



Clinical trial results:

A Phase II, single arm, multicenter study to determine the efficacy and safety of CTL019 in pediatric subjects with relapsed and refractory B cell acute lymphoblastic leukemia. 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	2015-003736-13
Trial protocol	Outside EU/EEA
Global end of trial date	24 May 2019

Results information

Result version number	v1 (current)
This version publication date	18 December 2019
First version publication date	18 December 2019

Trial information

Trial identification

Sponsor protocol code	CCTL019B2205J
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02228096
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)	EMA-001654-PIP01-14
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	24 May 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	24 May 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of tisagenlecleucel therapy as measured by ORR within 6 months after tisagenlecleucel administration, which includes CR and CRi as determined by IRC assessment for B cell ALL subjects.

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	14 August 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 64
Worldwide total number of subjects	64
EEA total number of subjects	0

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)	28
Adolescents (12-17 years)	26
Adults (18-64 years)	10

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The data reported is based on the final CSR of 2019. The study enrolled 75 participants but only 64 were infused as 11 discontinued prior to tisagenlecleucel (CTL019) infusion.

Pre-assignment

Screening details:

The study enrolled 75 participants but only 64 were infused as 11 discontinued prior to tisagenlecleucel (CTL019) infusion.

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 (CTL019) - All participants
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Arm description:

Pediatric participants with r/r B-cell ALL

Arm type	Experimental
Investigational medicinal product name	CTL019
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersion for infusion
Routes of administration	Intravenous use

Dosage and administration details:

A target per-protocol dose of tisagenlecleucel transduced cells for pediatric subjects consisted of a single infusion of 2.0 to 5.0×10^6 tisagenlecleucel transduced cells per kg body weight (for subjects ≤ 50 kg) and 1.0 to 2.5×10^8 tisagenlecleucel transduced viable T cells (for subjects >50 kg).

Number of subjects in period 1	tisagenlecleucel (CTL019) - All participants
Started	64
Enrolled into long-term f/u protocol	31
Completed	4
Not completed	60
Adverse event, serious fatal	12
Physician decision	3
Study terminated by Sponsor	24
Subject/guardian decision	2
New therapy for study indication	1
Lack of efficacy	18

Baseline characteristics

Reporting groups

Reporting group title	tisagenlecleucel (CTL019) - All participants
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Reporting group description:

Pediatric participants with r/r B-cell ALL

Reporting group values	tisagenlecleucel (CTL019) - All participants	Total	
Number of subjects	64	64	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	28	28	
Adolescents (12-17 years)	26	26	
Adults (18-64 years)	10	10	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous			
Units: Years			
arithmetic mean	12.4		
standard deviation	± 5.16	-	
Sex: Female, Male			
Units:			
Female	34	34	
Male	30	30	
Karnofsky/Lansky performance status			
Units: Subjects			
KL PS 100	18	18	
KL PS 90	28	28	
KL PS 80	13	13	
KL PS 70	2	2	
KL PS 60	1	1	
KL PS 50	2	2	
KL PS less than 50	0	0	
Race/Ethnicity, Customized			
Units: Subjects			
White	52	52	
Asian	5	5	
Other	7	7	
Weight			
Units: kg			
arithmetic mean	43.7		
standard deviation	± 20.10	-	

End points

End points reporting groups

Reporting group title	tisagenlecleucel (CTL019) - All participants
Reporting group description: Pediatric participants with r/r B-cell ALL	
Subject analysis set title	tisagenlecleucel (CTL019) - IRC assessment
Subject analysis set type	Full analysis
Subject analysis set description: Pediatric participants with r/r B-cell ALL	
Subject analysis set title	tisagenlecleucel (CTL019) - per IRC assessment
Subject analysis set type	Full analysis
Subject analysis set description: Pediatric participants with r/r B-cell ALL	
Subject analysis set title	tisagenlecleucel (CTL019) - Local assessment
Subject analysis set type	Full analysis
Subject analysis set description: Pediatric participants with r/r B-cell ALL	
Subject analysis set title	CR/CRI
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants had Complete remission (CR)/Complete remission with incomplete blood count recovery (CRI)	
Subject analysis set title	No Response (NR)
Subject analysis set type	Sub-group analysis
Subject analysis set description: No response was defined as failure to attain the criteria needed for any response categories or relapse	
Subject analysis set title	Unknown
Subject analysis set type	Sub-group analysis
Subject analysis set description: unknown was assigned in case the baseline assessment or the response assessment was not done, incomplete, indeterminate or not performed within the respective time frame.	
Subject analysis set title	CR/CRI
Subject analysis set type	Safety analysis
Subject analysis set description: Participants had Complete remission (CR)/Complete remission with incomplete blood count recovery (CRI)	
Subject analysis set title	No Response
Subject analysis set type	Safety analysis
Subject analysis set description: No response was defined as failure to attain the criteria needed for any response categories or relapse	
Subject analysis set title	Unknown
Subject analysis set type	Safety analysis
Subject analysis set description: unknown was assigned in case the baseline assessment or the response assessment was not done, incomplete, indeterminate or not performed within the respective time frame.	
Subject analysis set title	tisagenlecleucel (CTL019) - Local assessment
Subject analysis set type	Sub-group analysis
Subject analysis set description: Pediatric participants with r/r B-cell ALL	
Subject analysis set title	tisagenlecleucel (CTL019) - IRC assessment
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Pediatric participants with r/r B-cell ALL

Subject analysis set title	No response
Subject analysis set type	Safety analysis

Subject analysis set description:

No response was defined as failure to attain the criteria needed for any response categories or relapse

Subject analysis set title	NO CRS
Subject analysis set type	Safety analysis

Subject analysis set description:

No cytokine release syndrome

Subject analysis set title	Grade 1/2
Subject analysis set type	Safety analysis

Subject analysis set description:

Grade 1 and 2 of cytokine release syndrome post tisagenlecleucel infusion

Subject analysis set title	Grade 3
Subject analysis set type	Safety analysis

Subject analysis set description:

Grade 3 of cytokine release syndrome post tisagenlecleucel infusion

Subject analysis set title	Grade 4
Subject analysis set type	Safety analysis

Subject analysis set description:

Grade 4 of cytokine release syndrome post tisagenlecleucel infusion

Subject analysis set title	All Participants
Subject analysis set type	Safety analysis

Subject analysis set description:

All participants with & without CRS

Primary: Overall Remission Rate (ORR) per Independent Review Committee (IRC) (for ALL participants)

End point title	Overall Remission Rate (ORR) per Independent Review Committee (IRC) (for ALL participants) ^[1]
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End point description:

ORR is defined as the percentage of participants with a best overall disease response of complete remission (CR) or Complete remission with incomplete blood count recovery (CRi), where the best overall disease response is defined as the best disease response recorded from CTL019 infusion until the start of new anticancer therapy. Best response was assigned in the following order: CR, CRi, CR or CRi with residual mediastinal disease, No response and Unknown.

End point type	Primary
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End point timeframe:

within 6 months after CTL019 infusion

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 planned for this endpoint

End point values	tisagenlecleucel (CTL019) - IRC assessment			
Subject group type	Subject analysis set			
Number of subjects analysed	64			
Units: Percentage of participants				
number (confidence interval 95%)	70.3 (57.6 to 81.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with clinical response without stem cell transplantation (SCT) at month 6

End point title	Percentage of participants with clinical response without stem cell transplantation (SCT) at month 6
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End point description:

Evaluate the percentage of participants who achieved CR or CRi at Month 6 without SCT between tisagenlecleucel infusion and Month 6 response assessment.

End point type	Secondary
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End point timeframe:

Month 6

End point values	tisagenlecleucel (CTL019) - IRC assessment			
Subject group type	Subject analysis set			
Number of subjects analysed	64			
Units: Percentage of participants				
number (confidence interval 95%)	53.1 (40.2 to 65.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects who achieved CR or CRi and then proceeded to SCT while in remission prior to Month 6 response assessment

End point title	Percentage of subjects who achieved CR or CRi and then proceeded to SCT while in remission prior to Month 6 response assessment
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End point description:

Evaluate the percentage of subjects who achieved CR or CRi and then proceeded to SCT while in remission prior to Month 6 response assessment.

End point type	Secondary
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End point timeframe:

prior to Month 6

End point values	tisagenlecleucel (CTL019) - per IRC assessment			
Subject group type	Subject analysis set			
Number of subjects analysed	64			
Units: Percentage of participants				
number (confidence interval 95%)	7.8 (2.6 to 17.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of remission (DOR) per Local and IRC assessment

End point title	Duration of remission (DOR) per Local and IRC assessment
End point description:	DOR is the time from achievement of CR or CRi, whichever occurs first, to relapse or death due to ALL
End point type	Secondary
End point timeframe:	From CR or CRi to relapse or death up to 60 months

End point values	tisagenlecleucel (CTL019) - IRC assessment	tisagenlecleucel (CTL019) - Local assessment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	64		
Units: months				
median (confidence interval 95%)	999 (13.6 to 999)	999 (13.6 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with Bone marrow minimum residual disease (MRD) status by flow cytometry within 6 months post CTL019 infusion by Local & IRC assessment

End point title	Percentage of participants with Bone marrow minimum residual disease (MRD) status by flow cytometry within 6 months post CTL019 infusion by Local & IRC assessment
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End point description:

Evaluate the quality of response by assessing BOR of CR or CRi with MRD negative bone marrow 6 months after CTL019 infusion.

End point type	Secondary
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End point timeframe:

within 6 months

End point values	tisagenlecleucel (CTL019) - IRC assessment	tisagenlecleucel (CTL019) - Local assessment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	64		
Units: Percentage of participants				
number (confidence interval 95%)				
With BM MRD-ve (MRD% < 0.01%) (n = 27, 27)	67.2 (54.3 to 78.4)	67.2 (54.3 to 78.4)		
With BM 0.01% <= MRD% <5% (n=2, 2)	3.1 (0 to 999)	3.1 (0 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Relapse-free survival (RFS) for responders per Local and IRC and assessment

End point title	Relapse-free survival (RFS) for responders per Local and IRC and assessment
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End point description:

RFS is the time from achievement of CR or CRi whichever occurs first to relapse or death due to any cause during CR or CRi.

End point type	Secondary
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End point timeframe:

60 Months

End point values	tisagenlecleucel (CTL019) - IRC assessment	tisagenlecleucel (CTL019) - Local assessment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	64		
Units: months				
median (confidence interval 95%)	999 (13.6 to 999)	999 (13.6 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Event-free survival (EFS) per Local and IRC assessment

End point title	Event-free survival (EFS) per Local and IRC assessment
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End point description:

EFS is the time from date of CTL019 infusion to the earliest of death, relapse or treatment failure

End point type	Secondary
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End point timeframe:

60 Months

End point values	tisagenlecleucel (CTL019) - IRC assessment	tisagenlecleucel (CTL019) - Local assessment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	64		
Units: months				
median (confidence interval 95%)	15.6 (6.4 to 999)	15.6 (6.4 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)
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End point description:

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

End point type	Secondary
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End point timeframe:

60 Months

End point values	tisagenlecleucel (CTL019) - All participants			
Subject group type	Reporting group			
Number of subjects analysed	64			
Units: months				
median (confidence interval 95%)	29.9 (15.1 to 42.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects attaining CR or CRi and bone marrow MRD status by flow cytometry based on Local and IRC assessment

End point title	Percentage of subjects attaining CR or CRi and bone marrow MRD status by flow cytometry based on Local and IRC assessment
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End point description:

Evaluate the response subjects attaining CR or CRi and bone marrow MRD status at Day 28 +/- 4 days

End point type	Secondary
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End point timeframe:

Day 28

End point values	tisagenlecleucel (CTL019) - IRC assessment	tisagenlecleucel (CTL019) - Local assessment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	64		
Units: Percentage of participants				
number (confidence interval 95%)				
With BM MRD -ve: i.e. MRD% < 0.01% (n=46,46)	71.9 (59.2 to 82.4)	71.9 (59.2 to 82.4)		
With BM 0.01% <= MRD% < 5%: (n=1,1)	1.6 (0 to 999)	1.6 (0 to 999)		
With BM MRD% >= 5%(n = 1, 1)	1.6 (0 to 999)	1.6 (0 to 999)		
BM MRD not available (n = 4, 4)	6.3 (0 to 999)	6.3 (0 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: CTL019 transgene levels by qPCR CTL019 cells by in qPCR blood and bone marrow

End point title	CTL019 transgene levels by qPCR CTL019 cells by in qPCR blood and bone marrow
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End point description:

Characterize the in vivo cellular pharmacokinetic (PK) profile (levels,persistence, trafficking) of CTL019 cells in target tissues

End point type	Secondary
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End point timeframe:

Enrollment; D1; D4; D7; D11; D14; D21; D28; M3; M6; M9, M12; M18; M24, M30, M42, M48 for transgene levels in blood; Screening, D28, M3, M6 for transgene levels in bone marrow

End point values	CR/CRI	No Response (NR)	Unknown	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	52	6	6	
Units: copies/ug DNA				
geometric mean (geometric coefficient of variation)				
Enrollment blood (n=49,6,5)	999 (± 999)	999 (± 999)	999 (± 999)	
Day 1 (D1): blood (n= 41, 4, 6)	3680 (± 344.3)	3190 (± 348.6)	2440 (± 220.6)	
D4: blood (n= 48, 6, 6)	234 (± 197.8)	48.8 (± 282.4)	88.0 (± 71.0)	
D7: blood (n= 51, 6, 6)	4460 (± 616.2)	231 (± 499.1)	402 (± 114.7)	
D11: blood (n= 34, 4, 4)	21200 (± 262.3)	423 (± 52.7)	1920 (± 8318.1)	
D14: blood (n= 49, 6, 5)	12500 (± 292.1)	1600 (± 337.1)	42835.8 (± 9060)	
D21: blood (n= 49, 6, 5)	3720 (± 480.5)	7750 (± 334.5)	1050 (± 220743.9)	
D28: blood (n= 52, 6, 3)	1360 (± 650.3)	2770 (± 684.8)	515 (± 244650713.9)	
Month 3 (M3): blood (n=49, 2, 2)	220 (± 224.3)	690 (± 999)	564 (± 999)	
Month M6: blood (n=40, 1, 1)	146 (± 157.5)	999 (± 999)	127 (± 999)	
Month M9: blood (n=30, 0, 0)	117 (± 179.3)	999 (± 999)	999 (± 999)	
Month M12: blood (n=30, 0, 0)	113 (± 312.4)	999 (± 999)	999 (± 999)	
Month M18: blood (n=18, 0, 0)	87.2 (± 200.3)	999 (± 999)	999 (± 999)	
Month M24: blood (n=15, 0, 0)	92.7 (± 160.5)	999 (± 999)	999 (± 999)	
Month M30: blood (n=5, 0, 0)	59.9 (± 150.0)	999 (± 999)	999 (± 999)	
Month M36: blood (n=3, 0, 0)	10.7 (± 19.9)	999 (± 999)	999 (± 999)	
Month M42: blood (n=2, 0, 0)	35.3 (± 999)	999 (± 999)	999 (± 999)	
Month M48: blood (n=1, 0, 0)	999 (± 999)	999 (± 999)	999 (± 999)	
Screening: Bone marrow (BM) (n=47, 6, 6)	999 (± 999)	999 (± 999)	999 (± 999)	
D28 BM (n=50,4, 4)	646 (± 1009.7)	969 (± 166.8)	615 (± 4763885.9)	
M3 BM (n = 40, 0, 2)	179 (± 182.5)	999 (± 999)	542 (± 999)	
M6 BM (n = 32, 1, 0)	133 (± 121.7)	35.3 (± 999)	999 (± 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Humoral immunogenicity interpretation by day 28 disease response per IRC (Anti-CTL019 antibodies)

End point title	Humoral immunogenicity interpretation by day 28 disease response per IRC (Anti-CTL019 antibodies)
End point description:	Humary immunogenicity was measured by anti-CTL019 antibodies in human serum using a flow cytometry method. (Prevalence and incidence of immunogenicity to CTL019)
End point type	Secondary
End point timeframe:	Baseline; Day 14; Day 28; Month 3; Month 6; Month 12; Month 24

End point values	CR/CRi	No Response	Unknown	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	43	6	9	
Units: Percentage of participants				
number (not applicable)				
Baseline: Negative	23.3	33.3	33.3	
Baseline: Positive	69.8	66.7	66.7	
Day 14: Negative	37.2	0	33.3	
Day 14: Positive	88.4	100.0	66.7	
Day 28: Negative	14.0	0	0	
Day 28: Positive	86.0	100.0	22.2	
Month 3: Negative	7.0	0	0	
Month 3: Positive	67.4	16.7	11.1	
Month 6: Negative	7.0	0	0	
Month 6: Positive	51.2	16.7	11.1	
Month 12: Negative	0	0	0	
Month 12: Positive	23.3	0	0	
Month 24: Negative	2.3	0	0	
Month 24: Positive	7.0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Response as a function of baseline (BL) tumor burden: ORR within 6 months post CTL019 infusion by local investigator & IRC assessment

End point title	Response as a function of baseline (BL) tumor burden: ORR within 6 months post CTL019 infusion by local investigator & IRC assessment
End point description:	
ORR within 6 months after infusion per IRC and local assessment by baseline marrow tumor burden; ORR within 6 months after infusion per IRC and local assessment by baseline extramedullary disease presence.	
End point type	Secondary
End point timeframe:	
Within 6 months	

End point values	tisagenlecleucel (CTL019) - Local assessment	tisagenlecleucel (CTL019) - IRC assessment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42	42		
Units: percentage of participants				

number (confidence interval 95%)				
BL bone marrow tumor burden: Low (<50%) (n=10,10)	83.3 (51.6 to 97.9)	83.3 (51.6 to 97.9)		
BL BM tumor burden: High (≥50%) (n=19,19)	63.3 (43.9 to 80.1)	63.3 (43.9 to 80.1)		
BL extramedullary disease presence:Yes (n=2,2)	100 (0 to 999)	100 (0 to 999)		
BL extramedullary disease presence:No (n=27, 27)	67.5 (50.9 to 81.4)	67.5 (50.9 to 81.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Response as a function of baseline tumor burden: Bone marrow (BM) minimum residual disease (MRD) status by flow cytometry within 6 months post CTL019 infusion by local investigator and IRC assessment, by baseline bone marrow tumor burden

End point title	Response as a function of baseline tumor burden: Bone marrow (BM) minimum residual disease (MRD) status by flow cytometry within 6 months post CTL019 infusion by local investigator and IRC assessment, by baseline bone marrow tumor burden
End point description:	MRD status within 6 months after infusion by baseline bone marrow tumor burden(BMTB); MRD status within 6 months after infusion by baseline extramedullary disease presence (EDP).
End point type	Secondary
End point timeframe:	Within 6 months

End point values	tisagenlecleucel (CTL019) - Local assessment	tisagenlecleucel (CTL019) - IRC assessment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42	42		
Units: percentage of participants				
number (confidence interval 95%)				
BL BMTB with BM MRD -ve (MRD% < 0.01%: High	56.7 (37.4 to 74.5)	56.7 (37.4 to 74.5)		
BL BMTB with BM 0.01% ≤ MRD% < 5%: High	6.7 (0 to 999)	6.7 (0 to 999)		
BL BMTB with BM MRD -ve (MRD% < 0.01%: Low	83.3 (51.6 to 97.9)	83.3 (51.6 to 97.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Response as a function of baseline tumor burden: Bone marrow (BM) minimum residual disease (MRD) status by flow cytometry within 6 months post CTL019 infusion by local investigator and IRC assessment, by baseline extramedullary disease presence

End point title	Response as a function of baseline tumor burden: Bone marrow (BM) minimum residual disease (MRD) status by flow cytometry within 6 months post CTL019 infusion by local investigator and IRC assessment, by baseline extramedullary disease presence
End point description: MRD status within 6 months after infusion by baseline bone marrow tumor burden(BMTB); MRD status within 6 months after infusion by baseline extramedullary disease presence (EDP).	
End point type	Secondary
End point timeframe: Within 6 months	

End point values	tisagenlecleucel (CTL019) - Local assessment	tisagenlecleucel (CTL019) - IRC assessment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42	42		
Units: percentage of participants				
number (confidence interval 95%)				
BL EDP with BM MRD -ve (MRD% < 0.01%: Yes (n=2,2)	100 (15.8 to 100)	100 (15.8 to 100)		
BL EDP with BM MRD -ve (MRD% < 0.01%: No(n=25,25)	62.5 (45.8 to 77.3)	62.5 (45.8 to 77.3)		
BL EDP with BM 0.01% <= MRD% < 5%: No (n=2, 2)	5.0 (0 to 999)	5.0 (0 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Response as a function of baseline (BL) tumor burden: duration of remission (DOR) censoring HSCT by local investigator & IRC assessment, by baseline bone marrow tumor burden

End point title	Response as a function of baseline (BL) tumor burden: duration of remission (DOR) censoring HSCT by local investigator & IRC assessment, by baseline bone marrow tumor burden
End point description: DOR per IRC and local assessment by baseline marrow tumor burden; DOR per IRC and local assessment by baseline extramedullary disease presence.	
End point type	Secondary
End point timeframe: from FPFV to LPLV	

End point values	tisagenlecleucel (CTL019) - Local assessment	tisagenlecleucel (CTL019) - IRC assessment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42	42		
Units: months				
median (confidence interval 95%)				
BL bone marrow tumor burden: Low (<50%)	999 (5.4 to 999)	999 (5.4 to 999)		
BL bone marrow tumor burden: High (>=50%)	999 (5.3 to 999)	999 (5.3 to 999)		
BL extramedullary disease presence:Yes	999 (3.4 to 999)	999 (3.4 to 999)		
BL extramedullary disease presence:No	999 (5.9 to 999)	999 (5.9 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Participants achieving cellular immunogenicity net response by day 28 response per IRC

End point title	Participants achieving cellular immunogenicity net response by day 28 response per IRC
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End point description:

Activation of T cells in PBMC collected from subjects in response to mCAR19 -derived peptides was used to assess the cellular immunogenicity against tisagenlecleucel. CD4 and CD8 T cell net responses (in %) were calculated for 2 non-overlapping CTL019 peptide pools (i.e., Pool 1 and Pool 2). (Lymphocyte subsets of B and T cells and description of associated safety events)

End point type	Secondary
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End point timeframe:

Baseline; Day 14; Day 28; Month 3; Month 6; Month 12; Month 24

End point values	CR/CRi	Unknown	No response	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	43	9	6	
Units: Percentage of participants				
number (not applicable)				
Baseline: Pool 1 CD3+ CD4+ IFNg+ (n=38, 3, 6)	88.4	66.7	50.0	
Day 14: Pool 1 CD3+ CD4+ IFNg+ (n=34, 6, 4)	79.1	44.4	100	
Day 28: Pool 1 CD3+ CD4+ IFNg+ (n=41, 6, 2)	95.3	22.2	100	
Month 3: Pool 1 CD3+ CD4+ IFNg+ (n=32, 1, 1)	74.4	11.1	16.7	
Month 6: Pool 1 CD3+ CD4+ IFNg+ (n=23, 1, 1)	53.4	11.1	16.7	
Month 12: Pool 1 CD3+ CD4+ IFNg+ (n=5,0,0)	11.6	999	999	

Month 24: Pool 1 CD3+ CD4+ IFNg+ (n=5,0,0)	11.6	999	999	
Baseline: Pool 2 CD3+ CD4+ IFNg+ (n=38, 3, 6)	88.4	66.7	50.0	
Day 14: Pool 2 CD3+ CD4+ IFNg+ (n=34, 6, 4)	79.1	44.4	100	
Day 28: Pool 2 CD3+ CD4+ IFNg+ (n=41,6,2)	95.3	22.2	100	
Month 3: Pool 2 CD3+ CD4+ IFNg+ (n=32,1,1)	74.4	11.1	16.7	
Month 6: Pool 2 CD3+ CD4+ IFNg+ (n=23,1,1)	53.5	11.1	16.7	
Month 12: Pool 2 CD3+ CD4+ IFNg+ (n=5,0,0)	11.6	999	999	
Month 24: Pool 2 CD3+ CD4+ IFNg+ (n=5,0,0)	11.6	999	999	
Baseline: Pool 1 CD3+ CD8+ IFNg+ (n=38, 3, 6)	88.4	66.7	50.0	
Day 14: Pool 1 CD3+ CD8+ IFNg+ (n=34, 6, 4)	79.1	44.4	100	
Day 28: Pool 1 CD3+ CD8+ IFNg+ (n=41,6,2)	95.3	22.2	100	
Month 3: Pool 1 CD3+ CD8+ IFNg+ (n=32,1,1)	74.4	11.1	16.7	
Month 6: Pool 1 CD3+ CD8+ IFNg+ (n=23,1,1)	53.5	11.1	16.7	
Month 12: Pool 1 CD3+ CD8+ IFNg+ (n=5,0,0)	11.6	999	999	
Month 24: Pool 1 CD3+ CD8+ IFNg+ (n=5,0,0)	11.6	999	999	
Baseline: Pool 2 CD3+ CD8+ IFNg+ (n=38, 3, 6)	88.4	66.7	50.0	
Day 14: Pool 2 CD3+ CD8+ IFNg+ (n=34, 6, 4)	79.1	44.4	100	
Day 28: Pool 2 CD3+ CD8+ IFNg+ (n=41, 6, 2)	95.3	22.2	100	
Month 3: Pool 2 CD3+ CD8+ IFNg+ (n=32, 1, 1)	74.4	11.1	16.7	
Month 6: Pool 2 CD3+ CD8+ IFNg+ (n=23, 1, 1)	53.5	11.1	16.7	
Month 12: Pool 2 CD3+ CD8+ IFNg+ (n=5, 0, 0)	11.6	999	999	
Month 24: Pool 2 CD3+ CD8+ IFNg+ (n=5, 0, 0)	11.6	999	999	

Statistical analyses

No statistical analyses for this end point

Secondary: Peripheral blood PK parameters for tisagenlecleucel transgene levels by qPCR, by Day 28 disease response by Local & IRC assessment: AUC0-28d, AUC0-84d

End point title	Peripheral blood PK parameters for tisagenlecleucel transgene levels by qPCR, by Day 28 disease response by Local & IRC assessment: AUC0-28d, AUC0-84d
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End point description:

Characterize the in vivo cellular pharmacokinetic (PK) profile.

AUC0-28d and AUC0-84d is defined as the AUC from time zero to day 28 and 84 or other disease assessment days, in peripheral blood (% or copies/ μ g x days).

End point type	Secondary
End point timeframe:	
60 Months	

End point values	CR/CRi	No Response (NR)	Unknown	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	52	6	6	
Units: copies/ μ g*days				
geometric mean (geometric coefficient of variation)				
AUC0-28d (n= 52, 3, 1)	261000 (\pm 199.8)	151000 (\pm 71.7)	617000 (\pm 999999)	
AUC0-84d (n= 45, 2, 1)	368000 (\pm 182.9)	443000 (\pm 79.9)	1340000 (\pm 999999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Peripheral blood PK parameters for tisagenlecleucel transgene levels by qPCR, by Day 28 disease response by Local & IRC assessment: Cmax

End point title	Peripheral blood PK parameters for tisagenlecleucel transgene levels by qPCR, by Day 28 disease response by Local & IRC assessment: Cmax
End point description:	Characterize the in vivo cellular pharmacokinetic (PK) profile. Cmax is defined as the maximum (peak) observed in peripheral blood drug concentration after single dose administration (% or copies/ μ g).
End point type	Secondary
End point timeframe:	
60 Months	

End point values	CR/CRi	No Response (NR)	Unknown	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	52	6	6	
Units: copies/ μ gys				
geometric mean (geometric coefficient of variation)	28300 (\pm 197.0)	15100 (\pm 49.4)	52500 (\pm 91.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Peripheral blood PK parameters for tisagenlecleucel transgene levels by qPCR, by Day 28 disease response by Local & IRC assessment: Tmax

End point title	Peripheral blood PK parameters for tisagenlecleucel transgene levels by qPCR, by Day 28 disease response by Local & IRC assessment: Tmax
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End point description:

Characterize the in vivo cellular pharmacokinetic (PK) profile.

Tmax is defined as the time to reach maximum (peak) peripheral blood drug concentration after single dose administration (days)

End point type	Secondary
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End point timeframe:

60 Months

End point values	CR/CRi	No Response (NR)	Unknown	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	52	6	6	
Units: days				
median (full range (min-max))	9.84 (6.74 to 54.8)	20.0 (13.9 to 22.8)	11.9 (11.0 to 12.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Peripheral blood PK parameters for tisagenlecleucel transgene levels by qPCR, by Day 28 disease response by Local & IRC assessment: T1/2

End point title	Peripheral blood PK parameters for tisagenlecleucel transgene levels by qPCR, by Day 28 disease response by Local & IRC assessment: T1/2
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End point description:

Characterize the in vivo cellular pharmacokinetic (PK) profile.

T1/2 is defined as the half-life associated with the disposition phase slopes (alpha, beta, gamma etc.) of a semi logarithmic concentration-time curve (days) in peripheral blood

End point type	Secondary
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End point timeframe:

60 Months

End point values	CR/CRi	No Response (NR)	Unknown	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	52	6	6	
Units: days				
geometric mean (geometric coefficient of variation)	31.9 (± 415.1)	4.36 (± 421.2)	42.1 (± 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Peripheral blood PK parameters for tisagenlecleucel transgene levels by qPCR, by Day 28 disease response by Local & IRC assessment: Clast

End point title	Peripheral blood PK parameters for tisagenlecleucel transgene levels by qPCR, by Day 28 disease response by Local & IRC assessment: Clast
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End point description:

Characterize the in vivo cellular pharmacokinetic (PK) profile.

Clast is defined as the last observed quantifiable concentration in peripheral blood (% or copies/ug)

End point type	Secondary
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End point timeframe:

60 Months

End point values	CR/CRi	No Response (NR)	Unknown	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	52	6	6	
Units: copies/μg				
geometric mean (geometric coefficient of variation)	223 (± 283.4)	1980 (± 207.5)	80.3 (± 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Peripheral blood PK parameters for tisagenlecleucel transgene levels by qPCR, by Day 28 disease response by Local & IRC assessment: Tlast

End point title	Peripheral blood PK parameters for tisagenlecleucel transgene levels by qPCR, by Day 28 disease response by Local & IRC assessment: Tlast
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End point description:

Characterize the in vivo cellular pharmacokinetic (PK) profile.

)

Tlast is defined as the time of last observed quantifiable concentration in peripheral blood (days)"

End point type	Secondary
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End point timeframe:

60 Months

End point values	CR/CRi	No Response (NR)	Unknown	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	52	6	6	
Units: days				
median (full range (min-max))	179 (17.8 to 921)	26.9 (26.7 to 96.1)	210 (210 to 210)	

Statistical analyses

No statistical analyses for this end point

Secondary: CD19 status of bone marrow/blood relapse in patients who achieved CR or CRi

End point title	CD19 status of bone marrow/blood relapse in patients who achieved CR or CRi
End point description:	The CD19 status of bone marrow/blood relapse was relapse was categorized as follows: CD19 positive, CD19 dim, CD19 negative, CD19 positive/negative & unknown
End point type	Secondary
End point timeframe:	At time of relapse up to 60 months

End point values	tisagenlecleucel (CTL019) - All participants			
Subject group type	Reporting group			
Number of subjects analysed	64			
Units: Percentage of participants				
number (not applicable)				
CD19 positive	22.2			
CD19 dim	5.6			
CD19 negative	16.7			
CD19 positive/negative	16.7			
Unknown	55.6			

Statistical analyses

No statistical analyses for this end point

Secondary: CD19 site of initial relapse in patients who achieved CR or CRi

End point title	CD19 site of initial relapse in patients who achieved CR or CRi
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End point description:

The site of initial relapse was categorized as follows into 2 categories as follow: BM and/or blood relapse (with extramedullary relapse, without extramedullary relapse, unknown extramedullary disease status) and Extramedullary only (unknown).

End point type	Secondary
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End point timeframe:

At time of relapse up to 60 months

End point values	tisagenlecleucel (CTL019) - All participants			
Subject group type	Reporting group			
Number of subjects analysed	64			
Units: Percentage of participants				
number (not applicable)				
BM &/or blood relapse with extramed. relapse	11.1			
BM &/or blood relapse without extramed. relapse	44.4			
BM &/or blood relapse:UNK extramed. disease status	16.7			
Extramedullary only	27.8			
Unknown	16.7			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to B-cell recovery in participants who achieved CR or CRi by IRC

End point title	Time to B-cell recovery in participants who achieved CR or CRi by IRC
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End point description:

Time to B cell recovery was defined as the time from onset of remission to the earliest time when the percentage of CD19+ total B cell among viable WBC is $\geq 1\%$ or among lymphocyte is at least 3%.

End point type	Secondary
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End point timeframe:

during the whole study, up to 60 months

End point values	tisagenlecleucel (CTL019) - All participants			
Subject group type	Reporting group			
Number of subjects analysed	64			
Units: Percentage of participants				
median (confidence interval 95%)	35.5 (7.6 to 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: CD19+ B cell levels in peripheral blood by day 28 disease response by IRC assessment

End point title	CD19+ B cell levels in peripheral blood by day 28 disease response by IRC assessment
End point description: The levels (%) of CD19+ total B cells amongst viable white blood cells (WBC) in peripheral blood	
End point type	Secondary
End point timeframe: Enrollment/Pre-Chemotherapy; Pre-infusion; Baseline; Day 7; Day 14; Day 21; Day 28; Month 3; Month 6; Month 9; Month 12; Month 24; Month 36	

End point values	CR/CRi	Unknown	No Response	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	52	6	6	
Units: Percentage of participants				
arithmetic mean (standard deviation)				
Enrollment/Pre-Chemotherapy (n=50, 6,6,)	26.8 (± 28.733)	32.66 (± 28.102)	52.29 (± 36.758)	
Pre-infusion (n=1,0,1)	0.02 (± 999)	46.80 (± 999)	999 (± 999)	
Baseline(n=50, 6, 6)	25.11 (± 28.584)	29.50 (± 24.466)	52.29 (± 36.758)	
Day 7 (n=45, 6, 6)	1.06 (± 3.735)	23.18 (± 38.772)	34.40 (± 46.922)	
Day 14 (n=50, 6, 5)	0.73 (± 5.096)	3.43 (± 7.520)	33.76 (± 45.359)	
Day 21 (n=46, 6, 5)	0.01 (± 0.017)	16.13 (± 35.929)	19.67 (± 32.553)	
Day 28 (n=48,6,3)	0.02 (± 0.069)	0.02 (± 0.012)	34.97 (± 36.648)	
Month 3 (n=44,1,2)	0.79 (± 1.971)	11.26 (± 15.917)	0.57 (± 999)	
Month 6 (n=37,1,1)	1.86 (± 7.958)	0.01 (± 999)	9.70 (± 999)	
Month 9 (n=27,0,0)	0.63 (± 2.180)	999 (± 999)	999 (± 999)	
Month 12 (n=27,0,0)	0.85 (± 2.420)	999 (± 999)	999 (± 999)	
Month 24 (n=14,0,0)	1.74 (± 3.446)	999 (± 999)	999 (± 999)	
Month 36 (n=6,0,0)	1.10 (± 2.106)	999 (± 999)	999 (± 999)	

Statistical analyses

Secondary: key inflammatory markers and cytokine parameters in blood within 1 month by maximum cytokine release syndrome (CRS) grade: C Reactive Protein (CRP)

End point title	key inflammatory markers and cytokine parameters in blood within 1 month by maximum cytokine release syndrome (CRS) grade: C Reactive Protein (CRP)
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End point description:

C-Reactive Protein at Pre-infusion, baseline, and change from baseline for Days 7, 14, 21, 28, Month 3

End point type	Secondary
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End point timeframe:

Pre-infusion, Baseline, Day 7, Day 14, Day 21, Day 28, Month 3

End point values	NO CRS	Grade 1/2	Grade 3	Grade 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	14	31	8	11
Units: mg/L				
median (full range (min-max))				
Pre-infusion (n=14,29,8,9,60)	9.21 (2.9 to 34.0)	8.27 (2.0 to 1530.0)	7.45 (0.6 to 50.0)	9.00 (2.0 to 153.0)
Baseline (BL) (n=14,30,8,9,61)	9.21 (2.9 to 34.0)	9.04 (2.0 to 1530.0)	7.45 (0.6 to 50.0)	9.00 (2.0 to 153.0)
Change from BL Day7 (n=14, 30,8,9,61)	0.00 (-15.0 to 25.0)	15.00 (-460.0 to 215.0)	79.55 (-2.0 to 380.0)	108.00 (-125.0 to 255.0)
Change from BL Day 14 (n=14,30,8,9,61)	0.00 (-20.0 to 24.0)	0.00 (-1031.0 to 215.0)	10.50 (-42.0 to 199.0)	15.70 (-148.0 to 100.0)
Change from BL Day 21 (n=14,28,8,7,57)	0.00 (-14.0 to 29.5)	-0.80 (-1460.0 to 677.0)	2.00 (-42.0 to 37.0)	-3.00 (-57.0 to 73.0)
Change from BL Day 28 (n=14,27,8,9,59)	0.00 (-15.0 to 47.0)	-0.70 (-1487.0 to 47.0)	1.50 (-45.0 to 55.0)	-3.00 (-151.0 to 27.0)
Change from BL Month 3 (n=11,23,5,7,46)	0.00 (-12.1 to 101.0)	-1.00 (-1501.0 to 7.1)	0.00 (-3.0 to 120.5)	-1.00 (-149.0 to 13.0)

End point values	All Participants			
Subject group type	Subject analysis set			
Number of subjects analysed	64			
Units: mg/L				
median (full range (min-max))				
Pre-infusion (n=14,29,8,9,60)	9.00 (0.6 to 1530.0)			
Baseline (BL) (n=14,30,8,9,61)	9.00 (0.6 to 1530.0)			
Change from BL Day7 (n=14, 30,8,9,61)	9.10 (-460.0 to 380.0)			
Change from BL Day 14 (n=14,30,8,9,61)	0.00 (-1031.0 to 215.0)			
Change from BL Day 21 (n=14,28,8,7,57)	0.00 (-1460.0 to 677.0)			

Change from BL Day 28 (n=14,27,8,9,59)	0.00 (-1487.0 to 55.0)			
Change from BL Month 3 (n=11,23,5,7,46)	-0.65 (-1501.0 to 120.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: key inflammatory markers and cytokine parameters in blood within 1 month by maximum cytokine release syndrome (CRS) grade: Ferritin

End point title	key inflammatory markers and cytokine parameters in blood within 1 month by maximum cytokine release syndrome (CRS) grade: Ferritin
End point description:	Ferritin at Pre-infusion, baseline, and change from baseline for Days 7, 14, 21, 28, Month 3
End point type	Secondary
End point timeframe:	Pre-infusion, Baseline, Day 7, Day 14, Day 21, Day 28, Month 3

End point values	NO CRS	Grade 1/2	Grade 3	Grade 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	14	31	8	11
Units: ug/L				
median (full range (min-max))				
Pre-infusion (n=14,26,8,9,54)	1865.20 (459.0 to 5015.0)	2202.22 (230.0 to 18061.0)	1906.95 (357.0 to 4200.0)	2078.40 (487.0 to 13553.9)
Baseline (BL) (n=14,30,8,9,61)	1865.20 (459.0 to 5015.0)	2202.22 (230.0 to 18061.0)	1906.95 (357.0 to 4200.0)	2078.40 (487.0 to 13553.9)
Change from BL Day7 (n=14, 29,8,9,60)	-146.50 (- 721.4 to 710.0)	377.80 (- 1468.0 to 522220.0)	22735.10 (- 330.0 to 182380.0)	23788.71 (- 161.0 to 269529.0)
Change from BL Day 14 (n=14,30,8,9,61)	-321.30 (- 2035.1 to 520.0)	861.50 (- 3483.3 to 59435.9)	10728.40 (1262.0 to 104170.0)	18580.01 (707.0 to 110421.6)
Change from BL Day 21 (n=14,29,8,8,59)	58.00 (-2302.0 to 524.0)	331.00 (- 3571.6 to 43336.0)	3299.85 (- 600.0 to 121100.0)	3199.00 (-17.0 to 12957.4)
Change from BL Day 28 (n=14,27,8,9,58)	121.10 (- 2952.0 to 1510.0)	283.00 (-6443. to 9879.0)	1104.00 (- 890.0 to 331000.0)	1211.00 (- 606.0 to 12957.4)
Change from BL Month 3 (n=11,23,5,7,46)	-124.90 (- 2418.0 to 1985.5)	-358.00 (- 5415.0 to 7050.0)	-487.60 (- 1500.0 to 8140.0)	-377.00 (- 1808.2 to 2641.6)

End point values	All Participants			
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Subject group type	Subject analysis set			
Number of subjects analysed	64			
Units: ug/L				
median (full range (min-max))				
Pre-infusion (n=14,26,8,9,54)	1983.90 (230.0 to 18061.0)			
Baseline (BL) (n=14,30,8,9,61)	1983.90 (230.0 to 18061.0)			
Change from BL Day7 (n=14, 29,8,9,60)	358.90 (-1468.0 to 269529.0)			
Change from BL Day 14 (n=14,30,8,9,61)	973.00 (-3483.3 to 110421.6)			
Change from BL Day 21 (n=14,29,8,8,59)	490.00 (-3571.6 to 121100.0)			
Change from BL Day 28 (n=14,27,8,9,58)	280.50 (-6443.7 to 33100.0)			
Change from BL Month 3 (n=11,23,5,7,46)	-330.00 (-5415.0 to 8140.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: key inflammatory markers and cytokine parameters in blood within 1 month by maximum cytokine release syndrome (CRS) grade: INF-gamma

End point title	key inflammatory markers and cytokine parameters in blood within 1 month by maximum cytokine release syndrome (CRS) grade: INF-gamma
End point description:	INF-gamma at Pre-infusion, baseline, and change from baseline for Days 7, 14, 21, 28, Month 3
End point type	Secondary
End point timeframe:	Pre-infusion, Baseline, Day 7, Day 14, Day 21, Day 28, Month 3

End point values	NO CRS	Grade 1/2	Grade 3	Grade 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	14	31	8	11
Units: pg/mL				
median (full range (min-max))				
Pre-infusion (n=14,30,8,9,61)	29.63 (1.0 to 283.0)	23.39 (1.0 to 242.8)	15.73 (6.4 to 31.5)	5.79 (2.5 to 34.1)
Baseline (BL) (n=14,31,8,9,63)	29.63 (1.0 to 283.0)	22.51 (1.0 to 242.8)	15.73 (6.4 to 31.5)	4.77 (1.0 to 34.1)
Change from BL Day7 (n=14, 31,8,10,63)	0.47 (-167.9 to 140.6)	52.59 (-201.2 to 39452.4)	3023.82 (-14.7 to 162376.0)	1347.48 (60.2 to 89599.0)

Change from BL Day 14 (n=13,30,8,9,60)	-5.10 (-278.3 to 39.2)	-4.44 (-194.8 to 131.1)	58.65 (-14.3 to 1328.7)	102.04 (-2.2 to 8925.9)
Change from BL Day 21 (n=13,29,8,8,58)	-4.97 (-264.0 to 58.5)	1.06 (-219.7 to 1384.6)	0.53 (-22.8 to 1048.7)	5.23 (-4.0 to 167.1)
Change from BL Day 28 (n=14,28,8,9,59)	-6.93 (-269.9 to 60.4)	0.20 (-223.6 to 738.8)	-1.19 (-26.1 to 187.7)	0.36 (-4.7 to 138.4)
Change from BL Month 3 (n=11,22,6,6,45)	-6.08 (-278.6 to 167.5)	-14.58 (-173.9 to 7.6)	21.25 (-7.7 to 37.2)	-0.67 (-4.4 to 23.1)

End point values	All Participants			
Subject group type	Subject analysis set			
Number of subjects analysed	64			
Units: pg/mL				
median (full range (min-max))				
Pre-infusion (n=14,30,8,9,61)	20.22 (1.0 to 283.0)			
Baseline (BL) (n=14,31,8,9,63)	15.75 (1.0 to 283.0)			
Change from BL Day7 (n=14, 31,8,10,63)	72.09 (-201.2 to 162376.0)			
Change from BL Day 14 (n=13,30,8,9,60)	1.32 (-278.3 to 8925.9)			
Change from BL Day 21 (n=13,29,8,8,58)	-0.89 (-264.0 to 1384.6)			
Change from BL Day 28 (n=14,28,8,9,59)	-0.62 (-269.9 to 738.8)			
Change from BL Month 3 (n=11,22,6,6,45)	-5.71 (-278.6 to 167.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: key inflammatory markers and cytokine parameters in blood within 1 month by maximum cytokine release syndrome (CRS) grade: Interleuken-6 (IL-6)

End point title	key inflammatory markers and cytokine parameters in blood within 1 month by maximum cytokine release syndrome (CRS) grade: Interleuken-6 (IL-6)
End point description:	IL-6 at Pre-infusion, baseline, and change from baseline for Days 7, 14, 21, 28, Month 3
End point type	Secondary
End point timeframe:	Pre-infusion, Baseline, Day 7, Day 14, Day 21, Day 28, Month 3

End point values	NO CRS	Grade 1/2	Grade 3	Grade 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	14	31	8	11
Units: pg/mL				
median (full range (min-max))				
Pre-infusion (n=14,30,8,9,61)	2.42 (0.4 to 12.0)	2.89 (0.2 to 19.6)	1.00 (0.8 to 9.4)	2.27 (0.4 to 6.2)
Baseline (BL) (n=14,31,8,10,63)	2.42 (0.4 to 12.0)	2.83 (0.2 to 19.6)	1.00 (0.8 to 9.4)	1.84 (0.2 to 6.2)
Change from BL Day7 (n=14,31,8,10,63)	-0.23 (-9.6 to 4.3)	2.64 (-13.1 to 61.3)	52.75 (-0.6 to 7201.6)	141.68 (1.3 to 12615.8)
Change from BL Day 14 (n=13,30,8,9,60)	-0.36 (-2.3 to 4.1)	-0.67 (-13.4 to 21.5)	8.88 (-0.6 to 30.4)	165.16 (-0.2 to 5734.8)
Change from BL Day 21 (n=13,29,8,8,58)	-0.97 (-5.3 to 5.3)	-0.46 (-15.4 to 103.4)	1.65 (-0.6 to 265.2)	50.75 (-0.2 to 5734.8)
Change from BL Day 28 (n=14,28,8,9,59)	-0.98 (-7.8 to 1.9)	-0.28 (-17.5 to 33.0)	0.91 (-0.6 to 138.6)	38.13 (-0.0 to 2148.4)
Change from BL Month 3 (n=11,22,6,6,45)	0.34 (-10.8 to 22.7)	-0.59 (-8.9 to 1.2)	0.56 (-0.6 to 30.3)	0.40 (-0.9 to 3.2)

End point values	All Participants			
Subject group type	Subject analysis set			
Number of subjects analysed	64			
Units: pg/mL				
median (full range (min-max))				
Pre-infusion (n=14,30,8,9,61)	2.27 (0.2 to 19.6)			
Baseline (BL) (n=14,31,8,10,63)	1.99 (0.2 to 19.6)			
Change from BL Day7 (n=14,31,8,10,63)	2.64 (-13.1 to 12615.8)			
Change from BL Day 14 (n=13,30,8,9,60)	-0.11 (-13.4 to 5734.8)			
Change from BL Day 21 (n=13,29,8,8,58)	-0.09 (-15.4 to 5734.8)			
Change from BL Day 28 (n=14,28,8,9,59)	-0.03 (-17.5 to 2148.4)			
Change from BL Month 3 (n=11,22,6,6,45)	-0.19 (-10.8 to 30.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: key inflammatory markers and cytokine parameters in blood within 1 month by maximum cytokine release syndrome (CRS) grade: Interleuken-2 (IL-2)

End point title	key inflammatory markers and cytokine parameters in blood within 1 month by maximum cytokine release syndrome (CRS) grade: Interleuken-2 (IL-2)
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End point description:

IL-2 at Pre-infusion, baseline, and change from baseline for Days 7, 14, 21, 28, Month 3

End point type	Secondary
End point timeframe:	
Pre-infusion, Baseline, Day 7, Day 14, Day 21, Day 28, Month 3	

End point values	NO CRS	Grade 1/2	Grade 3	Grade 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	14	31	8	11
Units: pg/mL				
median (full range (min-max))				
Pre-infusion (n=14,30,8,9,61)	2.3 (2.3 to 2.3)	2.3 (2.3 to 2.3)	2.3 (2.3 to 2.3)	2.3 (2.3 to 2.3)
Baseline (BL) (n=14,31,8,10, 63)	2.3 (2.3 to 2.3)	2.3 (2.3 to 2.3)	2.3 (2.3 to 2.3)	2.3 (2.3 to 2.3)
Change from BL Day7 (n=14, 31,8,10,63)	3.33 (0.0 to 6.7)	3.15 (0.0 to 7.0)	13.14 (5.0 to 63.7)	7.48 (2.9 to 12.1)
Change from BL Day 14 (n=13,30,8,9,60)	999 (999 to 999)	0.00 (0.00 to 0.00)	999 (999 to 999)	4.56 (4.56 to 4.6)
Change from BL Day 21 (n=13,29,8,8,58)	999 (999 to 999)	999 (999 to 999)	999 (999 to 999)	999 (999 to 999)
Change from BL Day 28 (n=14,28,8,9,59)	999 (999 to 999)	999 (999 to 999)	999 (999 to 999)	999 (999 to 999)
Change from BL Month 3 (n=11,22,6,6,45)	999 (999 to 999)	999 (999 to 999)	999 (999 to 999)	999 (999 to 999)

End point values	All Participants			
Subject group type	Subject analysis set			
Number of subjects analysed	64			
Units: pg/mL				
median (full range (min-max))				
Pre-infusion (n=14,30,8,9,61)	2.3 (2.3 to 2.3)			
Baseline (BL) (n=14,31,8,10, 63)	2.3 (2.3 to 2.3)			
Change from BL Day7 (n=14, 31,8,10,63)	5.16 (0.0 to 63.7)			
Change from BL Day 14 (n=13,30,8,9,60)	0.00 (0.0 to 4.6)			
Change from BL Day 21 (n=13,29,8,8,58)	999 (999 to 999)			
Change from BL Day 28 (n=14,28,8,9,59)	999 (999 to 999)			
Change from BL Month 3 (n=11,22,6,6,45)	999 (999 to 999)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.0
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Reporting groups

Reporting group title	tisagenlecleucel (CTL019) - All
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Reporting group description:

Pediatric participants with r/r B-cell ALL

Serious adverse events	tisagenlecleucel (CTL019) - All		
Total subjects affected by serious adverse events			
subjects affected / exposed	52 / 64 (81.25%)		
number of deaths (all causes)	30		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Glioblastoma multiforme			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Myelodysplastic syndrome			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypotension			

subjects affected / exposed	7 / 64 (10.94%)		
occurrences causally related to treatment / all	6 / 7		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Physical deconditioning			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	7 / 64 (10.94%)		
occurrences causally related to treatment / all	2 / 9		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	41 / 64 (64.06%)		
occurrences causally related to treatment / all	44 / 44		
deaths causally related to treatment / all	0 / 0		
Graft versus host disease in gastrointestinal tract			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			

subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hypoxia			
subjects affected / exposed	4 / 64 (6.25%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	2 / 64 (3.13%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Pulmonary oedema			
subjects affected / exposed	2 / 64 (3.13%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	3 / 64 (4.69%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 1		
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
White blood cell count decreased			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural			

complications			
Procedural pain			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transfusion related complication			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrioventricular block second degree			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ventricular tachycardia			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Embololic stroke			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Encephalopathy			
subjects affected / exposed	4 / 64 (6.25%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Idiopathic intracranial hypertension			

subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	4 / 64 (6.25%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Disseminated intravascular coagulation			
subjects affected / exposed	2 / 64 (3.13%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Eosinophilia			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	23 / 64 (35.94%)		
occurrences causally related to treatment / all	23 / 27		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	3 / 64 (4.69%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Papilloedema			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vision blurred			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 64 (3.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Enterocolitis			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Stomatitis			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Ecchymosis			
subjects affected / exposed	1 / 64 (1.56%)		
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	4 / 64 (6.25%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Flank pain			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteonecrosis			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacterial sepsis			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Campylobacter infection			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Catheter site infection			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Cellulitis of male external genital organ				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Cholecystitis infective				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile colitis				
subjects affected / exposed	2 / 64 (3.13%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile infection				
subjects affected / exposed	3 / 64 (4.69%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Corona virus infection				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterovirus infection				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis norovirus				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				

subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Parainfluenzae virus infection				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	2 / 64 (3.13%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory syncytial virus infection				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Respiratory tract infection viral				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rhinovirus infection				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Rotavirus infection				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				

subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Septic embolus			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Staphylococcal infection			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	2 / 64 (3.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Vascular device infection			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vulvovaginal candidiasis			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Acidosis			

subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Decreased appetite			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour lysis syndrome			
subjects affected / exposed	2 / 64 (3.13%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	tisagenlecleucel (CTL019) - All		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	64 / 64 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	12 / 64 (18.75%)		
occurrences (all)	14		
Hypotension			
subjects affected / exposed	9 / 64 (14.06%)		
occurrences (all)	9		
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	4 / 64 (6.25%)		
occurrences (all)	4		
Chills			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Fatigue</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pyrexia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>10 / 64 (15.63%)</p> <p>11</p> <p>15 / 64 (23.44%)</p> <p>16</p> <p>4 / 64 (6.25%)</p> <p>4</p> <p>21 / 64 (32.81%)</p> <p>30</p>		
<p>Immune system disorders</p> <p>Cytokine release syndrome</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hypogammaglobulinaemia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>19 / 64 (29.69%)</p> <p>19</p> <p>33 / 64 (51.56%)</p> <p>36</p>		
<p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Epistaxis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hypoxia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nasal congestion</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Oropharyngeal pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pleural effusion</p>	<p>14 / 64 (21.88%)</p> <p>19</p> <p>10 / 64 (15.63%)</p> <p>12</p> <p>6 / 64 (9.38%)</p> <p>7</p> <p>5 / 64 (7.81%)</p> <p>5</p> <p>6 / 64 (9.38%)</p> <p>6</p>		

subjects affected / exposed	6 / 64 (9.38%)		
occurrences (all)	6		
Pulmonary oedema			
subjects affected / exposed	5 / 64 (7.81%)		
occurrences (all)	5		
Rhinitis allergic			
subjects affected / exposed	4 / 64 (6.25%)		
occurrences (all)	5		
Rhinorrhoea			
subjects affected / exposed	6 / 64 (9.38%)		
occurrences (all)	6		
Tachypnoea			
subjects affected / exposed	5 / 64 (7.81%)		
occurrences (all)	5		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	7 / 64 (10.94%)		
occurrences (all)	7		
Confusional state			
subjects affected / exposed	6 / 64 (9.38%)		
occurrences (all)	6		
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	5 / 64 (7.81%)		
occurrences (all)	7		
Alanine aminotransferase increased			
subjects affected / exposed	21 / 64 (32.81%)		
occurrences (all)	27		
Aspartate aminotransferase increased			
subjects affected / exposed	20 / 64 (31.25%)		
occurrences (all)	28		
Blood bilirubin increased			
subjects affected / exposed	8 / 64 (12.50%)		
occurrences (all)	12		
Blood creatinine increased			

subjects affected / exposed	9 / 64 (14.06%)		
occurrences (all)	12		
Blood fibrinogen decreased			
subjects affected / exposed	4 / 64 (6.25%)		
occurrences (all)	5		
Blood immunoglobulin M decreased			
subjects affected / exposed	4 / 64 (6.25%)		
occurrences (all)	4		
International normalised ratio increased			
subjects affected / exposed	9 / 64 (14.06%)		
occurrences (all)	11		
Lymphocyte count decreased			
subjects affected / exposed	16 / 64 (25.00%)		
occurrences (all)	20		
Neutrophil count decreased			
subjects affected / exposed	28 / 64 (43.75%)		
occurrences (all)	44		
Platelet count decreased			
subjects affected / exposed	20 / 64 (31.25%)		
occurrences (all)	36		
Prothrombin time prolonged			
subjects affected / exposed	9 / 64 (14.06%)		
occurrences (all)	12		
Weight decreased			
subjects affected / exposed	4 / 64 (6.25%)		
occurrences (all)	4		
White blood cell count decreased			
subjects affected / exposed	35 / 64 (54.69%)		
occurrences (all)	43		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	4 / 64 (6.25%)		
occurrences (all)	4		
Procedural pain			

subjects affected / exposed occurrences (all)	5 / 64 (7.81%) 5		
Cardiac disorders			
Sinus tachycardia subjects affected / exposed occurrences (all)	6 / 64 (9.38%) 6		
Tachycardia subjects affected / exposed occurrences (all)	15 / 64 (23.44%) 16		
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	6 / 64 (9.38%) 8		
Headache subjects affected / exposed occurrences (all)	24 / 64 (37.50%) 37		
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	27 / 64 (42.19%) 38		
Lymphopenia subjects affected / exposed occurrences (all)	4 / 64 (6.25%) 4		
Neutropenia subjects affected / exposed occurrences (all)	8 / 64 (12.50%) 10		
Thrombocytopenia subjects affected / exposed occurrences (all)	10 / 64 (15.63%) 13		
Eye disorders			
Periorbital oedema subjects affected / exposed occurrences (all)	4 / 64 (6.25%) 4		
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	11 / 64 (17.19%) 15		

Constipation			
subjects affected / exposed	7 / 64 (10.94%)		
occurrences (all)	8		
Diarrhoea			
subjects affected / exposed	22 / 64 (34.38%)		
occurrences (all)	26		
Nausea			
subjects affected / exposed	25 / 64 (39.06%)		
occurrences (all)	33		
Vomiting			
subjects affected / exposed	27 / 64 (42.19%)		
occurrences (all)	43		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	5 / 64 (7.81%)		
occurrences (all)	5		
Erythema			
subjects affected / exposed	5 / 64 (7.81%)		
occurrences (all)	6		
Hyperhidrosis			
subjects affected / exposed	4 / 64 (6.25%)		
occurrences (all)	5		
Petechiae			
subjects affected / exposed	4 / 64 (6.25%)		
occurrences (all)	4		
Pruritus			
subjects affected / exposed	4 / 64 (6.25%)		
occurrences (all)	4		
Rash			
subjects affected / exposed	8 / 64 (12.50%)		
occurrences (all)	9		
Rash maculo-papular			
subjects affected / exposed	5 / 64 (7.81%)		
occurrences (all)	5		
Renal and urinary disorders			

Acute kidney injury subjects affected / exposed occurrences (all)	5 / 64 (7.81%) 6		
Haematuria subjects affected / exposed occurrences (all)	5 / 64 (7.81%) 6		
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	5 / 64 (7.81%) 6		
Myalgia subjects affected / exposed occurrences (all)	5 / 64 (7.81%) 5		
Pain in extremity subjects affected / exposed occurrences (all)	10 / 64 (15.63%) 11		
Infections and infestations			
Gastroenteritis subjects affected / exposed occurrences (all)	4 / 64 (6.25%) 4		
Influenza subjects affected / exposed occurrences (all)	4 / 64 (6.25%) 4		
Otitis media subjects affected / exposed occurrences (all)	4 / 64 (6.25%) 6		
Rhinovirus infection subjects affected / exposed occurrences (all)	4 / 64 (6.25%) 6		
Sinusitis subjects affected / exposed occurrences (all)	4 / 64 (6.25%) 5		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	8 / 64 (12.50%) 10		
Urinary tract infection			

subjects affected / exposed occurrences (all)	4 / 64 (6.25%) 6		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	21 / 64 (32.81%)		
occurrences (all)	23		
Hypernatraemia			
subjects affected / exposed	4 / 64 (6.25%)		
occurrences (all)	6		
Hyperphosphataemia			
subjects affected / exposed	8 / 64 (12.50%)		
occurrences (all)	12		
Hypoalbuminaemia			
subjects affected / exposed	5 / 64 (7.81%)		
occurrences (all)	5		
Hypokalaemia			
subjects affected / exposed	19 / 64 (29.69%)		
occurrences (all)	23		
Hypophosphataemia			
subjects affected / exposed	10 / 64 (15.63%)		
occurrences (all)	10		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 August 2014	The protocol was amended in order to include additional safety information and includes Health Authority feedback regarding reporting of SAEs including CRS and deaths, updating CTL019 dosing, staggered-enrollment design, follow-up time required after a live birth, influenza testing 10 days prior to infusion, general toxicity management, and modified Serious Adverse Event (SAE) and Adverse Event (AE) reporting.
28 August 2015	The protocol was amended to: Ensure full alignment with the agreed binding measures detailed in the Pediatric Investigation Plan (PIP) opinion of the Paediatric Committee of the European Medicines Agency, issued on 20 March 2015, including the expansion of inclusion criteria to enroll patients with relapsed or refractory B-cell lymphoblastic lymphoma; Address recommendations from EMA Scientific Advice letter on 25 April 2014; Transfer the trial sponsorship from University of Pennsylvania IND to Novartis IND. Additional PK and cytokine sample time points were added to better define cell expansion and CRS, as well as the addition of exploratory endpoints that did not impact total sample collection requirements. Testing for CMV and EBV is not required at screening per current guidelines for autologous blood product therapy. Other changes have been instituted for purposes of clarity and feasibility based on experiences from ongoing trials
28 April 2016	The protocol was amended to institute updates on safety, CTL019 target cell dose ranges, patient management, and eligibility criteria based on experiences from ongoing trials and recommendations from Health Authorities, Study Steering Committee, and Data Monitoring Committee.

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: