point timeframe:	
60 months	

End point values	Tisagenlecleucel I - CR/PR	Tisagenlecleucel I - SD/PD/UNK		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	67		
Units: days				
median (full range (min-max))	9.02 (5.78 to 27.7)	8.84 (0.994 to 26.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (Pk): Cmax

End point title	Pharmacokinetics (Pk): Cmax
End point description:	
Cmax is the maximum (peak) observed in peripheral blood or other body fluid drug concentration after single dose administration. Cmax, based on the transgene level data by qPCR, was summarized by Month 3 response, per Independent Review Committee assessment.	
End point type	Secondary
End point timeframe:	
60 months	

End point values	Tisagenlecleucel I - CR/PR	Tisagenlecleucel I - SD/PD/UNK		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	67		
Units: copies/ug				
geometric mean (geometric coefficient of variation)	6070 (\pm 256.8)	5000 (\pm 391.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (Pk): Tlast

End point title	Pharmacokinetics (Pk): Tlast
End point description: Tlast is the time of last observed quantifiable concentration in peripheral blood. Tlast, based on the transgene level data by qPCR, was summarized by Month 3 response, per Independent Review Committee assessment.	
End point type	Secondary
End point timeframe: 60 months	

End point values	Tisagenlecleucel I - CR/PR	Tisagenlecleucel I - SD/PD/UNK		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	67		
Units: days				
median (full range (min-max))	930 (17.1 to 1830)	41.9 (0.994 to 1480)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (Pk): Clast

End point title	Pharmacokinetics (Pk): Clast
End point description: Clast is the last observed quantifiable concentration in peripheral blood. Clast, based on the transgene level data by qPCR, was summarized by Month 3 response, per Independent Review Committee assessment.	
End point type	Secondary

End point timeframe:

60 months

End point values	Tisagenlecleucel I - CR/PR	Tisagenlecleucel I - SD/PD/UNK		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	67		
Units: copies/ug				
geometric mean (geometric coefficient of variation)	188 (\pm 108.3)	341 (\pm 438.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (Pk): T1/2

End point title	Pharmacokinetics (Pk): T1/2
End point description: T1/2 is the half-life associated with the disposition phase slopes (alpha, beta, gamma etc.) of a semi logarithmic concentration-time curve in peripheral blood. T1/2, based on the transgene level data by qPCR, was summarized by Month 3 response, per Independent Review Committee assessment.	
End point type	Secondary
End point timeframe: 60 months	

End point values	Tisagenlecleucel I - CR/PR	Tisagenlecleucel I - SD/PD/UNK		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	49		
Units: days				
geometric mean (geometric coefficient of variation)	151 (\pm 487.5)	11.6 (\pm 196.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of immunogenicity to CTL019 (Humoral & Celular)

End point title	Incidence of immunogenicity to CTL019 (Humoral & Celular)
End point description: Humoral immunogenicity assessment included evaluation of pre-existing (pre-treatment) and post-treatment anti-mCAR19 antibodies and examination of the incidence of immunogenicity with treatment, together with antibody titers. Cellular immunogenicity assessment included the percentage of CD4 and CD8 T cell responses for both	

Pool 1 and Pool 2 peptides.

End point type	Secondary
End point timeframe:	
Baseline 9BL), Maximum (Max.) post-baseline during the duration of the study, up to 5 years	

End point values	Tisagenlecleucel I - CR	Tisagenlecleucel I - PR	Tisagenlecleucel I - SD	Tisagenlecleucel I - PD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	7	1	54
Units: participants				
Baseline (BL): Molecular Immunogenicity- Humoral	35	7	1	54
Max. post-BL: Molecular Immunogenicity - Humoral	37	7	1	54
BL: CTL019 Pool1 CD3+ CD4+ IFNg+ - Cell.	35	7	1	54
Max. post-BL:CTL019 Pool1 CD3+ CD4+ IFNg+ - Cell.	37	7	1	54
BL: CTL019 Pool 2 CD3+ CD4+ IFNg+ - Cell.	35	7	1	54
Max. post-BL:CTL019 Pool2 CD3+ CD4+ IFNg+ - Cell.	37	7	1	54
BL:CTL019 Pool1 CD3+ CD8+ IFNg+ - Cell.	35	7	1	54
Max. post-BL:CTL019 Pool1 CD3+ CD8+ IFNg+ - Cell.	37	7	1	54
BL: CTL019 Pool2 CD3+ CD8+ IFNg+ - Cell.	35	7	1	54
Max. post-BL:CTL019 Pool2 CD3+ CD8+ IFNg+ - Cell.	37	7	1	54

End point values	Tisagenlecleucel I - UNK	Tisagenlecleucel I - All Participants response		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	115		
Units: participants				
Baseline (BL): Molecular Immunogenicity- Humoral	16	113		
Max. post-BL: Molecular Immunogenicity - Humoral	15	114		
BL: CTL019 Pool1 CD3+ CD4+ IFNg+ - Cell.	16	113		
Max. post-BL:CTL019 Pool1 CD3+ CD4+ IFNg+ - Cell.	15	114		
BL: CTL019 Pool 2 CD3+ CD4+ IFNg+ - Cell.	16	113		
Max. post-BL:CTL019 Pool2 CD3+ CD4+ IFNg+ - Cell.	15	114		
BL:CTL019 Pool1 CD3+ CD8+ IFNg+ - Cell.	16	113		

Max. post-BL:CTL019 Pool1 CD3+ CD8+ IFNg+ - Cell.	15	114		
BL: CTL019 Pool2 CD3+ CD8+ IFNg+ - Cell.	16	113		
Max. post-BL:CTL019 Pool2 CD3+ CD8+ IFNg+ - Cell.	15	114		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were collected during post-infusion period up to max duration of 89 months for each patient. All AEs were reported 1 year after infusion & thereafter only AEs specified in protocol.

Adverse event reporting additional description:

AE: AE 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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.1
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Reporting groups

Reporting group title	Tisagenlecleucel - All Patients
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Reporting group description:

Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who received tisagenlecleucel manufactured at the Novartis manufacturing facility in Morris Plains, US and at the Fraunhofer Institut für Zelltherapie, Leipzig, Germany.

Serious adverse events	Tisagenlecleucel - All Patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	84 / 115 (73.04%)		
number of deaths (all causes)	76		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 1		
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malignant melanoma			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Myelodysplastic syndrome				
subjects affected / exposed	4 / 115 (3.48%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	1 / 2			
Neuroendocrine carcinoma				
subjects affected / exposed	1 / 115 (0.87%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 1			
Prostate cancer				
subjects affected / exposed	3 / 115 (2.61%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Refractory cytopenia with multilineage dysplasia				
subjects affected / exposed	1 / 115 (0.87%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tumour associated fever				
subjects affected / exposed	1 / 115 (0.87%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tumour haemorrhage				
subjects affected / exposed	1 / 115 (0.87%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Hypotension				
subjects affected / exposed	2 / 115 (1.74%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				
subjects affected / exposed	1 / 115 (0.87%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	9 / 115 (7.83%)		
occurrences causally related to treatment / all	4 / 5		
deaths causally related to treatment / all	0 / 0		
Multiple organ dysfunction syndrome			
subjects affected / exposed	3 / 115 (2.61%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Influenza like illness			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	4 / 115 (3.48%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Face oedema			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Haemophagocytic lymphohistiocytosis			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cytokine release syndrome			
subjects affected / exposed	31 / 115 (26.96%)		
occurrences causally related to treatment / all	32 / 32		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed	3 / 115 (2.61%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Cough				
subjects affected / exposed	1 / 115 (0.87%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Asphyxia				
subjects affected / exposed	1 / 115 (0.87%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Allergic bronchitis				
subjects affected / exposed	1 / 115 (0.87%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	2 / 115 (1.74%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 1			
Pulmonary haemorrhage				
subjects affected / exposed	1 / 115 (0.87%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	1 / 1			
Pulmonary embolism				
subjects affected / exposed	2 / 115 (1.74%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	1 / 115 (0.87%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oropharyngeal pain				

subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pharyngeal haemorrhage			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Confusional state			
subjects affected / exposed	3 / 115 (2.61%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Mental status changes			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
C-reactive protein increased			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Liver function test increased			

subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutrophil count decreased			
subjects affected / exposed	3 / 115 (2.61%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Platelet count decreased			
subjects affected / exposed	2 / 115 (1.74%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
White blood cell count decreased			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Upper limb fracture			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiopulmonary failure			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 1		
Cardio-respiratory arrest			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Cardiac failure congestive			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Acute polyneuropathy			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebral haemorrhage			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 1		
Demyelinating polyneuropathy			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Encephalopathy			
subjects affected / exposed	4 / 115 (3.48%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Ischaemic cerebral infarction			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolic encephalopathy			

subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Somnolence			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Status epilepticus			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	3 / 115 (2.61%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	2 / 115 (1.74%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Lymphadenopathy			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	10 / 115 (8.70%)		
occurrences causally related to treatment / all	6 / 8		
deaths causally related to treatment / all	0 / 0		
Bone marrow failure			

subjects affected / exposed	2 / 115 (1.74%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Anal fissure			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 1		
Vomiting			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Melaena			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Large intestinal obstruction			

subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematemesis			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 115 (1.74%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis acute			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urinary tract obstruction			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cystitis haemorrhagic			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic kidney disease			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 1		
Acute kidney injury			

subjects affected / exposed	4 / 115 (3.48%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myopathy			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Polyarthrititis			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Atypical pneumonia			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Candida infection				
subjects affected / exposed	1 / 115 (0.87%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebral toxoplasmosis				
subjects affected / exposed	1 / 115 (0.87%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile infection				
subjects affected / exposed	3 / 115 (2.61%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Corynebacterium infection				
subjects affected / exposed	1 / 115 (0.87%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Escherichia infection				
subjects affected / exposed	1 / 115 (0.87%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	2 / 115 (1.74%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	2 / 115 (1.74%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	1 / 115 (0.87%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumocystis jirovecii pneumonia				

subjects affected / exposed	2 / 115 (1.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	9 / 115 (7.83%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	1 / 115 (0.87%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pseudomonas infection				
subjects affected / exposed	1 / 115 (0.87%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	2 / 115 (1.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	3 / 115 (2.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Sinusitis				
subjects affected / exposed	1 / 115 (0.87%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Staphylococcal infection				
subjects affected / exposed	2 / 115 (1.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Systemic infection				

subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vaginal infection			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	2 / 115 (1.74%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Tumour lysis syndrome			
subjects affected / exposed	1 / 115 (0.87%)		
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	113 / 115 (98.26%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	28 / 115 (24.35%)		
occurrences (all)	29		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	8 / 115 (6.96%)		
occurrences (all)	7		
Chills			
subjects affected / exposed	14 / 115 (12.17%)		
occurrences (all)	14		
Fatigue			
subjects affected / exposed	28 / 115 (24.35%)		
occurrences (all)	24		
Influenza like illness			
subjects affected / exposed	9 / 115 (7.83%)		
occurrences (all)	4		
Oedema peripheral			
subjects affected / exposed	17 / 115 (14.78%)		
occurrences (all)	15		
Pain			
subjects affected / exposed	6 / 115 (5.22%)		
occurrences (all)	8		
Pyrexia			
subjects affected / exposed	35 / 115 (30.43%)		
occurrences (all)	33		
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	47 / 115 (40.87%)		
occurrences (all)	48		
Hypogammaglobulinaemia			

subjects affected / exposed occurrences (all)	10 / 115 (8.70%) 3		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion subjects affected / exposed occurrences (all)	6 / 115 (5.22%) 7		
Oropharyngeal pain subjects affected / exposed occurrences (all)	6 / 115 (5.22%) 5		
Hypoxia subjects affected / exposed occurrences (all)	8 / 115 (6.96%) 8		
Dyspnoea subjects affected / exposed occurrences (all)	16 / 115 (13.91%) 17		
Cough subjects affected / exposed occurrences (all)	19 / 115 (16.52%) 10		
Psychiatric disorders			
Insomnia subjects affected / exposed occurrences (all)	8 / 115 (6.96%) 6		
Confusional state subjects affected / exposed occurrences (all)	8 / 115 (6.96%) 9		
Anxiety subjects affected / exposed occurrences (all)	11 / 115 (9.57%) 8		
Investigations			
Blood creatinine increased subjects affected / exposed occurrences (all)	12 / 115 (10.43%) 15		
Blood immunoglobulin G decreased subjects affected / exposed occurrences (all)	7 / 115 (6.09%) 2		
White blood cell count decreased			

subjects affected / exposed	41 / 115 (35.65%)		
occurrences (all)	52		
Weight decreased			
subjects affected / exposed	14 / 115 (12.17%)		
occurrences (all)	11		
Platelet count decreased			
subjects affected / exposed	38 / 115 (33.04%)		
occurrences (all)	59		
Neutrophil count decreased			
subjects affected / exposed	40 / 115 (34.78%)		
occurrences (all)	57		
Lymphocyte count decreased			
subjects affected / exposed	7 / 115 (6.09%)		
occurrences (all)	5		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	12 / 115 (10.43%)		
occurrences (all)	11		
Nervous system disorders			
Dizziness			
subjects affected / exposed	14 / 115 (12.17%)		
occurrences (all)	14		
Headache			
subjects affected / exposed	24 / 115 (20.87%)		
occurrences (all)	21		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	15 / 115 (13.04%)		
occurrences (all)	18		
Neutropenia			
subjects affected / exposed	21 / 115 (18.26%)		
occurrences (all)	27		
Febrile neutropenia			
subjects affected / exposed	11 / 115 (9.57%)		
occurrences (all)	10		
Anaemia			

subjects affected / exposed	55 / 115 (47.83%)		
occurrences (all)	77		
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	6 / 115 (5.22%)		
occurrences (all)	5		
Nausea			
subjects affected / exposed	33 / 115 (28.70%)		
occurrences (all)	34		
Stomatitis			
subjects affected / exposed	7 / 115 (6.09%)		
occurrences (all)	5		
Vomiting			
subjects affected / exposed	9 / 115 (7.83%)		
occurrences (all)	8		
Diarrhoea			
subjects affected / exposed	36 / 115 (31.30%)		
occurrences (all)	33		
Constipation			
subjects affected / exposed	19 / 115 (16.52%)		
occurrences (all)	14		
Abdominal pain			
subjects affected / exposed	9 / 115 (7.83%)		
occurrences (all)	9		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	6 / 115 (5.22%)		
occurrences (all)	4		
Night sweats			
subjects affected / exposed	6 / 115 (5.22%)		
occurrences (all)	6		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	6 / 115 (5.22%)		
occurrences (all)	5		
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	16 / 115 (13.91%)		
occurrences (all)	11		
Back pain			
subjects affected / exposed	7 / 115 (6.09%)		
occurrences (all)	4		
Pain in extremity			
subjects affected / exposed	10 / 115 (8.70%)		
occurrences (all)	6		
Myalgia			
subjects affected / exposed	7 / 115 (6.09%)		
occurrences (all)	11		
Infections and infestations			
Influenza			
subjects affected / exposed	7 / 115 (6.09%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	9 / 115 (7.83%)		
occurrences (all)	4		
Pneumonia			
subjects affected / exposed	8 / 115 (6.96%)		
occurrences (all)	4		
Sinusitis			
subjects affected / exposed	8 / 115 (6.96%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	15 / 115 (13.04%)		
occurrences (all)	4		
Urinary tract infection			
subjects affected / exposed	10 / 115 (8.70%)		
occurrences (all)	5		
Metabolism and nutrition disorders			
Hypophosphataemia			
subjects affected / exposed	19 / 115 (16.52%)		
occurrences (all)	25		
Hyponatraemia			

subjects affected / exposed	9 / 115 (7.83%)		
occurrences (all)	9		
Hypomagnesaemia			
subjects affected / exposed	19 / 115 (16.52%)		
occurrences (all)	37		
Hypokalaemia			
subjects affected / exposed	26 / 115 (22.61%)		
occurrences (all)	27		
Hypocalcaemia			
subjects affected / exposed	6 / 115 (5.22%)		
occurrences (all)	8		
Decreased appetite			
subjects affected / exposed	15 / 115 (13.04%)		
occurrences (all)	13		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 February 2015	Protocol amendment 1 occurred before the study was initiated at any site. An interim analysis was added once the first DLBCL 50 patients were treated and followed up for 6 months; A safety run-in stage was conducted at the start of the study to enroll at least 3 patients to assess the acute safety profile and product characteristics of the Novartis manufactured tisagenlecleucel cell product; Exploratory endpoints which did not impact the overall sample collection requirements were added; The inclusion and exclusion criteria were modified to ensure a homogenous population; Language in the protocol was changed to be consistent with the approved tisagenlecleucel standard protocol language; protocol language associated with discontinuation from the clinical trial was updated.
12 November 2015	The protocol was amended mainly to implement clarifications in line with health authority feedback and to incorporate recent experience from the University of Pennsylvania (Penn) study CTL019A2101J/UPCC13413; At the time of this amendment, 7 patients had been enrolled. None of the enrolled patients would have been excluded from the trial had the amendment been in place prior to enrollment.
18 December 2015	The PET-CT was specified to be performed within 4 weeks of infusion but prior to start of lymphodepleting therapy. During the startup of the trial, it became evident that the baseline PET-CT required at screening could often be too far out from the actual tisagenlecleucel infusion to serve as a valid baseline for subsequent response assessments; It was clarified that at least one sentinel vial must be shipped together with the leukapheresis product.
07 July 2016	At the time of this amendment, 72 patients were enrolled and 29 patients were treated. Under the protocol version 03, patients with manufactured cell numbers falling below the target dose and acceptable dose ranges for this study were eligible to receive tisagenlecleucel therapy if the product met all other manufacturing release criteria. Preliminary dose expansion analyses suggested that these very low doses showed only minimal in vivo expansion and that patients were very unlikely to derive clinical benefit. Consequently, tisagenlecleucel doses lower than the protocol-specified range were no longer released. One additional study cohort was added: Cohort A aimed to assess efficacy and safety and characterize the in vivo cellular PK profile of tisagenlecleucel manufactured at the Fraunhofer Institut für Zelltherapie, Leipzig, Germany.
09 March 2017	At the time of enrollment completion in the Main Cohort, 3 Japanese patients were enrolled, treated, and in primary follow-up. Based on statistical considerations, a minimum of 9 Japanese patients were required to be treated to allow evaluation of the safety and efficacy of tisagenlecleucel in the Japanese patient population. Amendment 5 was implemented to allow enrollment of approximately 10 additional Japanese patients in the Main Cohort, to allow at least 6 additional patients to be treated, to ensure a minimum of 9 and maximum of 13 Japanese patients were treated with tisagenlecleucel.

15 April 2021	At the time of this amendment, enrollment to the Main Cohort and Cohort A was completed. The main reasons for Amendment 6 were: To change the required follow-up time for a newborn after live birth from 6 months to 12 months following pregnancy of a female patient or the partner of any male patient. This additional safety monitoring was not due to any new safety concern or emerging data but was added on a precautionary basis and aligned with current Novartis internal guidelines; To update the protocol safety language to reflect the current Novartis tisagenlecleucel program safety language; this included updates to the Potential Toxicities Section as well as updates to the highly effective contraceptive methods in a newly added Contraception Section; To add the requirement for urine or serum pregnancy testing at all study visits to align with standard tisagenlecleucel monitoring requirements. Changes to the Visit Evaluation Schedule were made starting at Month 30 and after all remaining patients were past the Month 30 follow-up; To add language on secondary malignancies and to follow up to align with the tisagenlecleucel program standard language; To specify that blood samples for RCL testing were banked beyond month 12, as long as all samples through Month 12 were negative.
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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: